AN OPEN-LABEL, SINGLE-ARM STUDY OF THE LONG-TERM SAFETY OF XALKORI® IN PATIENTS FROM CHINA WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING A TRANSLOCATION OR INVERSION EVENT INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) OR ROS1 LOCUS WHO HAVE PREVIOUSLY BEEN TREATED ON A STUDY OF XALKORI®

Investigational Product Number:	PF-02341066
Investigational Product Name:	Crizotinib
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	02 August 2019	Extended the study treatment duration until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever came first, to provide longer treatment access to the patients. Updated the AE and SAE collection and recording requirements to remove inconsistencies and to provide further clarifications. Clarified that scans outside the screening window may be used in this study. Updated "End of Trial" definition. Added "all AEs leading to permanent treatment discontinuation" into the endpoint.
Original protocol	22-March-2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale:

On August 26, 2011, the U.S. Food and Drug Administration (FDA) approved XALKORI® (crizotinib) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive as detected by an FDA-approved test.[1] Crizotinib received approvals for the treatment of ALK-positive advanced NSCLC in China in January 2013 and was approved for the treatment of c-ROS oncogene 1 (ROS1)-positive advanced NSCLC in China in September 2017.

This protocol permits continued access to crizotinib for patients with advanced NSCLC harboring translocation or inversion event involving the ALK or ROS1 gene locus who were enrolled and treated in Studies A8081005, A8081007, A8081014, A8081029, or A8081063 and are still receiving crizotinib treatment at the time of enrollment into this study. In addition, patients randomized to the chemotherapy arm in Studies A8081014 or A8081029 who have not yet crossed over to receive crizotinib treatment at the time of enrollment into this study are eligible to enroll into this study after investigator-assessed disease progression. This clinical trial is only open to patients in China. Patients will follow a schedule of visits and data collection for safety monitoring.

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the XALKORI® local product document (LPD).

Objectives:

To evaluate the long-term safety of crizotinib in patients with advanced NSCLC harboring a translocation or inversion of the ALK gene or ROS1 gene locus.

Endpoints:

All Grade 3-5 adverse events (AEs), all AEs leading to permanent treatment discontinuation, and all serious adverse events (SAEs) as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

Study Design:

This is a multi-center, open-label study in China only. Eligible patients include those with advanced NSCLC harboring a translocation or inversion of the ALK gene or ROS1 gene locus who were enrolled and treated in Studies A8081005, A8081007, A8081014, A8081029, or A8081063 and are still receiving crizotinib treatment at the time of enrollment into this study. In addition, patients, randomized to the chemotherapy arm in Studies A8081014 or A8081029 and have not yet crossed over to receive crizotinib treatment at the time of enrollment into this study are eligible to enroll into this study after investigator-assessed disease progression. Dose reductions and re-escalations are allowed based on tolerability.

Study Treatments:

Patients, who were receiving crizotinib prior to enrolling into this study, will continue to receive their current crizotinib dosing regimen. Patients in Study A8081014 or A8081029, who have not started crizotinib treatment prior to enrollment in this study, will receive the standard starting dose of crizotinib at 250 mg Twice Daily (BID) orally after investigator-assessed disease progression. Crizotinib will be supplied by the Sponsor.

Patients will continue single-agent crizotinib treatment on this study until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever comes first. Patients may continue crizotinib treatment as assigned beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression at the discretion of the investigator if the patient is still experiencing clinical benefit.

Statistical Methods:

Due to the nature of this rollover study, the number of patients to be enrolled is not predefined. However, it is expected that approximately 75 patients will be enrolled.

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive summaries of safety and demographic characteristics will be provided, and no inferential analyses are planned.

SCHEDULE OF ACTIVITIES

Schedule of Activities For Patients Who are Still Receiving Single-agent Crizotinib through Pfizer in Studies A8081005, A8081007, A8081014, A8081029 or A8081063.

[Note: This schedule is for patients who have received crizotinib for at least 8 cycles, ie, 224 days (1 cycle=28 days in this study). Please refer to Table 2 for patients who a) were randomized to chemotherapy treatment and have not yet crossed over to crizotinib treatment in Studies A8081014 or A8081029, or who b) have received crizotinib treatment for less than 8 cycles in 1 of those 2 studies.]

