Protocol B7461009

A PHASE 1 STUDY TO EVALUATE THE EFFECT OF HEPATIC IMPAIRMENT ON THE PHARMACOKINETICS AND SAFETY OF LORLATINIB IN ADVANCED CANCER PATIENTS

Statistical Analysis Plan (SAP)

Version: 1.0

Date: 24 August 2018

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7461009 is based on the Protocol dated 25 June 2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7461009. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. 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 Objectives

Primary:

- *To evaluate the effect of hepatic impairment on the steady state pharmacokinetics of lorlatinib.*

Secondary:

- *To evaluate the effect of hepatic impairment on the safety of lorlatinib in advanced cancer patients.*
- *To evaluate the antitumor activity of lorlatinib in advanced cancer patients.*

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[redacted]

2.2. Study Design

This will be a Phase 1, open-label, multi-center, multiple-dose, non-randomized, Phase 1 clinical trial of lorlatinib in advanced cancer patients with varying degrees of hepatic impairment and necessary age-, weight-, and gender-matched prospect normal hepatic function patients.

Patients in the study will be assigned to different groups according to their liver function. The criteria for stratification of patients based on their liver function (according to National Cancer Institute (NCI) guidance,[1]

https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Organ_Dysfunction_Protocol_Template.docx) are listed below:

Group	***Groups A1 and A2***	***Group B***	***Group C***	***Group D***
Hepatic Function	*Normal*	*Mild impairment*	*Moderate impairment*	*Severe impairment*
Total Bilirubin	*≤ ULN (Upper Limit of Normal)*	*B1: ≤ ULN* *B2: >1.0 x – 1.5 x ULN*	*>1.5 x – 3 x ULN*	*>3 x ULN*
AST (SGOT)	*≤ ULN*	*B1: >ULN* *B2: Any*	*Any*	*Any*

- *Patients must fulfill both total bilirubin and AST (serum glutamic oxaloacetic transaminase [SGOT]) criteria to be included in a group.*

- *No distinction will be made between liver dysfunction due to metastases or liver dysfunction due to other causes.*

- *All liver function tests for stratification must be completed within 24 hours prior to the start of treatment.*

- *Group B (Mild hepatic impairment): for the purpose of this study, the "mild" liver dysfunction may be defined according to either of two criteria (Groups B_1 and B_2), so that patients in Group B may come from either of these groups. Patients in Group B_1 and B_2 are thus considered to have comparable liver dysfunction and will be combined for dose level allocation and all analysis.*

- *Patients whose degree of hepatic dysfunction changes (becomes worse or better) between screening and initiation of protocol therapy may be re-assigned to a different hepatic dysfunction group. This change should be discussed with the Sponsor and properly documented. Patient stratification will only be done prior to initiation of the study treatment. Patients will not be re-assigned to a different hepatic dysfunction group once treatment with lorlatinib has been started.*

- *Groups A1 and A2 (Normal): patients with normal liver function will be included in this study as matching control patients (Group A1 for Group B and Group A2 for Group C). If the dose for moderate hepatic impairment group (Group C) is selected to be the recommended clinical dose of 100 mg QD, the control group A2 will not be needed to be enrolled. There will be no control group designated to match severe group. However, if a decision has been made to use the same dose for severe and moderate patients, the half of the control Group A2 will be matching Group C and half will be matching Group D.*

The enrollment of approximately 76 advanced cancer patients is anticipated in this study in order to have 8 PK-evaluable patients in each of Groups A1, A2, B and C, and 6 PK-evaluable patients in Group D for final statistical analysis. Evaluable patients are those who complete the planned PK sample collection on Cycle 2 Day 1 and have no lorlatinib dose modification until completion of Cycle 2 Day 1 PK evaluation. Patients who are not evaluable for PK will be replaced.

Each patient will be treated with repeated oral once daily doses of lorlatinib in 21-day cycles until disease progression, patient refusal, or unacceptable toxicity occurs.

