



CLINICAL PROTOCOL

PHASE 1B OPEN-LABEL STUDY OF THE SAFETY AND CLINICAL ACTIVITY OF CRIZOTINIB (PF-02341066) IN TUMORS WITH GENETIC EVENTS INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) GENE LOCUS

Compound: PF-02341066

Compound Name: Crizotinib

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	13 August 2015	<p>Dose modification and adverse event management guidances were revised based on updated safety information.</p> <p>Reduced Schedule of Activities was introduced for patients still ongoing after approval of Amendment 5.</p> <p>Text was added or replaced to ensure consistency with updated Pfizer global protocol template language, including contraception guidelines, pregnancy testing, and serious adverse event reporting for oncology studies after permanent discontinuation of crizotinib treatment.</p> <p>Corrections of typographical errors and other administrative inconsistencies were made throughout the protocol.</p>
Amendment 4	19 April 2013	<p>Protocol amended to reduce the required tumor imaging frequency in patients on PF-02341066 treatment for more than 10 cycles (ie, 30 weeks) as this will be consistent with the frequency of assessments used in clinical practice and reduce patient exposure to radiation. Frequency will be further reduced from Cycle 11 (assessment will be performed every 12 weeks), from Cycle 26 (assessment will be performed every 24 weeks) and from Cycle 52 (assessment will be performed every 52 weeks).</p> <p>Corrected footnotes 13 and 15 of schedule of events.</p> <p>New wording regarding Sponsor Qualified Medical Personnel (Section 4.5) added.</p> <p>Administration section text added in Section 5 regarding medication errors.</p> <p>Updated wording regarding AE reporting period section.</p> <p>Section 8 Adverse Event Reporting and Section 15 Communication of Results by Pfizer updated based on revised protocol template language.</p> <p>Replacement of the word “subject” with “patient” where needed, for internal consistency.</p>
Amendment 3	17 July 2012	<p>New safety language regarding renal cysts and number of cases of hepatotoxicity added; clarification in target patient population and testing modalities for ALK detection added; Cheson criteria (2007) added for NHL patients; frequency of clinic visits changed; new protocol template safety assessment language incorporated; washout period for prior chemotherapy modified; low-dose steroids added as needed for tumor fever; updates in toxicity assessment, management, and dose modifications made to align with other crizotinib protocols, concomitant medications section updated; efficacy analysis updated to specifically include subset analysis of ALCL patients; definition of objective response added; Appendix 4 added: NCI International Response Criteria for</p>

		Non-Hodgkin Lymphoma (2007).
Amendment 2	17 December 2010	Removal of 150 mg capsule strength; further clarification given on Dose Modifications for drug related toxicities; introduction of SAE reporting requirements for Drug Induced Liver Injury; inclusion/exclusion criteria updated.
Amendment 1	26 July 2010	Additional safety monitoring language for pneumonitis; inclusion/exclusion criteria updated.
Original protocol	25 March 2010	N/A

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

PROTOCOL SUMMARY

Background and Rationale:

ALK is a receptor tyrosine kinase first identified as part of the t(2;5) chromosomal translocation associated with most anaplastic large cell lymphoma (ALCL) and a subset of B-cell non-Hodgkin's lymphoma. *ALK* has been implicated in an increasing number of cancer settings. These include non-small cell lung cancer (NSCLC), neuroblastoma, inflammatory myofibroblastic tumour (IMT), diffuse large B cell lymphoma (DLBCL), and esophageal squamous cell carcinoma. The *ALK* genetic events include fusion/inversion, translocation, mutation, amplification, and aberrant expression.

Crizotinib (PF-02341066) is a small-molecule inhibitor of anaplastic lymphoma kinase (*ALK*) and the c-Met/HGFR receptor kinase which has shown compelling clinical activity in patients with NSCLC with *ALK* fusions events in the expanded cohort of a Phase 1 trial. In 50 evaluable patients, an objective response rate (ORR) of 64% and disease control rate (DCR) of 90% was reported by E.L. Kwak at the American Society of Hematology meeting in December of 2009.

Based on the Phase 1 study (A8081001), there is a limited patient experience with crizotinib in patients with tumors other than NSCLC with changes in the molecular genetic profile of the tumor involving the *ALK* gene locus. One patient with IMT achieved a partial response (PR) (1PR of 2 IMT patients enrolled) and one neuroblastoma patient with an *ALK* mutation achieved stable disease (SD) lasting in excess of 6 months (1 SD of 1 neuroblastoma patient enrolled). One patient with ALCL associated with *ALK* translocation has been studied to date. In addition, in an ongoing pediatric study there has been preliminary evidence of activity in a patient with IMT based on communication with the study principal investigator.

A dose of 250 mg given orally BID was found to be the recommended Phase 2 dose from the escalating part of the Phase 1 study. The most common treatment-related adverse events seen to date were nausea, vomiting, diarrhea, and visual disturbance, which were primarily Grade 1-2 in severity. Nausea and vomiting were independent of dose or duration of treatment and were managed effectively using I.V. or oral anti-emetics. Treatment-related visual disturbances were observed and occurred at doses of 200 mg BID or above. All of these visual events were Grade 1 in severity and were reversible upon discontinuation of crizotinib.

In a recent review of safety for crizotinib (PF-02341066) Pfizer has determined that there are 4 potential cases of pneumonitis which may be related to crizotinib (PF-02341066). One such case was a radiation recall pneumonitis. Based on the other 3 cases that were not linked to radiation treatment and relative to all enrolled adult patients (N=273) who have been treated with crizotinib (PF-02341066), as of July 16 2010, the current frequency of non-radiation recall pneumonitis is 1.1%. One of the 4 cases was fatal. The 3 other patients recovered from the event. One patient experienced radiation recall pneumonitis, was appropriately treated and was able to restart crizotinib (PF-02341066). The other 2 patients were permanently discontinued from crizotinib (PF-02341066). Interpretation of the 3 non-radiation recall cases was complicated by the underlying non-small cell lung cancer for

which the patients were being treated. In addition these 3 cases were complicated by the co-administration of other drugs known to potentially cause pneumonitis and/or other pulmonary complications. One of the cases was considered not related to crizotinib (PF-02341066) by the investigator. Based on this new safety information suspected cases of pneumonitis will be evaluated and patients with pre-existing interstitial fibrosis or interstitial lung disease will be excluded from the entering the study.

The crizotinib adverse drug reaction (ADR) list was updated in the crizotinib Investigator's Brochure (IB) to include the development of complex renal cysts. The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from several weeks to several months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended. Neither renal impairment nor clinically relevant proteinuria has been observed in any of the cases.

Additionally, the IB has updated the Effects on the Liver Section 7.6.4. With more than 1400 patients who have been treated with crizotinib in clinical trials, 2 new Hy's Law cases and 2 cases of fatal hepatic failure have recently (March 2012) been reported as serious adverse events related to crizotinib treatment (a fifth Hy's Law case had previously been reported in an earlier version of the IB). Of all 5 of these cases, 2 patients presented with anorexia, 2 patients presented with weakness and fatigue, and 1 patient presented with abdominal pain. Four of these 5 cases, including the 2 fatal cases, were observed within the first 2 months after the start of crizotinib treatment, while significant transaminase elevation was observed after 6 months of crizotinib treatment in the fifth case.

Based on the promising clinical activity seen in NSCLC, it is expected that crizotinib may also be active in other tumors in which growth is driven by *ALK* genetic events. Patients whose tumors are found to have a translocation, mutation, or amplification involving *ALK* will be enrolled into this study to explore the safety and potential clinical activity in diverse tumor types.

Objectives and Endpoints

Primary Objective:

- Assess the safety of oral single-agent crizotinib administered to patients with advanced *ALK*-positive anaplastic large cell lymphoma or other advanced malignancy known to have an *ALK* genetic event (other than non-small cell lung cancer [NSCLC]) and screen for efficacy in these patients.

Secondary Objectives:

- To determine pharmacokinetics (PK) in this patient population using population PK (POPPK) methods and explore correlations between concentration, response and/or safety findings.
- To correlate *ALK* genetic events (translocation, mutation/amplification) to outcome measures.

Endpoints:

Primary Endpoint:

- Type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
- Overall response rate (ORR) based on:
 - RECIST¹ version 1.1 for non-hematologic malignancies;
 - NCI International Response Criteria for Non-Hodgkin's Lymphoma for ALCL or other non-Hodgkin's lymphomas.²

Secondary Endpoints:

- PFS, overall survival (OS) at 6 months and 1 year, OS and duration of response (DR);
- Plasma concentrations of crizotinib;
- Proportion of patients with each of the *ALK* genetic events (translocation, mutation, amplification);
- Phosphorylation status of *ALK* in the tumor samples from surgery or biopsy pre and post treatment when available.

Study Design:

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

At least 40 patients are expected to be enrolled into this trial. The sample size may be adjusted based on the number of patients identified and safety or evidence of antitumor activity within patient groups.

Only *ALK* genetic event positive patients as determined by the investigative site may enter the study. *ALK* translocation/fusion, amplification, mutation and overexpression may be assessed by using any of the available technologies including fluorescence in-situ hybridization (FISH), immunohistochemistry (IHC), quantitative Polymerase Chain Reaction (qPCR), quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR), array Comparative Genomic Hybridization (aCGH) or direct sequencing. The methodology of *ALK* testing required will depend entirely on the malignancy in question and the existence of published data supporting a given methodology of *ALK* testing. For example, ALCL is the only disease for which IHC alone is acceptable to document *ALK* positivity, as IHC has been shown to correlate with *ALK* fusion events in ALCL and is widely accepted as a means of documenting *ALK* positivity in ALCL. For diffuse large B-cell lymphoma, IHC alone is not sufficient for enrollment, as an *ALK* gene fusion event must be documented by FISH or PCR. For neuroblastoma, *ALK* gene amplification must be documented by either FISH or aCGH, or a known *ALK* activating point mutation must be documented by PCR or direct sequencing (IHC alone is not acceptable). For inflammatory myofibroblastic tumor (IMT), IHC alone is not sufficient, unless the intercalated antibody-enhanced polymer (iAEP) method is used.¹² FISH or PCR demonstrating an *ALK* fusion event is acceptable for IMT. Other diseases will be considered for enrollment if publications exist supporting *ALK* mutation/fusion/amplification as an oncogenic driver for the disease in question.