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Table 1. Schedule of Activities

Visit identifier	Screening	Study Treatment[a]		End of Treatment (EOT)	Follow-up[j]
		Cycle 1	Cycles ≥2 Visit on Day 1 of every other cycle from cycle 2 (2, 4, 6)		
	≤28 Days Prior to Cycle 1 Day 1	Day 1 (±2 days)	Day 1 (±2 days for Cycle 2 and ±4 days for subsequent cycles)		
Procedures at Screening					
Informed Consent[b]	X				
Eligibility Criteria Evaluation	X				
Registration	X				
Demographic Characteristics[c]	X				
Medical/Oncology History[d]	X				
Procedures at Screening and On Study					
Contraceptive check (as appropriate)[e]	X	X	X	X	X

Table 1. Schedule of Activities

Visit identifier	Screening	Study Treatment[a]		End of Treatment (EOT)	Follow-up[j]
		Cycle 1	Cycles ≥2 Visit on Day 1 of every other cycle from cycle 2 (2, 4, 6)		
	≤28 Days Prior to Cycle 1 Day 1	Day 1 (±2 days)	Day 1 (±2 days for Cycle 2 and ±4 days for subsequent cycles)		
Pregnancy Test[f]	X	X	X	X	
Physical Examination[g]	X	Per routine clinical practice			
12-lead ECG	X	As clinically indicated			
Study Treatment					
Crizotinib		X			
Clinical Assessments					
Tumor Assessments[h]	X	Per routine clinical practice			
Adverse Events	X	X	X	X	X
Hematology[i]	X	X	X		
Chemistry[i]	X	X	X		

Cycle length is 28 days.

Abbreviations: EC = ethics committees; ECG = electrocardiogram; EOT = end of treatment; IRB = institutional review board.

a. During the non-visit cycles, the investigator is responsible for ensuring that the patient contacts the clinical site in order to provide an update of adverse events, concomitant medications, laboratory and pregnancy tests.

b. Informed Consent: Must be obtained prior to undergoing any study-related procedure.

c. Demographic Characteristics: patient age, gender, and ethnicity.

d. Medical/oncology history: prior anticancer therapy, medical history, extent of disease, ECOG performance status and other disease information.

e. Contraceptive check: please see Section 4.4.1. Contraception for further details.

f. Pregnancy Test: Pregnancy Test (serum or urine) for women of child-bearing potential should also be repeated whenever one menstrual cycle is missed, or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs, or if required by local regulations.

g. A complete physical examination at screening will include the assessment of all body systems, the measurement of body weight, height, blood pressure, temperature and pulse rate. Symptom directed physical examination will be performed as per routine clinical practice during the study.

h. On study tumor assessments should be performed according to site standard of care imaging modality. The most recent tumor assessment available may be utilized for tumor assessment at baseline, even if conducted more than 28 days prior to Cycle 1 Day 1. Abdominal scans should include complete visualization of both kidneys. The interval for monitoring disease status and for progression of disease should not be longer than every 6 months.

i. Hematology and Chemistry: Required tests are listed in Appendix 1 of the protocol. Hematology and Chemistry is performed on Day 1 of each treatment cycle and may be additionally performed as clinically indicated. Blood chemistry and hematology does not need to be repeated if acceptable screening assessment is performed within 7 days prior to Cycle 1 Day 1.

j. Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the patient may be done via a phone call.

Schedule of Activities For Patients who are pending for Crossover Treatment in Study A8081014 or A8081029

[Note: This schedule is for patients who a) were randomized to chemotherapy treatment and have not yet crossed over to crizotinib treatment in Studies A8081014 or A8081029, or b) have received crizotinib treatment for less than 8 cycles in one of those 2 studies]

The table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Table 2. Schedule of Activities For Patients who are pending for Crossover Treatment in Study A8081014 or A8081029

Visit identifier	Screening	Study Treatment[a]				End of Treatment (EOT)	Follow-up[j]
		Cycles 1, 2		Cycles 3-7	Cycles ≥8 Visit on Day 1 of every other cycle from cycle 8		
	≤28 Days Prior to Cycle 1 Day 1	Day 1 (±2 days)	Day 8, 15, 22 (±1 day) of each Cycle	Day 1(±2 days)	Day 1 (±4 days)		
Procedures at Screening							
Informed Consent[b]	X						
Eligibility Criteria Evaluation	X						
Registration	X						
Demographic Characteristics[c]	X						
Medical/Oncology History[d]	X						
Procedures at Screening and On Study							
Contraceptive check (as appropriate)[e]	X	X		X	X	X	X

Table 2. Schedule of Activities For Patients who are pending for Crossover Treatment in Study A8081014 or A8081029

Visit identifier	Screening	Study Treatment[a]				End of Treatment (EOT)	Follow-up[j]
		Cycles 1, 2		Cycles 3-7	Cycles ≥8 Visit on Day 1 of every other cycle from cycle 8		
	≤28 Days Prior to Cycle 1 Day 1	Day 1 (±2 days)	Day 8, 15, 22 (±1 day) of each Cycle	Day 1(±2 days)	Day 1 (±4 days)		
Pregnancy Test[f]	X	X		X	X	X	
Physical Examination[g]	X	Per routine clinical practice					
12-lead ECG	X	As clinically indicated					
Study Treatment							
Crizotinib		X					
Clinical Assessments							
Tumor Assessments[h]	X	Per routine clinical practice					
Adverse Events	X	X	X	X	X	X	X
Hematology[i]	X	X	X	X	X		
Chemistry[i]	X	X	X	X	X		

Cycle length is 28 days.