The planned dosing schedule for each treatment group is as follows:

Table 2. Lorlatinib Dosing Schedule

	Group B	*Group C*	*Group D*	*Group A1*	*Group A2*
Hepatic Function	***Mild***	***Moderate***	***Severe***	***Normal***	***Normal***
Starting Lorlatinib Dose	*100 mg QD*	*50 mg QD or otherwise determined in the first stage*	*determined based on preliminary safety and PK data*	*100 mg QD*	*the same dose as Group C at the second stage*
Lorlatinib Dose After PK Assessment	*100 mg QD*	*50 mg QD or otherwise determined in the first stage*	*determined based on preliminary safety and PK data*	*100 mg QD*	*100 mg QD*

The dose schedule may be modified as necessary for individual patients according to tolerability (see Table 2 for detailed dose modification strategy).

For Group C, a two-stage enrollment will be applied.

- *In the first stage, 3 PK-evaluable patients will be enrolled to receive the starting dose of 50 mg QD lorlatinib. On completion of PK sample collection through Cycle 2 Day 1 from these 3 patients, PK analysis will be performed. Upon review of the PK and tolerability of these 3 patients, a decision on dose schedule for remaining patients in the second stage will be made.*

- *In the second stage:*

    - *If it is decided to keep the planned dosing schedule (50 mg QD) for patients in Group C with moderately impaired liver function, 5 additional patients will be enrolled to have a total of 8 PK evaluable patients.*

- *If a different dosing schedule is proposed for the remaining patients in Group C based on safety and PK in the first 3 subjects, then more patients will be enrolled to this group to have 8 PK evaluable patients and receive the proposed dosing schedule. The control patients in Group A2 should receive the same lorlatinib dose as proposed for the second stage in Group C until completion of PK assessment on Cycle 2 Day 1 and then switch to 100 mg QD beyond Cycle 2 Day 1. At the new dose level, the first 3 patients should be dosed one at a time with at least one week apart until some safety information at this dose level is obtained.*

The enrollment for patients with severe hepatic impairment (Group D) will only be started when the dose for patients in the second stage of Group C has been determined and has been tolerated in at least one patient. The initial lorlatinib dose for Group D might be the same as the second stage Group C dose or otherwise determined by sponsor based on available preliminary safety and PK data at that time. The dosing regimen for Group D will be communicated to sites. Patients in Group D will not be matched by any control group. Initially (the first 3 patients), the patients should be dosed one by one with at least 1 week apart until some safety information is obtained at the dose level.

Patients in Groups A1 (Normal hepatic function) and B (Mild hepatic impairment) will receive a starting lorlatinib dose of 100 mg (4 × 25-mg tablets) QD. The first 3 patients in in Group C (Moderate hepatic impairment) will receive a starting lorlatinib dose of 50 mg (2 × 25-mg tablets) QD. Patients in control Group A2 (Normal hepatic function) will receive the same starting lorlatinib dose as stage 2 of Group C, which could be 50 mg (2 × 25-mg tablets) QD or as otherwise determined during the second stage of Group C, and switch to 100 mg (4 × 25-mg tablets) QD after completion of PK assessment on Cycle 2 Day 1.

Enrollment into control Group A2 will only be started after the first stage for Group C has been completed and a decision on dose schedule for the stage 2 subjects in Group C has been made. Patients in control group should match patients in the respective hepatic impaired group by the following criteria:

- *The mean body weight in control group will be within ±20 kg of the mean body weight of the patients in respective hepatic impaired group.*

- *The mean age in control group will be within ±10 years the mean age of the patients in respective hepatic impaired group.*

- *The gender ratio in control group will be similar (±2 patients per gender) to those in respective hepatic impaired group.*

Once all the patients complete their planned PK collection, data collection for the primary objective of the study will be accomplished. After data collection for the primary objective has been completed, the sponsor could generate a study report including all PK data and other data, as defined in the Sponsor-maintained statistical analysis plan. In this case, a supplement study reported will then be generated when all patients completed the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Plasma PK parameters of lorlatinib at steady state: AUC_{24} and C_{max}.

