Protocol A8081013

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

Statistical Analysis Plan (SAP)

Version: 3.0

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

The changes from version 2.0 are:

- Modified definitions of first tumor response date and PD date for PFS based on in consideration of tumor response data collection timing by RECIST or NCI International Response Criteria for Non-Hodgkin Lymphoma (Cheson criteria).
- Clarified the definition of duration of response.
- Clarified the on-treatment period time window.
- Clarified the definition of treatment-emergent adverse event.
- Modified the subgroups based on tumor types.
- Added data presentation for pediatric patients.

The changes from version 1.0 are:

- Clarified use of RECIST vs. NCI International Response Criteria for Non-Hodgkin Lymphoma (Cheson criteria) in definition of tumor response.
- Clarified timing of the final and other analyses.
- Added the response evaluable analysis set and definition of "adequate baseline".
- Updated definitions of PFS and duration of response.
- Updated definition of treatment emergent adverse events.
- Modified Sections 8.2.3 and 8.2.6 to remove analyses that are no longer planned.
- Safety will be analyzed by tumor group and overall.
- Specified that all safety and efficacy data will be analyzed by tumor group (lymphomas, inflammatory myofibroblastic tumors [IMT], other tumors).
- Included minor editorial clarifications and corrections to enhance clarity of the document.

2. INTRODUCTION

This document describes the planned statistical analyses for protocol A8081013 dated March 25, 2010 and all subsequent protocol amendments (latest Amendment 5, dated August 13, 2015). This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

2.1. Study Design

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

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.

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.

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.

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

2.2. Study Objectives

Primary Objective:

- Assess the safety of oral single-agent crizotinib administered to patients with advanced ALK-positive anaplastic large cell lymphoma (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 efficacy outcome measures including PFS and OS.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis is planned for this study.

Internal procedures for periodic safety review will be adopted. 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.

Unblinding is not applicable.

The final analysis will be performed after the last patient last visit; however, earlier analyses of the data may be performed for publication and regulatory reporting purposes.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no formal statistical hypotheses for this study.

4.2. Statistical Decision Rules

As the primary objective of this study is to assess the safety of oral, single agent crizotinib administered to patients with ALK-positive ALCL or other advanced malignancy (other than NSCLC) known to have an *ALK* genetic event and screen for efficacy in these patients, no statistical decision rules were set. 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 1. Probability of Observing Toxicity Given True Underlying Event Rates

	True Underlying Toxicity Rate		
Sample Size	**5%**	**10%**	**15%**
N=10	0.40	0.65	0.80
N=20	0.64	0.88	0.96
N=30	0.79	0.96	0.99
N=40	0.87	0.99	1.00

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis (FA) set includes all enrolled patients. This population may be employed in evaluating patient disposition.

5.2. Safety Analysis Set

The safety analysis (SA) set will include all patients enrolled who receive at least one dose of study medication.

This will be the primary set for summaries of demographics, safety, summaries of time-to-event efficacy data, and treatment evaluations.

5.3. Response Evaluable Analysis Set

The response evaluable (RE) analysis set will include all patients in the safety analysis set who have an adequate baseline tumor assessment by either RECIST 1.1[1] or Cheson[2] criteria.

This will be the primary set for evaluating all response related efficacy evaluations.

The following must be met to qualify for "Adequate Baseline" assessment:

- Baseline assessments of all lesions (target, and non-target) must be within 35 days, per protocol.
- All lesions recorded at baseline must have an associated status recorded on the eCRF.
- At least one target lesion present at baseline.
- Baseline lesions must be assessed with an acceptable method of tumor assessment as specified in the protocol and could include: CT Scan, MRI, Bone Scan (for confirmation of bone metastases).

5.4. Other Analysis Sets

5.4.1. PK Analysis Set

All patients in the SA set who have at least one PK blood sample will be included in the pharmacokinetic analysis set.

5.4.2. Molecular Profiling Set

All patients in the SA set with at least one data of molecular profiling will be included in the molecular profiling (MP) set.