Abbreviations: EC = ethics committee; ECG = electrocardiogram; EOT = end of treatment; IRB = institutional review board.

a. During the non-visit cycles, the investigator is responsible for ensuring that the patient contacts the clinical site in order to provide an update of adverse events, concomitant medications, laboratory and pregnancy tests.

b. Informed Consent: Must be obtained prior to undergoing any study-related procedure after disease progression is confirmed by investigator.

c. Demographic Characteristics: patient age, gender, and ethnicity.

d. Medical/Oncology History: prior anticancer therapy, medical history, extent of disease, ECOG performance status and other disease information.

e. Contraceptive check: please see Section 4.4.1. Contraception for further details.

f. Pregnancy Test: Pregnancy Test (serum or urine) for women of child-bearing potential also should be repeated whenever one menstrual cycle is missed, or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs, or if required by local regulations.

g. A complete physical examination at screening will include the assessment of all body systems, the measurement of body weight, height, blood pressure, temperature and pulse rate. Symptom directed physical examination will be performed as per routine clinical practice during the study.

h. On-study tumor assessments should be performed according to site standard-of-care imaging modality. The most recent tumor assessment available may be utilized for tumor assessment at baseline, even if conducted more than 28 days prior to Cycle 1 Day 1. Abdominal scans should include complete visualization of both kidneys. The interval for monitoring disease status and for progression of disease should not be longer than every 6 months.

i. Hematology and Chemistry: Required tests are listed in Appendix 1 of the protocol. Hematology and Chemistry is performed on Day 1 of each treatment cycle and may be additionally performed as clinically indicated. Blood chemistry and hematology does not need to be repeated if acceptable screening assessment is performed within 7 days prior to Cycle 1 Day 1. For the first 2 cycles, hematology and chemistry should be repeated on Day 8, 15, 22 (±1 day).

j. Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the patient may be done via a phone call.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Crizotinib (PF-02341066) is a selective adenosine triphosphate (ATP)-competitive small molecule oral inhibitor of the anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor (HGFR), Recepteur d'Origine Nantais (RON), and ROS1 receptor tyrosine kinases and their oncogenic variants (eg, c-Met/HGFR mutations and ALK or ROS1 fusion proteins). Consistent with this mechanism of action, crizotinib inhibited phosphorylation of c-Met/HGFR, selected ALK fusion or mutant variants and ROS1 fusion variants in tumor cells both in vitro and in vivo, and RON in vitro. Crizotinib exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion or selected mutations involving the ALK gene or ROS1 gene locus (ie, echinoderm microtubule-associated protein-like-4 [EML4]-ALK or nucleophosmin [NPM]-ALK fusion variants), exhibiting translocation of the ROS1 gene locus, or amplification of the c-Met/HGFR gene locus.

The results from single arm clinical Studies A8081001 and A8081005 supported accelerated marketing approval of crizotinib in the United States (US) in August 2011 for the treatment of patients with locally advanced or metastatic NSCLC that is ALK positive as detected by a Food and Drug Administration (FDA)-approved test. In March 2016, FDA approved crizotinib for a new indication for the treatment of patients with metastatic non-small cell lung cancer whose tumors are ROS-1 positive, which is based on Study A8081001 results in ROS1 positive patients.

1.2. Background and Rationale

Crizotinib received approval for the treatment of ALK-positive advanced NSCLC in China in January 2013 and was approved for the treatment of ROS1-positive advanced NSCLC in China in September 2017.

This protocol permits continued access to crizotinib for patients with advanced NSCLC harboring translocation or inversion event involving the ALK gene or ROS1 gene locus who had received crizotinib treatment in another Pfizer-sponsored clinical study (Studies A8081005, A8081007 and A8081014) and are still receiving crizotinib treatment at the time of enrollment into this study or currently receiving crizotinib treatment in Studies A8081029 and A8081063. In addition, patients in Studies A8081014 or A8081029 who were randomized to the chemotherapy treatment and do not cross over to receive crizotinib treatment at the time of enrollment into this study, will have the opportunity to receive crizotinib treatment in this study after investigator-assessed disease progression. This clinical trial is only open to patients in China.