3.2. Secondary Endpoint(s)

- Type, incidence, severity, seriousness, and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
- Objective response rate (ORR).
- Duration of response (DR).
- Plasma PK parameters of lorlatinib, if possible: AUC_{last}, T_{last}, and T_{max} after single dose; C_{min}, AUC_{last}, T_{last}, and CL/F at steady-state.
- Plasma PK parameters for metabolite(s) if possible: AUC_{24}, AUC_{last}, C_{max}, T_{max}, T_{last} $MRAUC_{24}$, $MRAUC_{last}$, and MRC_{max}

3.3. Baseline Variables

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug. The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.

No windowing will be applied when defining baseline. Any deviations from the protocol specified window will be documented as protocol deviations.

For efficacy analyses the last assessment prior to randomization will serve as the baseline assessment.

For safety (including Eastern Cooperative Oncology Group (ECOG) performance status) the last assessment performed on or prior to date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

Triplicate ECGs are collected; therefore the baseline for each ECG measurement is the average of the pre-dose measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average.

3.4. Analysis Sets

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

3.4.1. Full Analysis Set

The full analysis set includes all enrolled patients, regardless of whether or not treatment was received.

3.4.2. PK analysis sets

3.4.2.1. PK Concentration Analysis Set

The PK concentration analysis set is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

3.4.2.2. PK Parameter Analysis Set

The PK parameter analysis set is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

3.4.2.3. PK evaluable Analysis set

The PK evaluable analysis set is defined as all patients in the PK parameter analysis population who have (1) completed Cycle 2 Day 1 PK collection; (2) received lorlatinib dose on Cycle 2 day 1; (3) received at least 80% of total dose within 14 days prior to Cycle 2 Day 1; (4) no dose reduction in the first cycle.

3.4.3. Safety Analysis Set

The safety analysis (SA) population will include all enrolled patients who receive at least one dose of lorlatinib on Cycle 1, Day 1. The safety analysis population will be the primary population for evaluating patient characteristics, treatment administration, and safety.

3.4.4. Response Evaluable Analysis Set

The response evaluable analysis set includes all patients in the safety analysis population who have an adequate baseline tumor assessment.

4. GENERAL METHODOLOGY AND CONVENTIONS

Once all the patients complete their planned PK collection, data collection for the primary objective of the study will be accomplished. After data collection for the primary objective has been completed, the sponsor could generate a study report including all PK data and other data.

4.1. Hypotheses and Decision Rules

The study is not powered to detect treatment difference in PK parameters. No formal statistical hypothesis testing is planned, and no decisions will be made to the conduct of the study.

The sample size for this study is determined empirically based on feasibility and regulatory recommendation. Sufficient numbers of patients will be enrolled and dosed to obtain approximately 38 PK evaluable subjects (approximately 16 subjects in normal group, 8 patients each in mild and moderate groups, and 6 in severe group). Subjects may be replaced if not PK evaluable.

4.2. General Methods

4.2.1. Analyses for Binary Data

The point estimates of the rate will be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact Clopper-Pearson method based on the F-distribution.[2]

4.2.2. Analyses for Continuous Data

For continuous variables, summaries will include N, Mean, S.D., CV%, 25th quartile, median, and 75th quartile, min and max. One-way analysis of variance (ANOVA) will be used to test for difference between treatment groups.

4.2.3. Analyses for Categorical Data

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

4.2.4. Analyses for Time to Event Data

Time-to-event endpoint will be summarized using the Kaplan-Meier method[3] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval for each median will be provided (Brookmeyer R and Crowley JJ).[4]

4.3. Methods to Manage Missing Data

In compliance with Pfizer standards, 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 resolution cannot be prior to date of onset; if replacing resolution date with the 1st of the month results in a negative duration, the resolution date will be set to the onset 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).

For the analysis of safety endpoints, the Pfizer data standard rules for imputation will be applied.

4.3.1. Pharmacokinetic Concentrations

4.3.1.1. Concentrations Below the 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.)

4.3.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 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 of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

4.3.2. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

4.3.3. Efficacy Endpoints

For duration of response (DR), if calculation based on conventions result in a negative value, durations will be reset to 1 day.

For efficacy analyses no values will be imputed for missing data, except as specified in Section 5.2.2, where for time to event endpoint DR, non-event observations will be censored, and for ORR, patients with no post-baseline tumor evaluations will be counted as non-responders.