5.5. Treatment Misallocations

As in this study there is only one treatment arm, treatment misallocations are not applicable. Patients enrolled that do not receive any dose of crizotinib will be counted in the full analysis set only and will be described in patient disposition.

5.6. Protocol Deviations

Patients who don't receive any study medication will be excluded from all analyses, but will be described in patient disposition.

Patients without measurable disease at baseline will not be evaluated for Overall Response Rate.

Patients who are enrolled in the study but are later found to not have an *ALK* genetic event may be presented separately.

All deviations will be described when they appear and related to the statistical summaries or population, prior to database closure. They will be recorded in the protocol deviation log.

6. ENDPOINTS AND COVARIATES

For purposes of efficacy and safety endpoint definitions, the term "on-treatment" includes the period from the first dose of study treatment until and including 28 days after the last dose of study medication, or start of new anti-cancer drug therapy including transplant, whichever occurs first [minimum (28 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day)].

For purposes of censoring definitions for time to event endpoints, "anti-tumor treatment" includes any anticancer therapy (other than study medication), radiation to target or non-target lesions and surgery for removal of target or non-target lesions.

Analyses of endpoints dependent on disease assessments (ORR, PFS and DR) will be based on investigator assessment of tumor data according to RECIST 1.1[1] or the NCI International Response Criteria for Non-Hodgkin's Lymphoma[2] (Cheson criteria).

Protocol Amendment 3 modified the collection of tumor response data to use Cheson criteria to determine tumor response for Non-Hodgkin Lymphoma (NHL) patients. Patients with solid tumors continued to have response reported using RECIST 1.1. Since this change was made after patients had been enrolled and treated in the study, NHL patients may have tumor response collected by either RECIST 1.1 only, Cheson criteria only, or both (*ie,* both RECIST and Cheson criteria results are reported at the same visits, RECIST results are reported at some visits and Cheson criteria results reported at other visits). The following conventions will be followed when reporting response for these patients:

- If both RECIST and Cheson Criteria results are present then Cheson criteria results should be used to report BOR unless the Cheson has Indeterminate result, in which case the RECIST result will be reported. If only RECIST or only Cheson criteria results are present then BOR will be reported based on only RECIST or only Cheson criteria, respectively.

- If results from either Cheson or RECIST criteria are reported at baseline, patients will still be considered to meet the criteria for adequate baseline tumor assessment.

In this study two primary endpoints were defined: type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities for safety, and overall response rate (ORR) for efficacy.

6.1. Efficacy Endpoint(s)

Efficacy endpoints will be summarized in the RE or SA population, as described below for each endpoint, by tumor type: ALCL, inflammatory myofibroblastic tumors (IMT), or other tumor. All efficacy endpoints will be listed.

- **Overall Response Rate (ORR)** is the primary efficacy endpoint. It is defined as the percent of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST (1.1) as determined by the investigators, relative to patients in the RE set. ORR based on Cheson criteria is defined similarly however, confirmation of response is not required. If patient has tumor response assessed only by RECIST or Cheson, then ORR is based on the single result. If tumor response is assessed by both RECIST and Cheson, then ORR is reported based on tumor response by Cheson criteria unless the Cheson has indeterminate result, in which case the RECIST result will be reported.

  Patients will be considered non responders until proven otherwise. Thus, patients who:

  - Do not have CR or PR while on treatment, or
  - Do not have a post-baseline tumor evaluation, or
  - Receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or
  - Die, progress, or drop out for any reason prior to reaching a CR or PR, will be counted as non-responders in the assessment of ORR.

  To be assigned a status of PR or CR using RECIST 1.1 criteria, changes in tumor measurements in patients with responding tumors must be confirmed by repeat tumor assessment that should be performed at least 4 weeks after the criteria for response are first met. Confirmation of response is not required for status of PR or CR using Cheson criteria. If a patient has not achieved an objective response, but remains stable for at least 6 weeks after first dose, then the best overall response for such a patient will be stable disease.