Patients will follow Table 1 or Table 2, as appropriate, for the schedule of visits and data collection for safety monitoring.

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the XALKORI® LPD.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To evaluate the long-term safety of crizotinib in patients with advanced NSCLC harboring a translocation or inversion of the ALK gene or ROS1 gene locus.	• All Grade 3-5 AEs, all AEs leading to permanent treatment discontinuation, and all SAEs as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

3. STUDY DESIGN

This is a multi-center, open-label study in China only. Eligible patients include those with advanced NSCLC harboring translocation or inversion event involving the ALK gene or ROS1 gene locus, who were enrolled in Studies A8081005, A8081007, A8081014, A8081029 and A8081063 and are still receiving crizotinib treatment at the time of enrollment into this study. In addition, patients, randomized to the chemotherapy arm in Studies A8081014 and A8081029 and have not yet crossed over to receive crizotinib treatment at the time of enrollment into this study, are eligible to enroll into this study after investigator-assessed disease progression. Approximately 75 patients will be enrolled into this study. Dose reductions and re-escalations are allowed based on tolerability.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patients who were enrolled and treated in Studies A8081005, A8081007, A8081014, A8081029, or A8081063 and are still receiving crizotinib treatment at the time of enrollment into this study.

   OR

   Patients randomized to the chemotherapy arm in Studies A8081014 or A8081029 who have experienced investigator-assessed disease progression and have not yet crossed over to receive crizotinib treatment.

2. No ongoing NCI CTCAE Grade ≥3 or intolerable Grade 2 adverse events considered to be related to crizotinib treatment.

3. Eastern Cooperative Oncology Group (ECOG) performance status 0-3.

4. Adequate organ function as defined by the following criteria:

   - Hepatic function: Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN), or AST and ALT ≤5 × ULN if liver function abnormalities were due to underlying malignancy; total serum bilirubin ≤1.5 × ULN (except patients with documented Gilbert's syndrome);

   - Bone marrow function: absolute neutrophil count ≥1000/μL, platelets ≥50,000/μL; hemoglobin ≥8.0 g/dL;

   - Renal function: Serum creatinine ≤2.0 × ULN.

5. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study prior to enrollment.

7. Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Use of any anticancer drug subsequent to crizotinib prior to study entry.

2. Use of drugs or foods that are known potent Cytochrome P450 (CYP)3A4 inhibitors including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

3. Use of drugs that are known potent CYP3A4 inducers including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

4. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, associated with life-threatening arrhythmias, including but not limited to dihydroergotamine, ergotamine, and pimozide.

5. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

6. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

7. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 90 days after the last dose of investigational product.

4.3. Registration Criteria

The Sponsor must approve the enrollment of each patient. Patients will be registered into the study provided that they have satisfied all patient selection criteria and have withdrawn from their original crizotinib clinical study prior to enrollment in this study.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female patients who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 90 days after the last dose of crizotinib. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected an appropriate method of contraception for the individual patient from the permitted list of contraception methods (see below) and will confirm that the patient has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use highly effective contraception consistently and correctly and document the conversation and the patient's affirmation in the patient's chart (patients need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the patient.

All sexually active male patients must agree to prevent potential transfer of and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of crizotinib and continuing for 90 days after the last dose of investigational product.

Contraceptive checks will not be recorded on the Case Report Form (CRF), but all information will need to be available from the patient's medical record upon request by the Sponsor.

4.4.2. Sunlight Exposure

Patients treated with crizotinib should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is crizotinib.

5.1. Allocation to Treatment

Patients who were receiving crizotinib prior to enrolling into this study will continue to receive their current crizotinib dosing regimen. Patients, who were enrolled into the chemotherapy arms of Studies A8081014 or A8081029 and had not crossed over to crizotinib treatment prior to enrollment into this study will receive the standard starting dose of crizotinib (ie, 250 mg BID) orally after investigator-assessed disease progression. Available crizotinib dosing regimens are 250 mg BID, 200 mg BID, or 250 mg Once Daily (QD). Crizotinib will be supplied by the Sponsor.

Treatment will be administered orally in continuous fashion. For purposes of scheduling visits and assessments, treatment cycles are 4 weeks (28 days) in length.