4.3.4. ECG Parameters

For analyses of ECG parameters, no values will be imputed for missing data. If one or two of the triplicate measurements for an ECG parameter are missing, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and no analyses related to this time point will be performed.

5. ANALYSES AND SUMMARIES

All summaries will be provided by hepatic function group. Patients treated on different dose levels within the same hepatic function group will be categorized by dose level (eg, Group C split into Group C1 and C2).

5.1. Primary Endpoint(s)

5.1.1. Pharmacokinetic Analysis

5.1.1.1. Pharmacokinetic Parameter Analysis Methods

Pharmacokinetic parameters will be derived from the lorlatinib and its metabolite(s) concentration-time profile as described in Table 3.

Table 3. Pharmacokinetic Parameter Derivation

Parameter	***Definition***	***Method of Determination***
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})*	*linear-log trapezoidal method*
AUC_{24}	*Area under the plasma concentration-time profile during one dosing interval (24 hours)*	*linear-log trapezoidal method*
C_{max}	*Maximum plasma concentration*	*Observed directly from data*
C_{min}	*Minimum plasma concentration*	*Observed directly from data*
T_{max}	*Time for C_{max}*	*Observed directly from data as time of first occurrence*
CL/F	*Apparent clearance*	*Dose/AUC_{24} at steady-state*
$MRAUC_{last}$	*Metabolite ratio for AUC_{last}*	*$(AUC_{last}/MW)_{metabolite}/(AUC_{last}/MW)_{lorlatinib}$*
$MRAUC_{24}$	*Metabolite ratio for AUC_{24}*	*$(AUC_{24}/MW)_{metabolite}/(AUC24/MW)_{lorlatinib}$*
MRC_{max}	*Metabolite ratio for C_{max}*	*$(C_{max}/MW)_{metabolite}/(C_{max}/MW)_{lorlatinib}$*

MW= molecular weight; F= oral bioavailiability

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

The effect of the hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test and the Reference using a one-way ANOVA model based on natural log transformed data.

One-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{24}, AUC_{last} and C_{max} of lorlatinib at steady state for each of the hepatic impairment groups (Test) to the corresponding normal hepatic function group with the same dosing schedule (Reference). Group B (Test) will be compared to Group A1 (Reference) and Group C (Test) will be compared with Group A2 (Reference). If a decision has been made to use the same dose for severe and moderate patients, the half of the control Group A2 will be matching Group C and half will be matching Group D (test), and the corresponding pairwise comparisons will be made. Additionally, Group D will be compared to Group A1 (Reference), and Group C will be compared with A1. Estimates of the mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the

model. The mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

The following PK parameters will be summarized descriptively by analyte, hepatic function group and at C1D1 and C2D1for lorlatinib and its metabolites.

Parameter	Summary statistics
AUC_{24}, AUC_{last}, C_{max}, C_{min}, CL/F, $MRAUC_{24}$, $MRAUC_{last}$, MRC_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean.
T_{max}	N, median, minimum, maximum.

Box and whisker plots for individual subject parameters (lorlatinib AUC_{24}, AUC_{last} and C_{max}) will be presented against hepatic function group by analyte and overlaid with geometric means.

PK parameter analysis set will be used for performing the analysis.

5.1.1.2. Pharmacokinetic Concentration Analysis Methods

Presentations for lorlatinib and its metabolites concentrations will include:

- listings of all plasma concentrations sorted by analyte, hepatic function group (present in heading), cycle, subject id and nominal time postdose. The listing of plasma concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- summaries of plasma concentrations by analyte, hepatic function group, cycle and nominal time, where the set of statistics will include n, mean, median, standard deviation, geometric mean, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by analyte, hepatic function group and cycle (all cycles on the same plot for each hepatic function group per scale per analyte, based on the summary of plasma concentrations by analyte, hepatic function group, cycle and time postdose).

- mean plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by analyte, hepatic function group and cycle with one side up standard deviation (all cycles on the same plot for each hepatic function group per scale per analyte, based on the summary of plasma concentrations by analyte, hepatic function group, cycle and time postdose).

- individual plasma concentration time plots against actual time postdose by analyte, hepatic function group and cycle (on both linear and semi-log scales), (there will be separate spaghetti plots for each hepatic function group per scale and will be different lines for each cycle on the same individual plots).