Patients may continue treatment with crizotinib on this trial as long as there is evidence of clinical benefit in the judgment of the investigator.

Study Treatments:

Crizotinib, 250 mg BID, will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing. Crizotinib may be taken without regard to meals.

Cycles are defined in 21-day periods to facilitate scheduling of visits and assessments.

Table 1 provides the required Schedule of Activities. A reduced schedule of activities will be followed for all ongoing patients after IRB/EC approval of Amendment 5 (see Table 6, Appendix 5).

Data Analysis/Statistical Methods:

Sample Size Determination

The primary objective of this study is to assess the safety of oral, single agent crizotinib administered to patients with advanced ALCL or other advanced malignancies (other than NSCLC) known to have an *ALK* genetic event and to screen for efficacy in these patients. Estimation will be emphasized for the study endpoints.

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

Data Analysis

The study population for all analyses will include patients enrolled in the study who receive at least one dose of crizotinib. Data summaries/listings will be presented overall as well as separately for ALCL patients and patients with other malignancies (by tumor type, as applicable).

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration, efficacy, safety, biomarkers and pharmacokinetic parameters.

Table 1. Schedule of Activities

The Schedule of Activities 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.

Note: Refer to Table 6 ([Appendix 5](#)) for reduced schedule of protocol activities after IRB/EC approval of Amendment 5.

Protocol Activities	Screening	Study Treatment ^[1]			End of Treatment	
		Cycle 1		Cycles ≥2		
	≤28 Days Prior to Dosing	Day 1 (±2) ^[2]	Day 15 (±2)	Day 1 (±2; ±7 for imaging)	End of Txt/Withdrawal ^[3]	Post Txt Follow-up
Baseline Documentation						
Informed Consent ^[4]	X					
Medical/Oncology History ^[5]	X					
Baseline Signs/Symptoms		X				
Mandatory Tumor Tissue for Molecular Profiling ^[6]	X					
Physical Examination ^[7]	X	(X)		X	X	
ECOG Performance Status	X	X		X	X	
Ophthalmologic Examination ^[8]	X	See footnote 8 for details.				
Laboratory Studies						
Dipstick Urinalysis and Reflex Microscopy ^[18]	X (Korea only)	X (Korea only; for other countries, see footnote 18)				X (Korea only)
Hematology ^[9]	X	(X)	X	X	X	
Blood Chemistry ^[9]	X	(X)	X	X	X	
Coagulation ^[9]	X	(X)	X			
12-lead electrocardiogram ECG ^[10]	X	X		Cycle 2		
Female patients: Pregnancy Test (as appropriate) ^[11]	X				X	

Protocol Activities	Screening	Study Treatment ^[1]			End of Treatment	
		Cycle 1		Cycles ≥2		
		≤28 Days Prior to Dosing	Day 1 (±2) ^[2]	Day 15 (±2)	Day 1 (±2; ±7 for imaging)	End of Txt/Withdrawal ^[3]
Disease Assessments						
Radiographic studies for tumor assessment ^[12]	X			Beginning Cycle 3 then every other cycle through Cycle 10, from Cycles ≥11 every 12 weeks, from Cycle ≥26 every 24 weeks and from Cycle ≥52 every 52 weeks	X	
Bone marrow biopsy and/or aspirate (for patients with NHL only) ^[19]	X					X
Other Clinical Assessments						
Adverse Events ^[13]	X	X	X	X	X	X
Concomitant Medications/Treatments ^[14]	X	X	X	X	X	X
Survival Follow-up ^[15]						X
Study Treatment						
Crizotinib			Twice or Once Daily			
Special Laboratory Studies						
Optional Tumor Tissue for Molecular Profiling ^[16]					X	
Pharmacokinetics ^[17]		X		Cycles 2, 3, 5		

() – see footnote #2

Footnotes for Schedule of Activities

1. **Study Treatment:** All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. All cycles are 21 days in duration. After completion of 7 cycles, ongoing patients will only need to visit the clinic every other cycle for study assessments instead of every cycle. Enough study medication for two cycles of treatment will be dispensed at each clinic visit. During the non-visit cycle, patients must telephone the clinical site to provide an update of adverse events and concomitant medications and must still have required laboratory assessments performed.

Footnotes for Schedule of Activities	
2.	Cycle 1/Day 1: Blood chemistry, hematology, coagulation, and physical examination not required if acceptable screening assessment is performed within 7 days prior to the start of study treatment.
3.	End of Treatment/Withdrawal: Obtain these assessments if not completed during the previous 4 weeks on study (during the last 6 weeks for disease assessments).
4.	Informed Consent: Must be obtained prior to undergoing any trial specific procedure.
5.	Medical/Oncological history: To include information on prior regimens, surgery, and radiation.
6.	Mandatory Tumor Tissue for Molecular Profiling: These samples will be initially analyzed at the investigational site for the assessment by one of the following 1) <i>ALK</i> gene fusion by FISH, IHC and/or RT-PCR and sequencing, 2) <i>ALK</i> amplification events by FISH, qPCR, or aCGH, or 3) <i>ALK</i> activating point mutations determined by direct sequencing. The genotyping test employed for a selected sample will depend on the tumor type and expected <i>ALK</i> genetic event. Subsequently the tumor samples must be sent to the Pfizer designated central laboratory for confirmation, though this is not required for eligibility. Paraffin block(s) of adequate size to allow if possible for at least 10 slides with cuts that are 5-microns thick. If no block is available, then the sites should try to obtain, if possible, at least 10 slides with cuts that are 5-microns are acceptable. Archived or fresh tumor samples are acceptable. The mandatory tumor tissue may be obtained and analyzed outside of the 28 day screening window.
7.	Physical Examination: includes an examination of major body systems, height (at screening only); weight, blood pressure and pulse rate
8.	Ophthalmologic Examination: includes visual acuity and slit lamp and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when clinically indicated, when visual disturbances have been observed or when there has been a reported change in CTCAE grade.
9.	Hematology, Blood Chemistry and Coagulation: Required tests are listed in Appendix 1 of protocol. For patients on crizotinib therapy: If ALT Grade ≥ 3 or ALT Grade ≥ 2 and total bilirubin Grade ≥ 2 , then liver function tests need to be repeated every 48-72 hours until ALT Grade ≤ 2 . Crizotinib therapy should be withheld; see Table 3 . A 4 ml serum sample obtained just prior to the first dose of study medication will be stored frozen on-site through completion of the study for possible use as a baseline reference should additional laboratory tests be indicated, for example additional liver function testing to exclude drug induced liver injury (see Section 8 AE reporting).
10.	12-lead ECG: See Section 7.2.6 for collection details.
11.	Pregnancy Test: All female patients of child-bearing potential are required to have a negative pregnancy test at screening. The test should be repeated whenever one menstrual cycle is missed during the active treatment period or a potential pregnancy is otherwise suspected. The test should also be repeated at the end of the study to confirm the patient has not become pregnant during the study. Pregnancy tests may also be repeated as per the request of IRB/IECs or if required by local regulations.
12.	Tumor Assessments: RECIST 1.1 will be used to determine the solid tumor response, and the NCI International Response Criteria for Non-Hodgkin's Lymphoma (Cheson criteria, 2007) will be used for NHL. For patients with non-hematologic malignancies, CT or MRI scans will include chest, brain, abdomen and pelvis at screening but subsequently may include just involved sites of disease. For patients with NHL, PET and CT or MRI or PET/CT may be used for NHL at baseline and for restaging. Scans must include chest, abdomen, pelvis and neck for NHL patients at baseline, but subsequently may include only known and suspected sites of disease. Baseline PET scanning is required for all NHL patients. For all tumor types, brain must be included in subsequent tumor assessments if a patient has brain metastases, otherwise brain will only be evaluated when clinically indicated. Scans will be collected for a potential independent radiology review. CT or MRI scan should also be performed whenever disease progression is suspected (eg, symptomatic deterioration). Bone scans are required if bone metastases are suspected. A bone scan is also required at the time of confirmation of response for patients who have bone metastases.
13.	Adverse Events: Patients must be followed for adverse events from the time they signed the informed consent until at least 28 days after the last dose of study treatment. 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. Serious adverse events should be monitored and reported from the time that the patient provides informed consent as described in the protocol.
14.	Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.

Footnotes for Schedule of Activities

15. **Survival Follow-Up:** After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until the last patient experiences progressive disease on the study. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.
16. **Tumor Tissue for Molecular Profiling:** Sample will be sent to central laboratory ([Section 7.5](#)). An optional fresh tumor sample will be collected at the end of treatment if a patient discontinues due to disease progression.
17. **Pharmacokinetics:** See [Section 7.3.2](#) for collection details.
18. **Dipstick Urinalysis and Reflex Microscopy:** In Korea, repeat exams should be completed at Day 1 of every cycle and at the end of treatment; all other countries should perform as clinically indicated (for example, upon diagnosis of renal cysts). Reflex Microscopy required if urine dipstick is positive for blood or protein. See [Section 5.6.5](#) for further details.
19. **Bone Marrow Aspirate and/or Biopsy:** optional before study start and can be performed as clinically indicated during the study. Required at end-of-treatment visit (ie, within 6 to 9 weeks after the last dose of investigational product, and must be ≥ 4 weeks from the last response assessment) for patients who otherwise meet the criteria for a CR unless the patient had an adequate bone marrow biopsy which was negative for lymphoma and performed within 28 days before first dose of investigational product or unless the patient had previously undergone a bone marrow procedure confirming the CR.