5.2. Patient Compliance

Patients will be required to return all containers of study medication before dispensing crizotinib for new cycles. All drug returned will be documented on the drug accountability log. Patient compliance information will not be recorded on the CRF, but will need to be available from the patient's medical record upon request by the Sponsor.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

Crizotinib will be provided by the Sponsor as capsules 250 mg and 200 mg of oral study medication and will be packaged in High-Density Polyethylene (HDPE) bottles and labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Crizotinib will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

5.4. Administration

Patients who were receiving crizotinib prior to enrolling into this study will continue to receive their current dose of crizotinib. Patients who were enrolled into the chemotherapy arms of Studies A8081014 or A8081029 and have not started crizotinib treatment prior to enrollment into this study will receive the standard starting dose of crizotinib (ie, 250 mg BID). Patients will continue single-agent crizotinib treatment on this study until disease progression, unacceptable toxicity, consent withdrawal, or death, whichever comes first. Patients may continue crizotinib treatment as assigned beyond the time of RECIST-defined disease progression at the discretion of the investigator if the patient is still experiencing clinical benefit.

Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that crizotinib is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Crizotinib should be stored in its original container and in accordance with the drug label.

Storage conditions stated in the single reference safety document (SRSD) (ie, LPD) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of crizotinib receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until the Pfizer provides permission to use crizotinib. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take home investigational product including how to report temperature excursions.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All containers must be returned to the investigator by the patient at every visit and at the end of the trial.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Management of Selected Crizotinib-Related Adverse Events

5.7.1. Nausea and Emesis

Standard anti-emetics such as prochlorperazine or ondansetron may be used for the treatment of vomiting. Taking the medication with food may reduce nausea. Prophylactic anti-emetics may be used.

5.7.2. Diarrhea

CTCAE Grade 1: Symptomatic care such as loperamide (Imodium) or no intervention per investigator judgment.

CTCAE Grade 2: Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). No dose modification unless patient is intolerant or symptom is recurrent.

CTCAE Grade ≥3 (despite use of loperamide): Withhold treatment until recovery to Grade ≤1.

5.7.3. Bradycardia

Avoid using crizotinib in combination with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Heart rate and blood pressure should be monitored regularly. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia, crizotinib should be held and the use of concomitant medications should be re-evaluated. For management of patients who develop symptomatic bradycardia, see Table 4. The dosage of any medication known to be associated with bradycardia, eg, beta blockers, should be adjusted accordingly. It is important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.

5.7.4. Pneumonitis

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period.

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria.
- Blood culture should be performed in febrile patients.
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum).
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above).
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- A plasma sample for B-type Natriuretic peptide (BNP) to evaluate for evidence of Congestive Heart Failure (CHF).
- A blood sample for β-D-glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis jirovecii).
- If clinically appropriate, high dose corticosteroid treatment should be considered.

Should the event be fatal an autopsy is highly recommended to confirm /exclude the diagnosis.

For any case of drug-related pneumonitis discontinue crizotinib and contact the Sponsor. For appropriate dose modifications see Table 4.

5.8. Dose Modifications

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Patients will be monitored for toxicity and the dose of crizotinib may be adjusted as indicated in Table 4. Intrapatient dose reduction will be allowed depending on the type and severity of toxicity encountered as shown in Table 3. Patients requiring dosing less than 250 mg QD due to treatment-related toxicity will be discontinued from the study.

Table 3. Available Study Medication Dose Levels

Highest Dose Level	250 mg BID
-1 Dose Level	200 mg BID
-2 Dose Level	250 mg QD

Table 4. Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT or AST elevation with total bilirubin <2 × ULN (in absence of cholestasis or hemolysis).[a]	Continue at the same dose level.	Continue at the same dose level. Obtain repeat ALT or AST and total bilirubin when symptomatic or within 7 days.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment by reducing by one dose level. If Grade 3 ALT or AST elevation recurs reduce further (at most by 2 dose levels from the initial dose level). If recurrence at dose level -2, then discuss with Sponsor whether or not to discontinue permanently. If ALT or AST elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level.	See Grade 3.
ALT or AST elevation concurrent with total bilirubin elevation ≥2× ULN (in absence of cholestasis or hemolysis).[a]	Continue at the same dose level. Obtain repeat ALT or AST and total bilirubin within 48 hours, then repeat every 48-72 hours until ALT/AST Grade ≤1.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.

Table 4. Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Bradycardia (heart rate less than 60 beats per minute).	Continue at the same dose level.	Withhold until recovery to Grade ≤1 or to heart rate ≥60. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate ≥60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60.	Same as for Grade 2 bradycardia.	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg QD upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring Permanently discontinue for recurrence.
Pneumonitis (not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect).	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Left ventricular systolic dysfunction.	Continue at the same dose level.	Continue at the same dose level.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.