- median plots of the predose concentrations against day (including day 1 of cycle 2 as Day 29 on the same x-axis) by analyte and hepatic function group in order to assess the attainment of steady-state (all hepatic function group on the same plot),

- individual plots of the predose concentrations against day (including day 1 of cycle 2 as Day 29 on the same x-axis) by analyte and hepatic function group.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

PK concentration analysis set will be used for performing the analysis.

5.2. Efficacy Analyses

5.2.1. Best Overall Response

The frequency (number and percentage) of patients with BOR of CR, PR, SD, PD , non CR/non PD, and NE (not evaluable) will be provided along with a summary of the objective response rate (ORR) and the corresponding exact 95% 2-sided confidence interval using standard methods based on the binomial distribution, by hepatic function group. ORR is defined as the percent of patients with complete response (CR) or partial response (PR), that is subsequently confirmed, based on investigator evaluation, according to RECIST v1.1 (Appendix 1), relative to the response-evaluable population. Confirmed responses are those that persist on repeat imaging study at least 4 weeks after the initial documentation of response. Designation of best response of SD requires the criteria to be met at least once after the first dose of medication, at a minimum interval of 6 weeks. Since efficacy is a secondary objective in this study, tumor response derivation will not be performed programmatically and the investigator overall tumor assessment (IOTA) of best response will be used.

5.2.2. Duration of Response

Duration of response (DR) is defined as the time (in weeks) from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed, to the first documentation of objective tumor progression or death on study due to any cause, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. DR (in weeks) will be calculated as (first date of PD or death - first date of CR or PR +1)/7.02. DR will be calculated based on RE population for the subgroup of patients with a confirmed objective tumor response. The censoring rules for DR are presented as below.

Patients with inadequate baseline disease assessment are censored at the start date.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every odd-numbered cyles (6 weeks) until disease progression. while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). The allowable time window for disease assessments is ±1 week. Therefore time without adequate assessment is defined as 14 weeks (12 weeks +2 weeks). Patients lacking an evaluation of tumor response after treatment start or for whom the first on-study disease assessment occurs after Week 14 and shows progression, will also have their event time censored on the date of treatment start unless death occurs within (and including) Week 14 (in which case the death is an event).

If patients have at least 1 on-study disease assessment, PFS data will be censored on the date of the last evaluable on-study tumor assessment documenting absence of progressive disease for patients:

- Who are alive, on study, have not started anti-tumor treatment other than study medication and progression free at the time of the analysis;
- Who are given anti-tumor treatment other than the study medication and prior to documented disease progression or death on study. In this case, the last evaluable assessment prior to start of the anti-tumor treatment will be used.

For patients who have at least 1 on-study disease assessment and who have documentation of disease progression or death on study after ≥2, consecutive missed tumor assessments (ie, >14 weeks after last on-study tumor assessment), the date of censoring will be the last assessment documenting no progression prior to the missed assessments.

DR will be summarized by hepatic function group using the Kaplan-Meier method.[3] The median event time (if appropriate) and 2-sided 95% CI for the median[4] will be provided. Since the number of patients in each hepatic function group is small, and number of CR or PR would be even smaller, the use of Kaplan-Meier method may be limited and the DR will be also summarized using descriptive statistics.

5.3. Subset Analyses

None

5.4. Baseline and Other Summaries and Analyses

5.4.1. Baseline Summaries

Summaries of baseline variables, patient and disease characteristics and prior anti-cancer treatments will be provided on the safety analysis set. The summaries will be presented overall, by hepatic group and by tumor type (as appropriate). All data collected as part of screening will be listed.

The following demographic and baseline characteristics will be summarized by number and percentage:

- Gender(male, female).
- Age (<18, 18-44; 45-64, ≥65).
- Race (white, black, asian, other).
- Eastern Cooperative Oncology Group (ECOG) Performance status.

Age (continuous), height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2), will be summarized with descriptive statistics (mean, standard deviation, minimum, and maximum).