- **Progression Free Survival (PFS)** is defined as the time from the date of first dose of study medication to the date of the first documentation of objective tumor progression or death on treatment due to any cause, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. PFS (in weeks) will be calculated as (date of first event − date of first dose +1)/7.0. PFS will be summarized for the SA set.

  Tumor assessments will be performed within a time window of ± 7 days around the scheduled visits (at Screening, Day 1 of Cycle 3 and every 2 cycles thereafter). Unscheduled scans may be performed to confirm response (≥4 weeks after initial assessment of response) and when disease progression is suspected. If PD is documented between scheduled visits, the actual date of progression will be used as an un-censored value in the analysis of PFS. If PD is reported by both RECIST 1.1 and Cheson criteria, then the earliest date of PD by either RECIST or Cheson criteria will be used in PFS calculation. Otherwise the date of PD by either RECIST 1.1 (if all tumor assessments are by RECIST 1.1) or Cheson criteria (if all tumor assessments are by Cheson criteria) will be used.

Patients with inadequate baseline assessments will have their event time censored on the date of first dose of study medication. Patients lacking an evaluation of tumor response after first dose or for whom the first on-treatment tumor evaluation occurs more than 14 weeks after first dose, will also have their event time censored on the date of first dose unless death occurs ≤ Week 14 (in which case the death is an event).

If patients have at least 1 on-treatment disease assessment, PFS data will be censored on the date of the last evaluable on-treatment tumor assessment by either RECIST 1.1 or Cheson criteria documenting absence of progressive disease for patients:

- Who are alive, on treatment and progression free at the time of the analysis;
- Who discontinue treatment without documented disease progression and who do not progress or die on treatment;
- Who have documentation of disease progression or death >14 weeks after the last on-treatment tumor assessments;
- Who are given anti-tumor treatment other than the study medication while on treatment and prior to documented disease progression or death on treatment. In this case, the last evaluable assessment prior to start of the anti-tumor treatment will be used. One exception to this rule is for patients who have documented PD or death within 14 days of anti-cancer therapy, the PD or death will be considered an event.

- **Duration of Response (DR)** is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death on treatment due to any cause, whichever occurs first. If patient has tumor response assessed only by RECIST or Cheson, the first objective tumor response date will be based on single result of either RECIST 1.1 or Cheson criteria (note: RECIST 1.1 results should be subsequently confirmed but Cheson criteria do not require response confirmation). If tumor response is reported by both RECIST 1.1 and Cheson criteria, the earliest date of tumor response by either RECIST or Cheson criteria will be used. DR (in weeks) will be calculated as (first date of PD or death − first date of CR or PR as defined above+1)/7.0. If the tumor progression data include more than 1 date, the first date will be used. First date of PD will be defined the same as for PFS. Censoring for DR is identical to the censoring rules presented for PFS when patients have at least 1 on-treatment disease assessment. DR will only be calculated for the subgroup of patients with an objective tumor response. Summary statistics will be provided for patients with or without subsequent PD/death. Analysis for DR will also be done for patients with CR or PR separately.

- **Overall Survival (OS)** is defined as the time from the date of first dose of study medication to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose +1)/30.42. For patients still alive at the time of the analysis, for those who are lost to follow-up, and those who withdraw consent for additional follow-up, the OS will be censored on the last date that patients were known to be alive.

Patients lacking data beyond the first dose will have their OS censored at the date of first dose. OS will be summarized for the SA population.

- **Six Months and One-Year Survival Probability** is defined as the probability of survival at 6 months and 1 year, respectively, after the date of the first dose based on the Kaplan-Meier estimate.

6.2. Safety Endpoints

Safety will be summarized for the SA set overall and separately, as applicable, by tumor type (ALCL, IMT, other tumors). Type, incidence, severity, seriousness and relationship to study medications of AEs and any laboratory abnormalities are the primary endpoint for safety.