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1. INTRODUCTION

1.1. Indication

Crizotinib is indicated for the treatment of tumors with translocation, mutation, or amplification of the anaplastic lymphoma kinase (*ALK*) gene locus.

1.2. Background and Rationale

1.2.1. Role of *ALK* in Cancer

ALK is a receptor tyrosine kinase first identified as part of the t(2;5) chromosomal translocation associated with the majority of anaplastic large cell lymphoma (ALCL) and a subset of B-cell non-Hodgkin's lymphoma. *ALK* has been implicated in an increasing number of cancer settings as shown in the Table 2 however the relevance to clinical cancer treatment is still unknown.

Table 2. Malignancies with Events Involving the *ALK* Gene Locus

Setting	<i>ALK</i> Genetic change	Frequency %
Anaplastic Large Cell lymphoma (ALCL)	<i>ALK</i> translocation/fusion, NPM, TFG, TPM3-, TPM4- <i>ALK</i>	60-80 ³
Inflammatory myofibroblastic tumor (IMT)	<i>ALK</i> translocation/fusion, TPM3, TPM4, CARS, CLTC- <i>ALK</i>	56 ⁴
Neuroblastoma	Amplification of <i>ALK</i> locus Activating point mutations such as (germ line: G1128A, R1192P, R1275Q) (somatic: D1091N, M1166R, I1171N, F1174I, F1174L, F1245C, F1245V, I1250T)	20 ⁵
Breast Cancer	<i>ALK</i> translocation/fusion	2.4 ⁶
Colon Cancer	<i>ALK</i> translocation/fusion	2.4 ⁶
Esophageal squamous cancer	TPM4- <i>ALK</i>	Not reported
Diffuse large B cell lymphoma (DLBCL)	CLTC- <i>ALK</i> , NPM- <i>ALK</i>	Not reported
Other solid tumors: glioblastoma, melanoma, rhabdomyosarcoma	Wild type <i>ALK</i> overexpression	Not reported

There is evolving information about the role of *ALK* genetic events in a number of childhood and adult tumors. Mutations in *ALK* have been detected in a large number of neuroblastoma cell lines including both germline and somatic mutations.^{5, 7} *ALK* is detectable and is a positive prognostic factor in the setting of ALCL which is a T-cell disease and is most common with peak incidences in young adults (15-19 years of age) and children (5-14 years of age).⁵⁻¹¹ In a series of 38 patients with *ALK*-positive DLBCL, the patients identified had primarily B-cell disease and were adults with aggressive disease unlikely to respond to current standards of care.⁸ IMT is a rare tumor of mesenchymal origin which is only minimally responsive to conventional chemotherapy and radiation. It is associated with various *ALK* translocations with immunohistochemical reactivity for *ALK* restricted to the cytoplasm in 56% of cases.⁴ *ALK* expression is of uncertain pathogenic significance in several additional cancers and may represent physiologic expression rather than a seminal

pathogenic event.⁹ There is very limited clinical data using an *ALK* inhibitor in these settings.

1.2.2. Crizotinib (PF-02341066) Non-Clinical Data

Crizotinib is a competitive small-molecule inhibitor of the *ALK* and c-Met/HGFR receptor tyrosine kinase. The rationale for use of this mechanism to treat cancer is supported by an emerging paradigm in oncology that robust clinical efficacy can be obtained with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification. Recent examples include imatinib mesylate in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations, erlotinib in non-small cell lung cancer with mutant EGFR, trastuzumab in breast cancers with amplified HER-2/neu, and sunitinib targeting the VHL-dependent VEGF pathway in renal cell carcinoma. Crizotinib demonstrated activity against NPM-*ALK*, an oncogenic fusion protein variant of the *ALK*, which results from a chromosomal translocation which is implicated in the pathogenesis of human anaplastic large cell lymphoma.¹⁰ Consistent with its predicted mechanism of action, crizotinib inhibited target-dependent tumor cell proliferation or invasion, induced tumor cell apoptosis, and inhibited angiogenesis in nonclinical tumor models including neuroblastoma. Oral administration of crizotinib also demonstrated efficacy, including marked cytoreductive antitumor activity, in several tumor models that expressed activated c-Met/HGFR or NPM-*ALK*. The collective rationale for investigation of crizotinib in clinical studies is built on genetic alteration of its molecular targets, its predicted ability to target multiple processes that are common to cancer progression, and non-clinical efficacy data.

1.2.3. Crizotinib Clinical Data

An ongoing Phase 1 trial (A8081001) evaluating crizotinib as an oral single agent is being conducted to investigate safety, pharmacokinetics and pharmacodynamics in patients with advanced cancer (excluding leukemias). This trial includes a dose escalation component followed by a dose expansion component in a selected cohort of molecularly-defined patients referred to as the enriched population. During the dose escalation phase, crizotinib was administered under fasting conditions QD or BID on a continuous schedule. The objectives of the dose escalation component of the trial were to establish the maximum tolerated dose (MTD), dose limiting toxicities (DLTs), and PK of crizotinib in patients with advanced cancer. Enrollment for the dose escalation part of the trial is complete and 37 patients have been dosed. Three DLTs were observed including Grade 3 ALT increase in 1 patient at 200 mg QD and Grade 3 fatigue in 2 patients at 300 mg BID. The MTD was determined to be 250 mg BID administered in a continuous daily dosing regimen. The most common treatment-related adverse events seen to date were nausea, vomiting, diarrhea, and visual disturbance, which were primarily Grade 1-2 in severity. Nausea and vomiting were independent of dose or duration of treatment and were managed effectively using I.V. or oral anti-emetics. Treatment-related visual disturbances which consisted mainly of seeing shadows or streaks during changes in light were observed and occurred at doses of 200 mg BID or above. All of these visual events were Grade 1 in severity. In some patients, these events resolved with continued treatment but are reversible upon discontinuation of crizotinib.

In a recent review of safety for crizotinib (PF-02341066) Pfizer has determined that there are 4 potential cases of pneumonitis which may be related to crizotinib (PF-02341066). One such case was a radiation recall pneumonitis. Based on the other 3 cases that were not linked to radiation treatment and relative to all enrolled adult patients (N=273) who have been treated with crizotinib (PF-02341066), as of July 16 2010, the current frequency of non-radiation recall pneumonitis is 1.1%. One of the 4 cases was fatal. The 3 other patients recovered from the event. One patient experienced radiation recall pneumonitis, was appropriately treated and was able to restart crizotinib (PF-02341066). The other 2 patients were permanently discontinued from crizotinib (PF-02341066). Interpretation of the 3 non-radiation recall cases was complicated by the underlying non-small cell lung cancer for which the patients were being treated. In addition these 3 cases were complicated by the co-administration of other drugs known to potentially cause pneumonitis and/or other pulmonary complications. One of the cases was considered not related to crizotinib (PF-02341066) by the investigator. Based on this new safety information suspected cases of pneumonitis will be evaluated and patients with pre-existing interstitial fibrosis or interstitial lung disease will be excluded from the entering the study

The crizotinib adverse drug reaction (ADR) list was updated in the crizotinib Investigator's Brochure (IB) to include the development of complex renal cysts. The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from several weeks to several months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended. Neither renal impairment nor clinically relevant proteinuria has been observed in any of the cases.

Additionally, the IB has updated the Effects on the Liver Section 7.6.4. With more than 1400 patients who have been treated with crizotinib in clinical trials, 2 new Hy's Law cases and 2 cases of fatal hepatic failure have recently (March 2012) been reported as serious adverse events related to crizotinib treatment (a fifth Hy's Law case had previously been reported in an earlier version of the IB). Of all 5 of these cases, 2 patients presented with anorexia, 2 patients presented with weakness and fatigue, and 1 patient presented with abdominal pain. Four of these 5 cases, including the 2 fatal cases, were observed within the first 2 months after the start of crizotinib treatment, while significant transaminase elevation was observed after 6 months of crizotinib treatment in the fifth case. PK data are available for the first 80 patients enrolled in the ongoing Phase 1 trial. After oral administration of crizotinib single doses in the fasted state, peak plasma concentrations were reached at about 4 hours and followed by a multi-exponential decline with an average terminal half-life of 43 to 51 hours across doses. Following multiple oral dosing for 15 days or longer, crizotinib AUC_{tau} increased with median accumulation ratios ranging 1.7-3.4 after QD dosing and 4.0-5.9 after BID dosing, respectively. The repeated administration at 250 mg BID for 15 days or longer produced a median trough plasma concentration of 256 ng/mL (53 nM, free drug), exceeding the target efficacious levels (C_{eff}) predicted for inhibition of cMet and *ALK* based on preclinical mouse tumor models. Non-linearity of pharmacokinetics was observed

at 50 and 100 mg QD doses as the AUC_{tau} and C_{max} increased more than proportionally with the dose. However, patients receiving doses ranging from 100 mg QD to 300 mg BID generally demonstrated linear pharmacokinetics, as evidenced by proportional increases in mean AUC_{tau} and C_{max} after single or multiple doses.

Crizotinib showed time-dependent inhibition of CYP3A isozymes in human liver microsomes with a k_{inact} of 0.11 min^{-1} and K_i of $3.0 \text{ }\mu\text{M}$. In order to assess the effect of crizotinib on CYP3A activity in the GI tract and the liver, the PK of midazolam (a CYP3A substrate probe) following a single oral 2 mg dose was evaluated before (Day -7) and after (Cycle 2 Day 1) repeated administration of crizotinib at 250 mg BID in 13 patients. A 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Results from a pilot food effect study suggested that co-administration with a standard high-fat meal did not change the geometric mean of AUC_{24} and C_{max} of crizotinib following single 250-mg crizotinib doses in cancer patients.