BMI (kg/m^2) is computed as weight (kg) /(height (cm)*0.01)**2

Patient characteristics at study entry such as diagnosis, and medical history will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

The number and percentage of patients in each of the following prior anti-cancer therapy categories will be tabulated:

- Patients with at least one prior non-drug treatment/surgeries;
- Patients with at least one prior radiotherapy;
- Patients with at least one prior systemic therapy.

5.4.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, efficacy, as well as for safety (adverse events and laboratory data). Frequency counts (numbers and percentages) will be supplied for subject discontinuation(s) by hepatic function group.

5.4.2.1. Patient Disposition

Discontinuation from study will be summarized using full analysis set. Discontinuation from study treatment will be summarized using safety analysis set. Patients not completing the study will be listed along with the reason for their discontinuation.

Discontinuations from study treatment due to adverse events will be identified as either related or not related to study treatment. If causality is missing the event will be considered related to treatment. If multiple events lead to study treatment discontinuation and at least one was considered related, discontinuation will be reported as related to study treatment.

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by hepatic function group.

5.4.2.2. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg., lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.4.3. Study Treatment Exposure

Drug administration of PF-06463922 will be described on the Safety Analysis set in terms of:

- Duration of Treatment in months (Last Treatment Date – C1D1 date + 1)/30.44.
- Days on drug in months (duration of treatment in days– days of interruption)/30.44.
- Overall relative dose of PF-06463922. Details for calculation of relative dose are provided in Appendix 1.

The mean, median and range will be provided for these variables by hepatic function group.

Number and percentage of patients having dose reductions /interruptions will be provided by hepatic function group. An interruption is defined as a 0 mg dose administered for more than 1 day.

5.4.4. Concomitant Medications and Non-Drug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

5.4.5. Columbia Suicide Severity Rating Scale (C- SSRS)

Individual patient data will be presented in patient data listings.

5.5. Safety Summaries and Analyses

Summaries and analyses of safety parameters will be provided based on the on-treatment period unless otherwise specified, by hepatic function group for the Safety Analysis Set. For all safety analyses, only descriptive methods will be used without any formal statistical testing.

The on-treatment period is defined as the time from the first dose of study treatment through and including 28 days after last dose or start of new anti-cancer drug therapy, whichever occurs first [minimum (28 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day)]. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period. All other safety assessments which occur on the same day as the first dose of study treatment will be considered baseline assessments.

Safety data collected outside the on-treatment period as described above will be listed but not summarized.

5.5.1. Adverse Events

An adverse event is considered treatment emergent if:

- the event occurs for the first time during the on-treatment period and was not seen prior to the start of treatment (Cycle 1 Day 1), or
- the event was seen prior to the start of treatment but increased in severity during the on-treatment period.

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will be presented by hepatic function group, by system organ class and preferred term.

Patients who withdraw from study treatment because of an AE will be listed. Patient discontinuation will be determined from the end of treatment (EOT) evaluation (where reason for termination is “Adverse Event”) and the specific AE(s) will be determined from the AE CRF page (where action taken is “Withdrawn from Study” or action taken for study drug is “Permanently Discontinued”).

Adverse events associated with permanent discontinuation of the study drug or with temporary discontinuation/dose reduction will also be summarized (taking into consideration the action taken from the CRF AE page).

Clustered adverse events will be summarized by maximum CTCAE grade and causality (all-causality and treatment-related) together with other adverse events. Adverse Events pertaining to each cluster will be summarized separately, by cluster. The clustered events are described in a list in the product’s Safety Narrative Plan maintained by the Sponsor.

All causality and treatment-related SAEs will be summarized by MedDRA SOC, preferred term and maximum CTCAE grade. Patients who experienced a SAE during the SAE reporting period will be listed for all the patients in the safety analysis set. A summary of SAEs by preferred term, maximum CTCAE grade will be presented.

Deaths will be summarized by time period (on treatment vs. during follow-up) and cause of death. Deaths that occurred on or after first dose of study medication and within 28 days after the last dose of study medication are defined as on-treatment deaths. A listing of death data will also be provided and it will include all deaths that occurred during the reporting period for deaths which starts from the signing of the informed consent to the end of the follow up period for death.