All AEs reported after initiation of treatment (Cycle 1, Day 1) and pre-existing conditions that worsen after the initiation of treatment will be considered as treatment emergent (Treatment Emergent Adverse Event: TEAE).

AEs and laboratory measures will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

6.3. Other Endpoints

6.3.1. PK Endpoints

Plasma concentrations of Crizotinib.

6.3.2. Molecular Profiling Endpoints

Molecular profiling outcomes include one or more of the following:

- ALK translocation /fusions;
- ALK mutation;
- ALK gene amplification;
- ALK protein expression.

If available, the tumor tissue from surgery or biopsy pre and post treatment will be used to determine possible mechanisms for resistance to PF-02341066 treatment.

7. HANDLING OF MISSING VALUES

In compliance with Pfizer standards, for start date, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in 0 time duration will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration). However, for to/end dates, last of the month and day are used for partial dates.

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date. For primary and secondary efficacy analyses, no values will be imputed for missing data, except as specified in Section 6, where for time to event endpoints, non-event observations will be censored and for ORR, where patients with no post-baseline tumor evaluations will be counted as non-responders.

7.1. Missing PK Data

7.1.1. Concentrations Below Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

7.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, summary statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);

2. A deviation in sampling time is more than 10% from the nominal time or a concentration has been flagged anomalous by the pharmacokineticist.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned.

Descriptive statistics will be used to summarize all patient characteristics, treatment administration, efficacy endpoints, safety parameters, PK and biomarker variables.

Pediatric patients (<18 years) will be listed separately for ALCL and IMT in baseline characteristics, treatment administration, efficacy endpoints, safety parameters, PK and biomarker variables.

Data will also be displayed graphically, where appropriate.

8.1.1. Analyses of Time-to-Event Endpoints

Time-to-event endpoints (PFS, DR and OS) may be summarized, as appropriate, using the Kaplan-Meier method[3] and displayed graphically when appropriate. Median event times (and other quartiles) and 2-sided 95% CIs for each quartile will be provided (Brookmeyer R and Crowley JJ[4]).

Since the number of patients may limit the use of the Kaplan-Meier method, descriptive statistics may be presented (separately for patients who have an event and censored patients).

Data will be summarized separately by tumor type (ALCL, IMT, other tumors).

8.1.2. Analyses of Binary Endpoint

The rates of binary efficacy endpoints will be calculated and the 95% CI for the rate will be provided using the exact method based on the F-distribution.

Data will be summarized separately by tumor type (ALCL, IMT, other tumors).

8.1.3. Analyses of Continuous Data

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints.

Data will be summarized separately by tumor type (ALCL, IMT, other tumors).

8.1.4. Analyses of Categorical Data

The number and percentage of patients in each category will be provided for categorical variables.

Data will be summarized separately by tumor type (ALCL, IMT, other tumors).

8.2. Statistical Analyses

8.2.1. Primary Analysis

The best response will be summarized in the RE set which may exclude patients later found to not have an ALK genetic event. The number and percent of patients achieving objective response (CR or PR; confirmation required for RECIST 1.1) will be summarized with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. Data will be presented by tumor type (ALCL, IMT, other tumors).

8.2.2. Secondary Analyses

Data will be presented by tumor type (ALCL, IMT, other tumors).

- **PFS:** will be summarized in the SA set which may exclude patients who are found after enrolment to not have an ALK genetic event. The Kaplan-Meier method will be used and graphs displayed, where appropriate. The Hall Wellner 95% confidence band will be provided for individual Kaplan-Meier curve for each tumor type (ALCL, IMT, other tumors), as appropriate. The median event time (and other quartiles) and corresponding 2-sided 95% CIs may be provided.

- **DR:** will be summarized in RE set using Kaplan-Meier methods and displayed graphically where appropriate. DR will be calculated for the subgroup of patients with objective response (confirmation required for RECIST 1.1). The median event time (and other quartiles) and 2-sided 95% CI for the median will be provided if appropriate. Summary statistics for DR including mean, median, standard deviation, range will be provided for patients with and without subsequent progression or death. Summary will also be provided by CR and PR.