Table 4. Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Prolonged QTc.	Continue at the same dose level.	Continue at the same dose level Assess electrolytes and concomitant medications Correct any electrolyte or magnesium abnormalities.	Withhold until recovery to Grade ≤1, and then resume treatment by reducing the dose by one dose level.	Discontinue treatment and do not retreat.
Visual disturbance.[b]	Continue at the same dose level Repeat ophthalmologic examination.[b]	Continue at the same dose level Repeat ophthalmologic examination.[b]	Interrupt crizotinib until recovery. Repeat ophthalmologic examination.[b] Resume treatment by reducing the dose by one dose level.	Discontinue crizotinib and do not retreat. Repeat ophthalmologic examination.[b]
Non hematologic General (except those described above), eg, neuropathy, edema (including peripheral edema and localized edema), fatigue, and skin rash (including erythematous, macular, papular, and pruritic rash).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose or reduce the dose by 1 level at the discretion of the investigator.[c]	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.[c]
Hematologic (excluding lymphopenia).[d]	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 dose level after discussion with the Sponsor.[d]	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment.[d]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; v = version; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; ULN = upper limit of normal.

a. Patients entering with ALT and/or AST ≥5 × ULN (ie, Grade ≥3) due to underlying malignancy will be monitored for potential drug related increases at which point dose modifications will be discussed with the Sponsor.

b. Ophthalmologic examination includes visual acuity, fundoscopy, and slit lamp and should be performed by an ophthalmologist. Ophthalmologic examinations should be repeated during the study whenever a vision disorder AE is observed or NCI CTCAE v4.03 grade change occurs from the previous visit.

c. Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

d. Patients who develop Grade 3 or 4 lymphopenia without other dose limiting events (eg, opportunistic infection) may continue study treatment without interruption.

5.9. Concomitant Treatment(s)

Anticancer therapy with agents other than crizotinib is not allowed.

Medications intended solely for supportive care (ie, antiemetics, analgesics) are allowed. Documentation of these medications will not be collected on the CRF but will need to be available from the patients' medical record upon request by the sponsor.

The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of potent CYP3A inhibitors are not allowed in the study. Caution must be exercised in patients receiving crizotinib in combination with other CYP3A substrates, particularly those with narrow therapeutic indices. Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended. Low-dose acetaminophen (<2 g/day) is allowed.

The use of permitted concomitant medication must be in accordance with the China crizotinib LPD.

5.9.1. Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Crizotinib treatment should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after.

The effect of crizotinib in wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect). In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

6. STUDY PROCEDURES

Informed Consent: All patients being considered for this study must sign an informed consent document prior to any study-related procedures that are not considered to be standard of care and prior to receiving study drug.

Registration: The investigator will assign subject numbers sequentially to the patients as they are screened for the study. Assessments for screening and all other study time points are detailed in Table 1 and Table 2.

6.1. Screening

See Table 1 and Table 2 for Schedule of Activities.

6.2. Study Period

See Table 1 and Table 2 for Schedule of Activities.

6.2.1. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the patient may be done via a phone call.

6.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal Section) section) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

Reasons for trial treatment discontinuation may include:

- Disease progression as determined by investigator unless the patient is considered to have ongoing clinical benefit by the investigator;
- Unacceptable toxicity;
- Global deterioration of health related symptoms;
- Protocol noncompliance;
- Pregnancy;
- Withdrawal of consent;
- Patient loss to follow up;
- Death;
- Study termination by Sponsor;
- Participation in other studies involving investigational drug(s) or using any drug of cancer therapy during study participation.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessment

Safety will be assessed by physical examination (including blood pressure, temperature and pulse rate) and laboratory tests, and other procedures as necessary according to standard of care and in accordance with each site's institutional guidelines to monitor for adverse events related to the underlying disease, treatment with crizotinib, or treatment with other supportive therapies. Information generated from physical examinations will be captured in the patient's own medical record and not recorded on CRFs for this protocol. Information generated from these assessments will be used to determine if an adverse event occurred as defined in Section 8. All Grade 3-5 AEs, all AEs leading to permanent treatment discontinuation, and all SAEs will be recorded on CRFs and will be classified by type, incidence, severity (graded by the National Cancer Institute CTCAE Version 4.03), timing, seriousness, and relatedness.

7.1.1. Laboratory Safety Assessments

For a list of required hematology and blood chemistry tests, see Appendix 1.