Crizotinib (PF-02341066) has shown compelling clinical activity in patients with NSCLC with EML4-ALK fusions events enrolled in the expanded cohort of a Phase 1 trial. In 50 evaluable patients, an ORR of 64% and clinical benefit rate (CBR) of 90% was reported by E.L. Kwak at the American Society of Hematology meeting in December of 2009. To date, based on the Phase 1 study (A8081001), there is a limited patient experience in patients with tumors other than NSCLC with changes in their molecular genetic profile involving the *ALK* gene locus. One patient with IMT achieved a PR which has been ongoing for 1.5 years (1PR of 2 IMT patients enrolled) and one patient with adult neuroblastoma harboring an *ALK* mutation achieved stable disease (SD) lasting in excess of 6 months (1 SD of 1 neuroblastoma patient enrolled). One patient with ALCL associated with *ALK* translocation has been studied to date but failed to achieve a clinical response. In addition, in an ongoing pediatric study there has been preliminary evidence of activity in a patient with IMT based on communication with the study principal investigator. Complete information on crizotinib (PF-02341066) may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective:

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

Secondary Objectives:

- To determine PK in this patient population using population PK (POPPK) methods and explore correlations between PK, response and/or safety findings.
- To correlate *ALK* genetic events to outcome measures.

2.2. Endpoints

Primary Endpoint:

- Type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
- ORR based on RECIST version 1.1¹ for solid tumors and the NCI International Response Criteria for Non-Hodgkin Lymphoma for patients with ALCL or other NHL (2007)²

Secondary Endpoints:

- PFS, OS at 6 months and 1 year, OS and DR.
- Plasma concentrations of crizotinib.
- Proportion of patients with each of the *ALK* genetic events (translocation, mutation, amplification).
- Phosphorylation status of *ALK* in the tumor samples from surgery or biopsy pre and post treatment when available.

3. STUDY DESIGN

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

At least 40 patients are expected to be enrolled into this trial. The sample size may be adjusted based on the number of patients identified and safety or evidence of antitumor efficacy within patient groups. In addition, the eligibility criteria may be modified to exclude patients based on the lack of efficacy demonstrated in specific patient groups.

Only *ALK* genetic event positive patients, as determined by the investigative site, may enter the study. *ALK* translocation/fusion, amplification, mutation and overexpression can be assessed by using any of the available technologies including fluorescence in-situ hybridization (FISH), Immunohistochemistry (IHC), quantitative Polymerase Chain Reaction (qPCR), quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR), array Comparative Genomic Hybridization (aCGH) or direct sequencing. The methodology of *ALK* testing required will depend entirely on the malignancy in question and the existence of

published data supporting a given methodology of ALK testing. For example, ALCL is the only disease for which IHC alone is acceptable to document ALK positivity, as IHC has been shown to correlate with ALK-fusion events in ALCL and is widely accepted as a means of documenting ALK positivity in ALCL. For diffuse large B-cell lymphoma, IHC alone is not sufficient for enrollment; an ALK gene fusion event must be documented by FISH or PCR. For neuroblastoma, ALK gene amplification must be documented by either FISH or aCGH, or a known ALK activating point mutation must be documented by PCR or direct sequencing; IHC alone is not acceptable. For inflammatory myofibroblastic tumor (IMT), IHC alone is not sufficient, unless the intercalated antibody-enhanced polymer (iAEP) method is used.¹² FISH or PCR demonstrating a fusion event is acceptable for IMT. Other diseases will be considered for enrollment if publications exist supporting ALK mutation/fusion/amplification as an oncogenic driver for the disease in question.

Patients may continue treatment with crizotinib on this trial as long as there is evidence of clinical benefit in the judgment of the investigator.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Histologically or cytologically proven diagnosis of ALCL or other advanced malignancy other than NSCLC for whom no standard therapy is available
2. Positive for
 - a. Translocation or inversion event involving the *ALK* gene locus (eg, NPM-*ALK* fusion) as determined by immunohistochemistry (IHC) or any other suitable molecular tools such as FISH or RT-PCR or sequencing. Cases of *ALK* positive anaplastic large cell lymphoma must be positive for *ALK* expression by IHC.

OR

- b. *ALK* amplification events defined as *ALK*/CEP2 ratio of ≥ 5 in $\geq 15\%$ of evaluated cells by FISH or as greater than 7 copies by qPCR or aCGH.

OR

- c. *ALK* activating point mutations determined by direct sequencing of the *ALK* gene locus including but not limited to G1128A, R1192P, R1275Q, D1091N, M1166R, I1171N, F1174I, F1174L, F1245C, F1245V, I1250T.*ALK*.
- 3. Patients with brain metastases are eligible if neurologically stable for at least 2 weeks, and have no ongoing requirement for corticosteroids, for example, dexamethasone and are not taking any medications contraindicated in Exclusion Criteria #[12-14](#).
- 4. Any major surgery must have been completed at least 4 weeks prior to study entry. Any prior chemotherapy, including corticosteroids intended to treat lymphoma, must have been completed at least 2 weeks prior to the study entry. However, low-dose, low-potency steroids (ie, up to 100 mg hydrocortisone per day) may be used for the treatment of tumor fever in patients with lymphoma up to 48 hrs prior to the first dose of crizotinib. Any prior radiation performed with curative (ie, not only palliative) intent or minor surgeries/procedures must have been completed at least 2 weeks prior to the initiation of study medication. Palliative radiation (≤ 10 fractions) must have been completed 48 hrs prior to crizotinib therapy commencing. Any acute toxicity must have been recovered to Grade ≤ 1 (except alopecia).
- 5. Solid tumors must be measurable per RECIST version 1.1, and lymphomas must be measurable per NCI International Response Criteria for Non-Hodgkin's Lymphoma (see [Appendix 3](#) and [Appendix 4](#)).
- 6. Female or male, 15 years of age or older. Admission of minors to the study will be as appropriate according to institutional approvals. For patients enrolled in Japan: consent from a legally acceptable representative is required for all patients who are under 20 years old.
- 7. ECOG performance status 0-3.
- 8. Adequate organ function as defined by the following criteria:
 - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN), or AST/ALT $\leq 5 \times$ ULN if the enzyme elevation is considered to be due to a cancer-related cause such as liver metastases
 - Patients with an ALT $> 5 \times$ ULN considered to be due to a cancer-related cause such as liver metastases, may enroll after discussion with the sponsor.
 - Total serum bilirubin $\leq 1.5 \times$ ULN.
 - Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$ ($\geq 750/\mu\text{L}$ for hematologic malignancies).
 - Platelets $\geq 30,000/\mu\text{L}$.
 - Hemoglobin $\geq 8.0 \text{ g/dL}$ ($\geq 7.0 \text{ g/dL}$ for hematologic malignancies).

- Serum creatinine $\leq 2.0 \times$ ULN.
- 9. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.
- 10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
- 11. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the trial:

1. Mutations or amplification involving the *c-Met* gene but not the *ALK* gene locus.
2. Current treatment on another therapeutic clinical trial.
3. Prior therapy specifically directed against *ALK*, including prior treatment with crizotinib.
4. Prior allogeneic bone marrow transplant.
5. Clinically apparent or known carcinomatous meningitis, or leptomeningeal disease unless neurologically stable for at least 2 weeks and under treatment.
6. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
7. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, or cerebrovascular accident including transient ischemic attack.
8. Ongoing uncontrolled congestive heart failure.
9. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥ 2 , uncontrolled atrial fibrillation of any grade, or machine-read ECG with QTc interval > 470 msec.
10. History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.
11. Pregnancy or breastfeeding.

12. Use of drugs or foods that are known potent CYP3A4 inhibitors within 7 days prior to the first dose of crizotinib, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% of ketoconazole cream, may be allowed.
13. Concurrent use of drugs that are known potent CYP3A4 inducers within 12 days prior to the first dose of crizotinib, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort
14. Use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market).
15. Prior malignancy (other than current malignancy): patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or in situ cervical cancer, or prostate cancer) within the last 3 years.
16. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions, or end-stage renal disease on hemodialysis or laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for study entry.
17. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.

4.3. Randomization Criteria

This is an open-label single-arm study. Randomization is not applicable.

4.4. Life Style Guidelines

4.4.1. Contraception

In this study, patients of childbearing potential will receive crizotinib, which has been associated with teratogenic risk. After IRB/EC approval of Amendment #5, all male patients who are able to father children and female patients who are of childbearing potential must agree to use 2 methods of highly effective contraception throughout the study and continued for at least 90 days after the last dose.

The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient from the list of permitted list of contraception methods (see below), and will confirm the patient has been instructed in their consistent and correct use. After IRB/EC approval of Amendment #5, patients need to affirm that they meet at least two of the selected methods of contraception.

The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities ([Table 1](#)) and document such conversation in the patient's chart.

In addition, the investigator or his/her 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 patient's 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:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the patient 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 spermicide (ie, foam, gel, film, cream, 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 post vasectomy 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).
6. Female partner who meets the criteria for non-childbearing potential, as described below.

Female patients of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

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

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose.

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.

4.4.3. Alcohol Consumption

Patients should be advised to avoid alcohol consumption while receiving crizotinib.

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 Investigational Site Folder.

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 compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

All patients will receive crizotinib.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Crizotinib (PF-02341066) will be provided as capsules containing 200 mg or 250 mg of study medication and will be packaged in HDPE bottles.

5.2.2. Preparation and Dispensing

The study medication should be dispensed at each visit according to the schedule of treatment administration (Section 5.2.3). Dispensing will be done by a qualified staff member in bottles provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.2.3. Administration

Crizotinib (PF-2341066), 250 mg BID, will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing. Crizotinib may be taken without regard to meals. Cycles are defined in 21-day periods to facilitate scheduling of visits and assessments.