The number of patients experiencing CR and PR may be small and thereby the reliable use of the Kaplan-Meier method will be limited and in this case, descriptive statistics or listings will be provided.

- **OS:** will be summarized in the SA set and estimates of the OS curves obtained from the Kaplan-Meier method may be presented. OS curve may also be displayed graphically. The Hall Wellner 95% confidence band will be provided for individual Kaplan-Meier curve for each tumor type (ALCL, IMT, other tumors), as appropriate. The median (and other quartiles) event time and corresponding 2-sided 95% CIs for the median may be provided.

- **6-months and 1-year survival probability:** will be estimated using the Kaplan-Meier method and a 2-sided 95% confidence interval for the log [-log (1-year survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6 months and 1-year survival probabilities themselves. Survival probabilities for additional time points may also be estimated.

8.2.3. Safety Analyses

All safety analyses will be carried out on the SA set and presented by tumor type (ALCL, IMT, other tumors), or for overall study patients as appropriate.

- **Adverse events (AEs)** - All AEs reported after initiation of treatment and pre-existing conditions that worsen after the initiation of treatment will be considered as treatment emergent (Treatment Emergent Adverse Event: TEAE). In the case that a patient receives new anticancer therapy including transplant, an AE occurring after the anticancer therapy start date will not be included in the patient summary but will be listed. All AEs will be coded by system organ class (SOC) and preferred term using the most recent version of MedDRA. The severity of all AEs will be coded by the Investigator using NCI CTCAE Version 4.0.

  An overall summary of AEs will be provided. The number and percentage of patients who experienced any AE, any serious adverse event (SAE), any treatment-related AE, any treatment-related SAE, grade 3 or 4 AE, grade 5 AE, who had dose reduction associated with an AE, and who discontinued because of an AE will be presented. Treatment-related AEs are those judged by the Investigator to be at least possibly related to study medication or for which relatedness is recorded as “unknown” by the Investigator.

  All AEs will be summarized by MedDRA SOC and preferred term (PT). A summary of AEs by preferred term and maximum CTCAE grade will be presented. A summary of AEs by preferred term and maximum CTCAE grade group
  (Grade 1-2 vs. Grade 3-4 vs. Grade 5) will also be presented. A summary of TEAEs by PT (decreasing frequency) will also be presented. The aforementioned summaries will also be presented by relationship to study drug. Summary tables may also be generated for clustered adverse events which combine several PTs associated with an event of interest (eg, events associated with visual disturbance). The clustered events are described in a list in the product’s Safety Review Plan maintained by the Sponsor.

Summaries of safety data by preferred term and clustered term in descending frequency will also be reported overall regardless of tumor type. Patients who experience AEs during the AE reporting period will be listed.

All AEs and treatment related AEs will be presented across all cycles.

Deaths will be summarized by time period (on-treatment vs. during follow-up) and cause of death. Deaths that occurred on or after the first dose of study medication and within 28 days after the last dose of study medication are defined as on-treatment deaths. Death data will also be listed, and the listing will include all deaths that occurred during the reporting period for deaths.

Patients who withdraw from study treatment because of an AE will be listed. Patient discontinuation will be determined from the AE CRF page (where action taken is "Permanently Discontinued"). Patients who temporarily discontinue study treatment or have a dose modification associated with an AE will also be listed.

Treatment emergent SAEs and treatment-related SAEs will be summarized by MedDRA SOC and preferred term. Patients who experienced an SAE during the SAE reporting period will be listed.

- **Hematology and Blood chemistry –** Hematology and blood chemistry results will be graded according to the NCI CTCAE Version 4.0. A summary of worst on treatment abnormality and a shift summary of baseline grade by maximum post-baseline CTCAE grade will be presented, as appropriate. Patients who developed toxicities of grade ≥3 will also be listed.

- **ECOG Performance Status –** ECOG performance status will be summarized at baseline.