Hematology and blood chemistry will be performed to verify patients' eligibility at Screening, on Day 1 of the first cycle, then on Day 1 of each subsequent cycle of treatment for all patients and may be additionally performed as clinically indicated. Patients who were randomized to the chemotherapy and did not cross over to receive crizotinib treatment in Studies A8081014 or A8081029 will have additional blood chemistry and hematology tests on Day 8, 15 and 22 in the first 2 cycles.

During the non-visit cycles, the investigator is responsible for ensuring that the patients have hematology and blood chemistry tests conducted and contacts the clinical site in order to provide an update of adverse events, concomitant medication, laboratory, and pregnancy tests which are conducted at an external facility or at the study site. The laboratory test parameters that need to be assessed (eg, hematology, blood chemistry) are the same as those that are assessed when a patient visits a study site for a regular visit, as in Appendix 1. A copy of laboratory test results is to be provided at the next visit to study site if laboratory tests are conducted at an external facility.

Blood chemistry and hematology do not need to be repeated if acceptable screening assessment is performed within 7 days prior to Cycle 1/Day 1.

If ALT/AST Grade ≥3 or ALT/AST Grade ≥2 and total bilirubin Grade ≥2, then liver function tests need to be repeated every 48-72 hours until ALT/AST Grade ≤1.

7.1.2. Physical Examination

A complete physical examination at screening will include the assessment of all body systems, the measurement of body weight, height, blood pressure, temperature and pulse rate. Symptom directed physical examination will be performed as per routine clinical practice during the study. Physical examinations will not be recorded on the CRF but will need to be available from the patient's medical record upon request by the Sponsor.

7.1.3. Electrocardiogram (ECG) Measurements

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Additional ECGs should be performed as clinically indicated. If the machine-read QTc is prolonged (≥500 msec), then the ECG should be read by a cardiologist and the QTc should be determined manually by a cardiologist at the site for confirmation (to look for spurious QT effect). ECG measurements will not be recorded on the CRF, but all ECG information will need to be available from the patient's medical record upon request by the Sponsor.

7.1.4. Pregnancy Test

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed at the screening. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive crizotinib. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. During the non-visit cycles, the investigator is responsible for ensuring that the patients have pregnancy test conducted and contacts the clinical site in order to provide an update of the pregnancy test which are conducted at an external facility or at the study site. A copy of pregnancy result is to be provided at the next visit to study site if the test is conducted at an external facility. In the case of a positive confirmed pregnancy, the patient will be withdrawn from the study.

Additional pregnancy tests may also be undertaken if requested by institutional review board/Ethics Committee (IRB/EC) or if required by local regulations.

Pregnancy test results will not be recorded on the CRF, but all information will need to be available from the patient's medical record upon request by the Sponsor.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by each site in accordance with instructions provided in its package insert. Patients who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

7.2. Tumor Assessments

Tumor assessments are to be performed at screening and as per routine clinical practice and according to the patient's clinical status thereafter. Tumor assessment evaluations will be conducted as per local practice at each institution. Tumor assessments will not be recorded on the CRF, but all tumor assessment information will need to be available from the patient's medical record upon request by the sponsor. The interval for monitoring disease status and for progression of disease should not be longer than 6 months.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 4 types of events: (1) SAEs; (2) non-serious Grade 3 or 4 adverse events (AEs); (3) non-serious Grade 1 or 2 AEs if leading to permanent treatment discontinuation, and (4) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event*	**Recorded on the CRF***	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious Grade 3 or 4 AE*	All	None
Non-serious Grade 1 or 2 AEs leading to permanent treatment discontinuation*	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

*For the specific details around CRF recording and safety reporting, see Section 8.1.4.1 and Section 8.1.4.2.

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product will be reported as described in the following paragraphs, however, only Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as all SAEs will be recorded on the CRF.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below), requiring immediate notification to Pfizer or its designated representative. For all Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as all SAEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that

recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious Grade 3-4 AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as all SAEs will be reported on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as all SAEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of a SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of crizotinib.

Specifically, for those patients who roll-over from the parent studies A8081029 and A8081063, the active recording/reporting periods start at the end of the active reporting period for the parent studies (ie, 28 calendar days after the last dose).

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

Specifically, for those patients who roll-over from the parent studies A8081029 and A8081063, any SAEs occurring within 28 calendar days from the last dose of Crizotinib in the parent study are still reported as an SAE in the parent study, and not in the rollover study A8081067.

After the end of the active reporting period for the parent studies A8081029 and A8081063 (ie, 28 calendar days after the last dose), safety reporting for the rollover study (A8081067) follows the standard process, as per protocol.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as SAEs are recorded on the CRF from the time the patient provides informed consent, through and including a minimum of 28 calendar days after the last administration of crizotinib.