Patients will swallow the study medication whole and will not manipulate or chew the medication prior to swallowing. Patients should be instructed that if they vomit anytime after taking a dose, then they must not “make it up” with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed.

5.2.4. Compliance

Patients receiving crizotinib will be required to return all bottles of study medication at the beginning of each cycle or every other cycle if beyond Cycle 7. The number of capsules remaining will be documented and recorded.

5.3. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product 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, IB), will be superseded by storage conditions stated in the labeling.

Returned medication for crizotinib should be stored separately from medication that needs to be dispensed. Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

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

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions.

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

5.4. Drug Accountability

The Investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. All containers must be returned to the Investigator by the patient.

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 study 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.

To ensure adequate records, crizotinib will be accounted for in the case report form (CRF) and drug accountability inventory forms as instructed by the sponsor. Unless otherwise authorized, at the end of the clinical trial, all crizotinib supplies unallocated or unused by the patients must be returned to the sponsor or its designee.

5.5. Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify their investigators at the first occurrence of any adverse event.

Dose modifications may occur in 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as indicated in [Table 3](#). Dosing interruption and/or intrapatient dose reduction by 1 and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered (Dose Level -1 is 200 mg BID; Dose Level -2 is 250 mg QD). Management of patients requiring more than 2 dose reductions due to treatment-related toxicity should be discussed with the Sponsor.

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.

5.6. Management of Selected Crizotinib-Related Adverse Events

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.

5.6.1. Nausea and Vomiting

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.

5.6.2. Diarrhea

CTCAE Grade 1: Symptomatic care such as loperamide (Imodium) or no intervention at 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 Grades 3-4 (despite use of loperamide): Withhold treatment until recovery to Grade ≤ 1 .

5.6.3. Bradycardia

For a heart rate <40 beats per minute, evaluate the patient fully including an assessment of concomitant medications. Adjust the dosage of any medication known to be associated with bradycardia (eg, beta-blockers). If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold crizotinib dosing until recovery to Grade ≤ 1 . Patient may continue treatment only with the agreement of both the sponsor and investigator. After IRB/EC approval of Amendment 5, concurrent use of crizotinib with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible due to the increased risk of symptomatic bradycardia. Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see [Table 3](#).

5.6.4. 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 confirm or exclude the diagnosis of pneumonitis during this period in the absence of tumor progression in the lungs, other pulmonary disease, infection, or radiation effects:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacterial pathogens;
- Blood culture should be performed in febrile patients. Consider appropriate serologies (mycoplasma, legionella, CMV, other viruses, etc.)
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology).
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture, microbiology, and cytology.
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- A plasma sample for BNP (B-type Natriuretic Peptide) to evaluate for evidence of CHF.
- For Asian patients, a blood sample for β -D-glucan to evaluate for the presence of protozoal pneumonia (eg, *Pneumocystis jirovecii*).

If clinically appropriate, high-dose corticosteroid treatment should be initiated.

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 (see [Table 3](#)).

5.6.5. Renal Cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

- Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be performed at the time of the renal cysts

diagnosis and as scheduled per protocol. After approval of Amendment 5, investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

- In addition, multitest dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and Day 1 of each cycle thereafter; in Korea, dipstick urinalysis should be performed in all patients at screening and on Day 1 of each cycle thereafter and at end of treatment.
- Urine reflex microscopy is required whenever urine dipstick is positive for blood or protein.

Table 3. Crizotinib Dose Modifications for Treatment-Related Toxicity (CTCAE v4.0)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT or AST elevation with total bilirubin <2 X ULN (in absence of cholestasis and hemolysis)	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.	See footnote for possible patient entry criteria [§] 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 Grade 3 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 bilirubin elevation ≥2X ULN (in absence of cholestasis or hemolysis)	Continue at the same dose level. Obtain repeat ALT or AST and total bilirubin within 48 hrs, then repeat every 48-72 hours until ALT/AST is Grade <1	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
Pneumonitis (not attributable to disease progression in the lung, infection, other pulmonary disease, 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

Table 3. Crizotinib Dose Modifications for Treatment-Related Toxicity (CTCAE v4.0)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Bradycardia (heart rate less than 60 beats per minute)	Continue at the same dose level.	<p>Withhold until recovery to Grade ≤ 1 or to heart rate ≥ 60</p> <p>Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications</p> <p>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</p> <p>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</p>	Same as for Grade 2 bradycardia	<p>Permanently discontinue if no contributing concomitant medication is identified</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate ≥ 60, with frequent monitoring.</p> <p>Permanently discontinue for recurrence</p>
Prolonged QTc	Continue at the same dose level	<p>Continue at the same dose level. Assess electrolytes and concomitant medications</p> <p>Correct any electrolyte or magnesium abnormalities</p>	<p>Withhold until recovery to Grade ≤ 1, then resume at 200 mg twice daily.</p> <p>In case of recurrence, withhold until recovery to Grade ≤ 1, then resume at 250 mg once daily.</p> <p>Permanently discontinue in case of further Grade ≥ 3 recurrence.</p>	Discontinue treatment and do not retreat

Table 3. Crizotinib Dose Modifications for Treatment-Related Toxicity (CTCAE v4.0)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Visual disturbance‡	Continue at the same dose level Repeat ophthalmologic examination‡	Continue at the same dose level Repeat ophthalmologic examination‡	Interrupt crizotinib until recovery. Repeat ophthalmologic examination‡ Resume treatment by reducing the dose by 1 dose level	Discontinue crizotinib and do not retreat. Repeat ophthalmologic examination‡
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.*	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*.
Hematologic (excluding lymphopenia**†)	Continue at the same dose level.	Continue at the same dose level.	See footnote for possible patient entry criteria.† 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**.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**.

* 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.

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

† Patients entering with platelet counts ≥30,000 (<50,000 Grade 3) will be monitored for drug related decreases at which point dose modifications will be discussed with the Sponsor.

‡ 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 v4.0 grade change occurs from the previous visit.

§ Patients entering with ALT >5xULN (ie, Grade ≥3) in the presence of liver mets/tumor-related cause will be monitored for drug related increases at which point dose modifications will be discussed with the Sponsor.

If a patient has a significant toxicity from crizotinib treatment which fails to recover within 42 (6 weeks) days or, in the opinion of the investigator, requires discontinuation of the treatment based on the severity of the adverse event, then further dosing with crizotinib should be discussed with the sponsor.

5.7. Concomitant Medication(s)

All concomitant treatments, blood products, as well as non-drug interventions (eg, paracentesis) received by patients from screening to 28 days after the last dose of study treatment will be recorded on the CRF.

Systemic anticancer therapy with agents other than crizotinib (including corticosteroids for lymphoma) is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.7.1. Crizotinib

The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of potent CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, neflifavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice are not allowed in the study. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

In vitro data indicate that the most pronounced inhibitory potential of crizotinib was observed toward CYP3A4 (testosterone)-mediated drug metabolism. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19, and 2D6.

Crizotinib also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A. Caution must be exercised in patients receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A, such as alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. In particular, co-administration of crizotinib with CYP3A4 substrates with narrow therapeutic indices including, but not limited to, ergotamine, dihydroergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation.

Additionally, the concurrent use of non-prescription drugs, complimentary medicines (excluding vitamins) or herbal supplements is not recommended. Patients should avoid using acetaminophen at doses in excess of 2 grams per day.

5.7.2. Antiemetic and Antidiarrheal Therapy

Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. Patients may receive prophylaxis of treatment-induced diarrhea.

5.7.3. Hematopoietic Growth Factors

The use of hematopoietic growth factors is at the discretion of the treating physician and is in line with local regulatory guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

5.7.4. Other Concomitant Medications

Anti-inflammatory or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Patients on this trial may be supported with appropriate hormone replacement therapy as clinically indicated in the absence of disease progression or unacceptable treatment-associated toxicity.

Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

Low dose acetaminophen (<2 g/day) is allowed.

Medications that are known to prolong the QT interval and bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be used with caution during the study.

5.8. Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. 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) for any surgical procedures during the study. The appropriate interval of time between surgery and crizotinib required to minimize the risk of impaired wound healing and bleeding has not been determined. 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. Postoperatively, the decision to reinitiate crizotinib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.9. Rescue/Escape/Salvage (Select One) Therapy

Not applicable.

6. STUDY PROCEDURES

6.1. Screening

See [Table 1](#) for Schedule of Activities.

6.2. Study Period

For procedures during the study period, see [Table 1](#) for Schedule of Activities. A reduced schedule of assessments will be followed for all ongoing patients after IRB/EC approval of Amendment 5 (see [Table 6, Appendix 5](#)).

Sufficient study medication for a maximum of 6 cycles of treatment will be dispensed at each clinic visit. During the non-clinical visit cycles, laboratory tests should be performed every cycle and the Investigator is responsible for ensuring the patient contacts the clinical site in order to provide an update of adverse events and concomitant medications. Where possible, laboratory tests should be performed at the clinical site's local laboratory. Where that is not possible, patients will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit; process depends on local medical practice. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.

6.3. Follow-Up Visit

For follow-up visit procedures, see [Table 1](#). After IRB/EC approval of Amendment #5, post-treatment follow-up visits for survival status will no longer be required (see [Table 6, Appendix 5](#)).

6.4. 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 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.

Reasons for trial treatment discontinuation may include (further collection of data can still occur):

- Disease progression by RECIST 1.1¹ or NCI International Response Criteria for Non-Hodgkin's Lymphoma (2007).²
- Unacceptable toxicity.
- Need for treatment delay for more than 6 weeks due to lack of toleration should be discussed with the sponsor.
- Protocol non-compliance.
- Pregnancy.