- **Vital Signs –** The number and percent of patients in each of the following minimum and maximum blood pressure, body weight and pulse rate categories will be presented:

Vital Sign	Category
Blood Pressure	Maximum Change from baseline (decrease) in SBP of ≤ -40 mmHg
	Maximum Change from baseline (decrease) in SBP of ≤ -60 mmHg
	Maximum Change from baseline (increase) in SBP of ≥40 mmHg
	Maximum Change from baseline in DBP (decrease) of ≤ -20 mmHg
	Maximum Change from baseline in DBP (decrease) of ≤ -40 mmHg
	Maximum Change from baseline in DBP (increase) of ≥20 mmHg
Body Weight	Maximum change from baseline body weight ≥10%
	Maximum change from baseline body weight ≤ - 10%
Pulse Rate	Maximum Pulse Rate >120 bpm
	Minimum Pulse Rate <50 bpm
	Maximum Change from baseline (increase) ≥30 bpm
	Minimum Change from baseline (decrease) ≤ -30 bpm

- **ECG** - Triplicate ECG measurements will be obtained at all time points except a single ECG measurement at screening. The triplicate data will be averaged and all summary statistics and data presentations will use the 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 will be used for the data analysis and interpretation. The commonly used Bazett's and Fridericia's correction will be applied.

  Categorical analysis of ECG data will be conducted and summarized as follows. All planned and unplanned post-dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

  Categorical analysis of the QTcF/QTcB data will be conducted and summarized as follows:

  1. The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- 60, and ≥60 ms);

  2. The number of and percentage patients with maximum post-dose QTcF/QTcB (<450, 450-<480, 480- <500, and >500 ms);

  3. PR changes from baseline ≥50% if absolute baseline value was <200 ms, and ≥25% if absolute baseline value was ≥200 ms;

  4. QRS changes from baseline ≥50% if absolute baseline value was <100 ms, and ≥25% if absolute baseline value was ≥100 ms.

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

The following ophthalmologic analyses will be performed. If there are fewer than five patients with ophthalmological exam data, only listings will be provided.

- **Visual Acuity Exam Results:** Visual acuity at baseline will be summarized for each eye. The worst change from baseline in visual acuity will be summarized by eye.

- **Biomicroscopy (Slit Lamp) and Fundoscopy Exam Results:** For baseline results, percentage of patients falling into each category of the examination status (normal, mild, moderate or severe) will be summarized for each eye structure by eye.

  For post-baseline results, percentage of patients falling into each category of the examination status (normal, mild, moderate or severe) will be summarized for the worst on study finding for each eye structure by eye.

8.2.4. Baseline Characteristics and Other Summaries

Descriptive statistics will be used to summarize patient disposition, baseline characteristics, and treatment administration/compliance, and presented by tumor type and overall (ALCL, IMT, other tumors). Summary of patient disposition and baseline characteristics will also be provided for overall study population.

- **Patient Disposition** - patients not meeting 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 may be summarized in the FA set.

- **Baseline Characteristics** - patient characteristics such as age, gender, height, weight, ethnicity, primary diagnosis, performance status (ECOG), smoking history, prior therapy, extent of disease, and medical history will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables in the SA set. A summary of B-Symptoms at baseline will be provided for lymphoma patients.

- **Treatment Administration/Compliance** – Administration of study medication in the SA set will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, dose modifications, and dose interruptions (more than one day).

8.2.5. Analyses of Pharmacokinetic Endpoints

Concentration data of crizotinib will be listed by patient and by actual collection time and day. The plasma concentration data may be combined with similar data from other studies for population PK analysis and the results will be reported separately if performed.

Concentration-QTc modeling analysis may 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 mode 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. The results on the concentration-QTc analysis will be reported separately if performed.

The analysis population is the PK analysis set.

8.2.6. Analyses of Molecular Profiling

Patient listing of baseline molecular profiling results including *ALK* fusion/translocation, mutations, amplification and overexpression will be provided.

9. REFERENCES

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4. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics 1982; 38:29-41.