Specifically, for those patients who roll-over from the parent studies A8081029 and A8081063:

- All SAEs that occurs within 28 calendar days from the last dose of Crizotinib in the parent study are recorded in the AE page of the CRF of the parent study and as medical history in the CRF of the rollover study A8081067.

- All Non-serious AEs that occur within 28 calendar days from the last dose of Crizotinib in the parent study are recorded in the AE page of the CRF of the parent study and are recorded as medical history in the CRF of the rollover study A8081067.

After the end of the active reporting period for the parent studies A8081029 and A8081063 (ie, 28 calendar days after the last dose), study recording in the CRF for the rollover study (A8081067) follows the standard process as per protocol.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all Grade 3-5 AEs, AEs leading to permanent treatment discontinuation, as well as all SAEs. The investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see Requirements). If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be a Grade ≥3 AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

NCI CTCAE v4.03 will be used to determine if a laboratory-associated AE will be reported. Laboratory test values will not be collected on the CRF but will need to be available from the patient's medical record upon request by the Sponsor. However, for laboratory-associated AEs, only SAEs, Grade ≥3 AEs, or AEs leading to permanent treatment discontinuation will be documented on the AE page of the CRF.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as a SAE with CTCAE Grade 5 (see section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of a SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

The investigator will use the following definitions of Severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the Section on Requirements).

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST or ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **or** ALT **or** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the Liver Function Test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for a SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study patient are to be captured on the medication error CRF, which is a specific version of the AE page. In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by Pfizer. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Due to the nature of this rollover study, the number of patients to be enrolled is not predefined. However, it is expected that approximately 75 patients will be enrolled.

9.2. Efficacy Analysis

Efficacy will not be analyzed in this study.

9.3. Analysis of Other Endpoints

No statistical methods will be employed to test a specific hypothesis in this study.

Descriptive statistics will be used to summarize safety data collected in this study as appropriate.

Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior anticancer therapy, medical history, extent of disease and ECOG performance status will be tabulated.

No inferential analyses are planned.

9.4. Safety Analysis

Safety data will be summarized for all patients receiving at least 1 dose of crizotinib.

All Grade 3-5 AEs, AEs leading to permanent treatment discontinuation and all SAEs with onset after initiation of treatment will be considered as treatment-emergent AEs. AE incidence rates will be described both with and without regard to causality. All AEs will be coded by system organ class, MedDRA preferred term, and severity grade using NCI CTCAE v4.03.

The following safety data will be summarized:

- Grade 3-5 AEs and AEs leading to permanent treatment discontinuation – number and percent of patients with all-causality and treatment-related AEs.
- SAEs – number and percent of patients with all-causality and treatment-related SAEs.
- All recorded safety data on the CRF will be listed.

9.5. Data Monitoring Committee

An External Data Monitoring Committee (E-DMC) will not be established for the study. For the purpose of this protocol, sponsor procedures for periodic safety review will be applied to review individual and summary data collected in the safety and clinical databases.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and

investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients’ personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial

End of Trial is defined as the date of the last visit of the last patient in the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of crizotinib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time period set by Pfizer]. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202570s000ltr.pdf.

Appendix 1. Laboratory Safety Assessments

Hematology Panel	Blood Chemistry Panel
Hemoglobin	AST
Absolute neutrophil count	ALT
Platelets	Total bilirubin
	Alkaline phosphatase
	Serum creatinine

Appendix 2. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ATP	Adenosine triphosphate
AST	Aspartate Aminotransferase
BAL	Bronchoalveolar Lavage
BID	Twice Daily
BNP	B-type Natriuretic peptide
CFDA	China Food and Drug Administration
CHF	Congestive Heart Failure
CK	Creatine Kinase
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAI	Dosage and administration instruction
DILI	Drug-induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy
EML	Echinoderm Microtubule Associated Protein-Like
EOT	End of Treatment
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HDPE	High-Density Polyethylene
HGFR	Hepatocyte Growth Factor Receptor
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
LFT	Liver Function Test

Abbreviation	Term
LPD	Local Product Document
N/A	Not Applicable
NCI	National Cancer Institute
NPM	Nucleophosmin
NSCLC	Non-Small Cell Lung Cancer
PCD	Primary Completion Date
PI	Principal Investigator
PT	Prothrombin Time
QD	Once Daily
QTc	QT interval corrected by heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RON	Recepteur d'Origine Nantais
US	United States
SAE	Serious Adverse Event
SRSD	Single Reference Safety Document
TBili	Total Bilirubin
SAP	Statistical Analysis Plan
ULN	Upper Limit of Normal