Reasons for trial discontinuations (no further collection of data) withdrawal from study follow up may include:

- Withdrawal of consent.
- Patient lost to follow-up (data may still be collected from other sources, eg, vital records, as allowed by local regulations).
- Death.
- Study terminated by Sponsor.

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 the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific 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.

Note: after IRB/EC approval of Amendment #5, post-treatment follow-up visits for survival status will no longer be required.

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 can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/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 fashion.

Assessment of efficacy, adverse events, laboratory safety assessment (hematology, coagulation, and chemistry), physical examination, ECG, tumor measurements, biomarker sampling and PK sampling will be done according to time points specified in [Table 1](#).

After IRB/EC approval of Amendment #5, Schedule of Activities will be further reduced as indicated in [Table 6 \(Appendix 5\)](#).

7.1. Efficacy Assessments

On-study tumor assessments are to be performed at the beginning of Cycle 3 and every other cycle up to and including Cycle 10. After Cycle 10 tumor assessments will be performed every 12 weeks, and will be reduced to every 24 weeks from Cycle ≥ 26 and to every 52 weeks from Cycle ≥ 52 . CT or MRI scan should also be performed whenever disease progression is suspected (eg, symptomatic deterioration). The determination of anti-tumor activity will be based on objective tumor assessments made according to the RECIST version 1.1 or NCI International Response Criteria for Non-Hodgkin's Lymphoma (2007) ([Appendix 3](#) and [Appendix 4](#)). The CT scans used for tumor assessments should be performed with contrast agents unless contraindicated for medical reasons. The same imaging modality should be used throughout the study to measure disease. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans. CT or MRI scans will include chest, abdomen and pelvis at screening (and neck for patients with NHL). Subsequent staging scans may include only known sites of disease, unless scanning of additional sites is clinically indicated. CT/MRI head is required at screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases, otherwise brain will only be evaluated when clinically indicated. Bone scans are required if bone metastases are suspected. A bone scan is also required at the time of confirmation of response for patients who have bone metastases. Scans will be collected for a potential independent radiology review. PET scanning should be used to evaluate for complete response in those NHL patients whose CT/MRI scans suggest only a partial response. Once a normal PET scan (ie, a PET scan suggesting complete response) has been obtained in a patient with NHL, repeat PET scanning is not required unless there is clinical evidence to suggest disease progression. Bone marrow biopsy and/or aspirate should also be performed to document complete response for any NHL patients known to have bone marrow involvement at baseline or for any NHL patient whose marrow status was unknown at baseline.

When new effusions or ascites are present and represent the only potential site of disease progression, cytologic analysis should be performed and the results, malignant or non-malignant, should be recorded on the CRF.

Measurable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

After IRB/EC approval of Amendment #5, tumor assessments will be performed as per local clinical practice (see [Table 6](#), [Appendix 5](#)), and will no longer be recorded on the CRF. The collection of scans for independent radiology review will be discontinued. However, tumor assessment information should be retained in the patient's file for documentation purposes.

7.2. Safety Assessments

Safety assessments will include collection of AEs, serious adverse events, vital signs, physical examination, 12-lead ECGs, laboratory assessments including pregnancy tests, ophthalmological examinations and verification of concomitant treatments.

7.2.1. Adverse Events

Adverse events will be classified by type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.2. Pregnancy Testing

Prior to IRB/EC approval of Amendment 5, for female patients of childbearing potential, a pregnancy test, with sensitivity of at least 25 mIU/mL, will be done at screening, before investigational product administration, whenever one menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected), and at the end of treatment visit to confirm the patient has not become pregnant during the study.

After IRB/EC approval of Amendment 5, for female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely performed at every cycle during the active treatment period, at the end of study treatment, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from treatment but may remain in the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.2.3. Laboratory Safety Assessments

For a listing of hematology, coagulation and blood chemistries, see [Appendix 1](#).

7.2.4. Physical Examination

A complete physical examination will include the assessment of relevant body systems, the measurement of body weight, height (screening only) and vital signs. Blood pressure and pulse rate will be obtained in the sitting position. Blood pressure should be measured in the dominant arm, ie, writing arm, and recorded to the nearest mmHg. The same arm should be used throughout the study.

7.2.5. Performance Status

ECOG Performance Status scale will be used (see [Appendix 2](#)).

7.2.6. ECG Measurements

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Triplicate ECG measurements will be obtained at all time points except a single ECG measurement at screening. For triplicate measures, three consecutive 12-lead ECGs will be collected approximately 2 minutes apart. It is required that the machine used has a capacity to calculate the standard intervals automatically. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. Additional ECGs will be performed as clinically indicated. If the QTc is prolonged (≥ 500 msec), then the ECG should be read by a

cardiologist at the site for confirmation, and the values obtained by the cardiologist should also be entered into the CRF. Crizotinib should be withheld until the drug relationship of the event is determined (rule out electrolyte imbalance or influence of concomitant medication). In case of a QTc interval measurement ≥ 500 msec (Grade ≥ 3) dosing should be interrupted, and permanently discontinued for a Grade 4 QTc prolongation. For Grade 3 or 4 QTc prolongations, continuous electrocardiogram (ECG) monitoring will be done under physician supervision until the QTc recovers to Grade ≤ 1 . Triplicate ECG surveillance will again be performed when crizotinib is restarted on a reduced dose due to Grade 3 QTc prolongation as described in [Table 3](#). The timing of the triplicate assessment of ECGs should be prior to (0 hour) and 2-6 hours after morning dosing of crizotinib on Day 1 of Cycles 1, 2, and 3.

7.2.7. Ophthalmology Examinations

At screening, each patient will have an ophthalmologic exam including visual acuity and slit lamp. Additional eye examinations will be performed as clinically indicated.

Findings from the ophthalmology examinations should be reported as adverse events if a finding is considered to be an adverse event by the investigator or Sponsor.

7.3. Pharmacokinetics

7.3.1. Plasma Pharmacokinetic Assessment

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). During the trial, actual collection times may change but the number of samples will remain the same.

PK samples will be assayed using validated analytical method(s) in compliance with Pfizer standard operating procedures. Details regarding the sample handling and shipping will be provided in the Lab Manual.

7.3.2. Plasma Pharmacokinetic Assessment for Crizotinib

Plasma samples for crizotinib will be obtained prior to and 2-6 hours following morning dosing on Day 1 of Cycles 1, 2, 3 and 5. No pre-dose sample is required on Day 1 of Cycle 1. Additional blood samples may be requested from patients experiencing unexpected or serious adverse events.

As part of understanding the pharmacokinetics of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for crizotinib and its metabolites (if possible). The results of such analyses may be included in the clinical report.

At each time point, blood samples (3 mL) for PK will be collected into appropriately labeled collection tubes containing K₂EDTA at protocol-specified times. Once collected, samples should be processed immediately and kept out of direct sunlight due to the light sensitive

nature of crizotinib. Blood samples will be placed immediately on ice-bath and centrifuged at approximately 1700 g for 10 minutes at 4° C. Plasma samples will be harvested and stored in appropriately labeled tubes at approximately -20°C within 1 hour of collection.

7.4. Tumor Tissue for Molecular Profiling

Tumor sample must be provided to the designated central laboratory for retrospective confirmation of *ALK* genetic event by a Pfizer designated central laboratory. However this information will not be used to determine eligibility to enter the trial.

7.5. Tumor Tissue for Biomarker Analysis

An optional tumor sample will be collected at the end of treatment if a patient discontinues due to disease progression. The tumor tissue will be used to determine possible mechanisms for resistance to crizotinib treatment. There is no restriction on the type of tumor sample, so cytology specimens as an alternative to solid tumor specimens may also be collected.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. 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.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event 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 trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse

events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

- Adverse events (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least one dose of investigational product through the patient's last visit.
- If a patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

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

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breast feeding;
- Medication error;

- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as adverse events 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 adverse events.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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.

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

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

8.6. 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;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the section on [Severity Assessment](#)).
- Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

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 adverse event 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.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on [Serious Adverse Event Reporting Requirements](#)).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of

drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
 - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).
- **Concurrent with**
 - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥ 3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational 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. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to 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 should be 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 adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment 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 adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned 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 adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.8. Severity Assessment

The investigator will use the following definitions of Severity in accordance with CTCAE Version 4.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC 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 4.0 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 adverse event. A severe event is not necessarily a serious adverse event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 adverse event; 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 the section on [Reporting 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 a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly 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 women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. 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 study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a SAE Report form and Exposure during pregnancy (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 subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) 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 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 an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, 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 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 serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. 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 study 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.

8.11. 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 investigational product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on [Patient Withdrawal](#))

Withdrawal due to adverse event should be distinguished from withdrawal due to other causes, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study patient. In addition, each study patient will be questioned about adverse events.

8.14. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or 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 or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

A primary objective of this study is to assess the safety of oral, single agent crizotinib administered to patients with advanced ALCL or other malignancy (other than NSCLC) known to have an *ALK* genetic event and screen for efficacy in these patients. Estimation will be emphasized for the study endpoints.

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

The table below shows the probability of observing toxicity with different sample sizes given various true underlying toxicity rates. For example, with 40 patients, the probability of observing toxicity occurring at least 5% of the time is 87%.

Table 4. Probability of Observing Toxicity Given True Underlying Event Rates

	True Underlying Toxicity Rate		
	5%	10%	15%
Probability of Observing at Least 1 Adverse Event N=10	0.40	0.65	0.80
Probability of Observing at Least 1 Adverse Event N=20	0.64	0.88	0.96
Probability of Observing at Least 1 Adverse Event N=30	0.79	0.96	0.99
Probability of Observing at Least 1 Adverse Event N=40	0.87	0.99	1.0

9.2. Efficacy Analysis

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

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

9.2.1. Analysis of Primary Endpoint

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

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

Safety Analysis: Frequencies of patients experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Severity of the AEs will be graded according to the NCI CTCAE Version 4.0.

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

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

9.2.2. Analysis of Secondary Endpoints

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

9.3. Analysis of Other Endpoints

9.3.1. Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

9.3.2. Baseline Characteristics

Demographic characteristics such as patient age, gender, weight, ethnicity, prior cancer therapy, medical history and ECOG performance status will be tabulated.

9.3.3. Treatment Administration/Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered and dose intensity.

9.3.4. Analysis of Clinical Labs

Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment. The tables will list the day and cycle of treatment, dose, and associated NCI CTCAE toxicity grade. Summary tables will be prepared to examine the distribution of these toxicities per cycle.

Graphic displays and shift tables may be provided to illustrate the results over time on study.

9.3.5. Electrocardiogram Data

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged. All summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. QT measurements corrected by heart rate (QTc) using Bazett's (QTcB) and Fridericia's (QTcF) methods will be used for data summaries and interpretation.

9.3.6. Concomitant Medications

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary. Patients who received concomitant medications will be listed. Follow-up systemic therapy for the primary diagnosis will be summarized by categories of follow-up therapy and will be listed for each patient as appropriate.

9.3.7. Analysis of Pharmacokinetic Endpoints

Concentration data of crizotinib will be listed by patient and by actual collection time and day.

Concentration-QTc modeling analysis will be conducted using the ECG data from this study and/or combined data with other clinical studies of crizotinib. A separate study specific QT correction factor will be estimated for the QT-RR measurements in each clinical study of crizotinib. Linear, log-linear, and/or saturable models will be examined for the concentration-QTc relationship. Exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model. Diagnostic evaluation will be included to explore the adequacy of the model.

Population pharmacokinetic analysis of samples collected in this study will be performed in accordance with the FDA guidance on Population Pharmacokinetics (February 1999). All patients treated with crizotinib and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the population analysis. The plasma concentration data set from this study will be pooled with data sets from additional crizotinib studies. Population pharmacokinetic analysis will involve mixed effects modeling performed using appropriate software (eg, NONMEM). The data from the analysis will describe the PK following multiple dose administration of crizotinib and describe covariates that are important determinants of crizotinib disposition.

In addition, population PK/PD analysis will be explored, as necessary, based on emerging safety/clinical response data.

The results of these modeling analyses may be reported separately from the clinical study report.

9.3.8. Analysis of Molecular Profiling Endpoints

The types of *ALK* fusion/translocation, mutations, amplification and overexpression will be tabulated by tumor type. Summaries of baseline molecular profiling results will be provided. Changes will be summarized for those patients with both pre and post treatment and end of treatment/withdrawal molecular profiling results.

9.4. Interim Analysis

No interim analysis is planned.

9.5. Data Monitoring Committee

An external Data Safety Monitoring Committee 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.

Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines.
- Routine monitoring of non-serious adverse events as they are recorded in the CRFs.
- Periodic teleconferences with the principal investigators on individual studies to share experiences and ensure communication.

Findings of the periodic safety reviews, according to Sponsor procedures will be documented in the project files and action taken as appropriate. Findings having immediate implication for the management of patients on study will be communicated to all principal investigators in the timeframe associated with unexpected and drug-related SAEs.

In addition, an internal review committee including at least a medical oncologist and statistician will provide periodic review of safety data.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is 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.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (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.

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 case report form (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 is true. Any corrections to entries made in the CRFs, 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's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or 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/assent documents, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement, 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 to an independent third party arranged by Pfizer. 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 (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent 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 legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

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 is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the study patient. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his/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 or legal guardian, 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/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.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative parent(s), or legal guardian and the patient's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent/assent 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which 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 in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of Trial in all other participating countries is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application [CTA]).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug 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 or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a timed period deemed appropriate by each institutional IRB/IEC. 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final patient 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 pre-specified protocol or was terminated.

EudraCT

Pfizer posts 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

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 has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. 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, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. EA Eisenhauer et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-27, 2009.
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Appendix 1. Required Laboratory Tests

	Conventional Units	Conversion Factor	SI Units
<u>Hematology</u>			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	10 ³ /mm ³	x 10 ⁹	10 ¹² /L
White blood count (WBC)	10 ³ /mm ³	x 10 ⁶	10 ⁹ /L
White blood cell differential	%	x 0.01	fraction
<u>Chemistry</u>			
Total bilirubin	mg/dL	x 17.1	µmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
ALKaline phosphatase	U/L	N/A	U/L
Total protein	g/dL	x 10	g/L
Albumin	g/dL	x 10	g/L
Sodium	MEq/L	x 1.0	mmol/L
Potassium	MEq/L	x 1.0	mmol/L
Chloride	MEq/L	x 1.0	mmol/L
Calcium	mg/dL	x 0.25	mmol/L
Phosphorus	mg/dL	x 0.323	mmol/L
Blood urea nitrogen (BUN)*	mg/dL	x 0.357	mmol/L
Urea *	n/a	n/a	mmol/L
Creatinine	mg/dL	x 88.4	µmol/L
Uric acid	mg/dL	x 0.059	mmol/L
Magnesium	mg/dL	X 0.41	mmol/L
Glucose	mg/dL	x 0.055	mmol/L
LDH	U/L	N/A	U/L
<u>Coagulation</u>			
Protome INR	(unitless)	N/A	(unitless)
* either/or			
In cases of suspected Drug-Induced Liver Injury (DILI) - values eventually to be reported on SAE form and eCRF AE page as appropriate			
Creatine kinase (aka CPK)	U/L	N/A	U/L
Indirect bilirubin	mg/dL	x 17.1	µmol/L
Direct bilirubin	mg/dL	x 17.1	µmol/L
Gamma-glutamyl transferase (GGT)	U/L	N/A	U/L

Appendix 2. ECOG Performance Status

Grade ECOG

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 3. RECIST Version 1.1 Tumor Assessment Criteria

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below ¹¹:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-Measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥ 10 but <15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary Lesions:

If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥ 15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.
(Note: the appearance of one or more new lesions is also considered progression).

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by RECIST version 1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 5.

Table 5. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = inevaluable.

Best Overall Response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trials) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment

has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

Appendix 4. NCI International Response Criteria for Non-Hodgkin Lymphoma

A. Introduction

Response criteria for Non-Hodgkin Lymphoma (NHL) are based on the 1999 NCI International Workshop to standardize response criteria for NHL and recent updates to these criteria reported in 2007. These updates incorporate additional technologies and assessments, which have become more widely available and have demonstrated predictive value. The updates also eliminate a commonly misinterpreted response category. Response criteria are based on assessments of tumor measurements and clinical findings.

B. Required Assessments

The following assessments are required at screening/baseline and at each subsequent time point required in the protocol:

1. Objective tumor measurements.
2. Clinical assessment including ECOG score, “B-symptoms,” (eg, fever, night sweats, weight loss) and liver and spleen size.
3. Bone marrow biopsies (or aspirates if biopsies were not obtainable), preferably bilateral, optimally of at least 20 mm in aggregate. Note: A bone marrow biopsy must be performed only to confirm a complete response (CR) if initially positive, or if clinically indicated by new abnormalities in the peripheral blood counts or blood smear.
4. Biochemical markers if definitely assignable to NHL (eg, lactate dehydrogenase).

C. Methods of Measurement

1. Computed tomography (CT) will be used to measure index lesions selected for response assessment; MRIs may be used if CT scans are not available or if the patient cannot tolerate CT scans (eg, are intolerant of CT contrast media). Positron emission tomography (PET) using [18F] fluorodeoxyglucose (FDG), when available, should also be considered together with CT results. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed by using an 8-mm or less contiguous reconstruction algorithm. CT scans of the chest, abdomen, and pelvis are required for each assessment.

Note: A CT scan of the neck should be obtained if cervical disease is present.

2. Lesions on standard radiographs are not acceptable as measurable lesions.
3. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of the investigational product treatment and never more than 4 weeks before the beginning of treatment.

4. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening/baseline and during the study.
5. Lesions noted on physical examination, such as skin nodules and lymph nodes, will be considered measurable only if they are superficial and are ≥ 10 mm at initial assessment. As often as possible, the same investigator using the same method of measurement should assess these lesions at all visits.

D. Baseline Documentation of “Index” and “NonIndex” Lesions

1. Up to a maximum of 6 of the largest dominant lesions should be identified and recorded as ***Index lesions*** and measured at baseline. These nodes or masses should be selected according to the following features:
 - They should be clearly measurable in at least 2 perpendicular dimensions;
 - They should be from as disparate regions of the body as possible;
 - They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved; and
 - They should be suitable for accurate repeated measurements (eg, relationship to identifiable landmarks).
2. The product of the longest transverse diameter and the longest perpendicular transverse diameter will be recorded for all Index lesions. The sum of the product diameters (SPD) for all Index lesions will be calculated and reported as the baseline SPD. The baseline individual product diameters and the baseline SPD will be used as the references by which the objective tumor response will be characterized.
3. All other lesions (or sites of disease) should be identified as NonIndex lesions and must also be recorded at baseline. Both nodal and non-nodal (eg, masses present in the liver and/or spleen) are recorded. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

E. Response Criteria

1. **Complete Response (CR)** requires the following:
 - a. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy.

- b. All lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1 cm in their short axis after treatment. NOTE for PET scans: for patients with no pretreatment PET scan or when a PET scan was positive before treatment, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- c. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Other organs considered to be enlarged before therapy as a result of involvement by lymphoma such as liver and kidneys, must have decreased in size.
- d. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥ 20 mm biopsy core). If a sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

2. Partial Response (PR) requires the following:

- a. $\geq 50\%$ decrease in SPD of the six largest dominant nodes or nodal masses.
- b. No increase in the size of other nodes, liver, or spleen.
- c. Splenic and hepatic nodules must regress by $\geq 50\%$ in the SPD, or for single nodules, in the greatest transverse diameter.
- d. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- e. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report (eg, large-cell lymphoma, or low-grade lymphoma such as small, lymphocytic small cleaved, or mixed small and large cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before treatment and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

- f. No new sites of disease.
- g. NOTES for PET: For patients with follicular, diffuse large B-cell, or mantle-cell lymphomas (ie, typically FDG-avid lymphomas) and with no pretreatment PET scan or with a positive pretreatment PET scan, the post-treatment PET should be positive in at least one previously involved site. For patients with other NHLs (ie, variably FDG-avid lymphomas/FDG-avidity unknown) and without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular or mantle-cell lymphomas, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

3. **Stable disease (SD)** is defined as less than a PR (see above) but is NOT progressive disease (see below, progressive disease).
 - a. *NOTES for PET: For patients with follicular, diffuse large B-cell, or mantle-cell lymphomas (ie, typically FDG-avid lymphomas), the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET. For patients with other NHLs (ie, variably FDG-avid lymphomas/FDG-avidity unknown) and without a pretreatment PET scan or with a negative pretreatment PET, there must be no change in the size of the previous lesions on the post-treatment CT scan.*
4. **Relapsed disease (after CR)/ Progressive disease** (after PR or SD) requires the following:
 - a. NOTE: Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes $\leq 1.0 \times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.
 - b. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of treatment, even if other lesions are decreasing in size. *NOTE for PET: Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.*
 - c. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.

- d. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- e. NOTE for PET: Lesions should be PET positive if observed in a typical FDG-avid lymphoma (ie, follicular, diffuse large B-cell, or mantle-cell lymphomas) or the lesion was PET positive before treatment unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).
- f. NOTE: Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Evaluation of Non-Index Lesions: Although a clear progression of "Non Index" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel.

Response Criteria for Non-Hodgkin Lymphoma				
Response Category	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	Regression to normal size on CT ^a	Not palpable, nodules disappeared	infiltrate cleared on repeat biopsy ^b
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of ≤6 largest dominant masses; no increase in size of other nodes ^c	≥50% decrease in SPD of nodules; ^d no increase in size of liver or spleen	Irrelevant if positive pretreatment; cell type should be specified
SD	Failure to attain CR, PR or progressive disease	On CT: no new sites; no change in size of previous lesions ^e		
Relapsed or Progressive Disease	New lesion or increase by ≥50% of previously involved sites from nadir	New lesion(s) >1.5 cm (any axis); ≥50% increase in SPD of >1 node; or ≥50% increase in longest diameter of previously identified node >1 cm in short axis ^f	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Reference: Cheson DB, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised Response Criteria for Malignant Lymphomas. *J Clin Oncol*. 2007; 25: 579-586.

- a. For FDG-avid lymphomas (ie, follicular, diffuse large B-cell, or mantle-cell) with PET scan positive before treatment, post-treatment mass of any size permitted if PET negative.
- b. If indeterminate by morphology, immunohistochemistry should be negative.
- c. For FDG-avid lymphomas (ie, follicular, diffuse large B-cell, or mantle-cell) with PET scan positive before treatment, ≥1 PET positive at previously involved site.
- d. For single nodule, ≥50% decrease in greatest transverse diameter.
- e. For FDG-avid lymphomas (ie, follicular, diffuse large B-cell, or mantle-cell), PET positive at prior sites of disease and no new sites on CT or PET. For variably FDG-avid lymphomas/FDG-avidity unknown (ie, other NHLs) and negative pretreatment PET, no change in the size of the previous lesions on CT.
- f. Lesions PET positive if typical FDG-avid lymphoma (ie, follicular, diffuse large B-cell, or mantle-cell lymphomas) or PET positive before treatment.

Abbreviations: **CR** = complete response; **CT** = computed tomography; **FDG** = [¹⁸F]fluorodeoxyglucose; **NHL** = Non-Hodgkin lymphoma; **PET** = positron emission tomography; **PR** = partial response; **SD** = stable disease; **SPD** = sum of the product diameters.

F. Response Evaluation

1. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of progressive disease at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
2. Evaluation of Best Overall Response: The best overall response is the best response recorded from the start of the treatment until progressive disease/recurrence (taking as reference for progressive disease, the smallest measurements recorded since the treatment started).
3. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks after the criteria for response are first met.

G. Duration of Response

1. Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started.
2. Stable Disease: SD is measured from the start of the treatment until the criteria for progressive disease are met, taking as reference the smallest measurements recorded since the treatment started. The minimal time interval for duration of SD is 4 weeks.
3. Time to Progression: Time to progression is the interval from the start of the treatment until the first date that recurrence or progression, or death secondary to progression is documented, censored at the last evaluation.

Appendix 5. Reduced Schedule of Activities

After IRB/EC approval of Amendment 5, Table 6 provides an overview of the reduced required Schedule of Activities. 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 reduced Schedule of Activities in order to conduct evaluations or assessments required to protect the well-being of the patient.

Sufficient study medication for a maximum of 6 cycles of treatment will be dispensed at each clinic visit. During the non-clinical visit cycles, the investigator is responsible for ensuring the patient contacts the clinical site in order to provide an update of adverse events and concomitant medications. Reduced hematology and blood chemistry laboratory tests will still be required on Day 1 of the non-clinical visit cycles (see Table 6). Of note, post-study survival status will no longer be collected after IRB/EC approval of Amendment 5.

Table 6. Reduced Schedule of Activities

Protocol Activities	Study Treatment ^[1]	End of Treatment	
	Visits on Day 1 of every 6 Cycles (maximum interval allowed) (± 4 days; except as noted below)	End of Txt/Withdrawal ^[2]	Post Txt Follow-up
Physical Examination ^[3]	X	X	
Blood Pressure and Pulse Rate	X	X	
Ophthalmologic Examination ^[4]	X		
Laboratory Studies			
Dipstick Urinalysis and Reflex Microscopy ^[6]	X (Korea only) All other countries: as clinically indicated	X (Korea only)	
Hematology ^[5]	Day 1 of alternate cycles (± 4 days)	X	
Blood chemistry and LFTs: ALT/AST/alkaline phosphatase/total bilirubin/creatinine ^[5]	Day 1 of each cycle (± 4 days)	X	
Pregnancy Test (as appropriate) ^[7]	Day 1 of each cycle (± 4 days)	X	
Contraceptive check ^[8]	Day 1 of each cycle (± 4 days)	X	
Disease Assessments			
Radiographic studies for tumor assessment ^[9]	As per local clinical practice		
Other Clinical Assessments			
Adverse Events ^[10]	X	X	X
Concomitant Medications/Treatments ^[11]	X	X	
Study Treatment			
Crizotinib	Twice daily		
Special Laboratory Studies			
Optional Tumor Tissue for Molecular Profiling ^[12]		X	

Footnotes for Schedule of Activities
1. All assessments should be performed prior to dosing with study medications unless otherwise indicated. All cycles are 3 weeks in duration. Sufficient study medication for a maximum of 6 cycles of treatment will be dispensed at each clinic visit. During the non-clinical visit cycles, the Investigator is responsible for ensuring the patient contacts the clinical site in order to provide an update of adverse events and concomitant medications.
2. End of Treatment/Withdrawal: Obtain blood pressure, pulse rate, hematology and LFTs, and physical examination if not completed during the previous 4 weeks on study.
3. Physical Examination: Includes an examination of major body systems and weight.
4. Ophthalmologic Examination: Includes visual acuity, slit lamp, and fundoscopy, and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when visual disturbances have been observed and when there is an increase in the grade for visual disturbances.
5. Hematology, Liver function tests and Urinalysis: Required tests are listed in Table 7 . Where possible, laboratory tests should be performed preferably at the clinical site's local laboratory, and, when not possible, patients will provide the laboratory test results copy (from the non-clinical site laboratory), eg, by telephone, and bring a copy of the laboratory test results at the visit; process depends on local medical practice. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes. If ALT or AST \geq Grade 3 or ALT or AST \geq Grade 2 and total bilirubin \geq Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST Grade \leq 1.
6. Reflex Microscopy required if urine dipstick is positive for blood or protein.
7. Serum/Urine Pregnancy Test: For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely performed at every cycle during the active treatment period, at the end of study treatment, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
8. Contraceptive Check: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if alone or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
9. Tumor Assessments: Will be repeated at the frequency as per local clinical practice, and will no longer be recorded on the CRF. However, tumor assessment information should be retained in the patient's file for documentation purposes.
10. Adverse Events: For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Adverse events (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least one dose of investigational product through the patient's last visit.
11. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded up to 28 days post the last dose of study treatment.
12. Tumor Tissue for Molecular Profiling: Sample will be sent to central laboratory (see Section 7.5). An optional fresh tumor sample will be collected at the end of treatment if a patient discontinues due to disease progression.

Table 7. Reduced Laboratory Tests

	Conventional Units	Conversion Factor	SI Units
<u>Hematology</u>			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	10 ³ /mm ³	x 10 ⁹	10 ¹² /L
White blood count (WBC)	10 ³ /mm ³	x 10 ⁶	10 ⁹ /L
White blood cell differential	%	x 0.01	fraction
<u>Liver Function Tests</u>			
Total bilirubin	mg/dL	x 17.1	μmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Creatinine	mg/dL	x 88.4	μmol/L
In cases of suspected Drug Induced Liver Injury (DILI) as described in Section 8.6.2, values to be reported on SAE form			
Creatine kinase (CPK)	U/L	N/A	U/L
Indirect bilirubin	mg/dL	x 17.1	μmol/L
Direct bilirubin	mg/dL	x 17.1	μmol/L
Gamma-glutamyl transferase (GGT)	U/L	N/A	U/L
<u>Urinalysis</u>			
Dipstick and Reflex Microscopy	(unitless)	N/A	(unitless)