5.5.2. Laboratory Data

Hematology, biochemistry, and lipid results will be programmatically graded according to the NCI CTCAE Version 4.03.

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed on treatment for each lab assay. Worst case is defined as the maximum post-baseline CTCAE grade using scheduled and unscheduled visits. The analyses will summarize laboratory tests on the entire study period. Shift tables of baseline grade by maximum post-baseline CTCAE grade will also be presented.

Patients who developed Grade ≥3 toxicity will be listed.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, by graphically displaying post-baseline:

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN.

- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥2×ULN, ALT ≥3×ULN or AST ≥3×ULN will be provided.

5.5.3. Vital Signs

Baseline values and change from baseline values will be summarized with descriptive statistics by hepatic group and for each nominal visit over time.

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

5.5.4. Electrocardiogram

A triplicate 12-lead will be used for all ECG assessments.

All patients require a triplicate ECG measurement at screening and at each scheduled time point during treatment. A mean score is calculated for the replicate measurements having the same nominal visit, and will be reported.

QT, RR, HR, PR, QRS, QTcF (Fridericia correction), and QTcB (Bazett's correction) data will be provided by sites on the ECG page of the CRF.

The analysis of ECG results will be provided for safety analysis set patients with baseline and on-treatment ECG data by hepatic group and for each nominal visit over time. ECG measurements collected closest prior to the first dose of study drug will be used as the baseline ECG for analysis.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis as individual values obtained at unscheduled time points.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute value and changes from baseline in QT, QTcF, QTcB, HR, RR, PR, QRS after treatment by hepatic group and nominal visit.

The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated:

Absolute Value (msec)	≥450 -<480
	≥480 -<500
	≥500
Absolute Change (msec)	30-<60
	≥60

The number (%) of subjects with maximum post-dose PR interval values and maximum increases from baseline in the following categories will be tabulated:

Absolute Value (msec)	<160
	≥160 - <180
	≥180 - <200
	≥200 - <220
	≥220 - <240
	≥240 - <260
	≥260
Absolute Change (msec)	40-<60
	≥60-<80
	≥80
Relative Change from baseline	>25%

Shift tables will be provided for baseline vs worst on study PR using the categories in the above table. The effect of drug concentrations on QTc change (and PR interval) from baseline will be explored graphically.

5.5.5. Left Ventricular Ejection Fraction

LVEF% will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time. In addition, LVEF% will be summarized as frequency (number and percentage) of patients with:

- a shift from baseline normal to at least one result below the institutional lower limit of normal during the on-treatment period;
- ≥20-point decrease from baseline in LVEF%.

A patient will be included in the categories above if any post-baseline assessment (including unscheduled assessments) meet the criteria; however only post-baseline assessments which use the same method of assessment (ECHO or MUGA) as baseline will be considered.

5.5.6. Physical Examination

Individual patient data will be listed.

5.5.7. ECOG Performance Status

The ECOG shift from baseline to the highest score during the post-baseline period will be summarized by hepatic function group.

6. INTERIM ANALYSES

No formal interim analysis is planned. However, an interim PK and safety analysis will be done when 3 PK evaluable patients have been enrolled in group C1 to determine the dose regimen for groups C2 and D. Final analyses of PK and all other endpoints will follow the official database release at the end of the study. In case an early reporting of PK results is necessary, the study database will be released for final reporting of PK, safety and efficacy data after PK collection in all patients is completed. Then, a supplement report will be generated to only include additional safety and efficacy data after all patients completed the study.

7. REFERENCES

1. National Cancer Institute Phase 1 Organ Dysfunction – Hepatic Template Version 3.0, http://ctep.cancer.gov/protocolDevelopment/docs/hepatic_dysfunction_v3.doc.

2. Clopper, C., Pearson, E. S. "The use of confidence or fiducial limits illustrated in the case of the binomial". 1934; Biometrika 26: 404–413.

3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

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

8. APPENDICES

Appendix 1. Relative Dose

Overall exposure will be summarized as dose received relative to intended dose (relative dose [RD]).

Actual total dose in a cycle or overall is the sum of the actual doses of PF-06463922 received in a cycle or overall, respectively.

Relative dose [RD]: The basic intent is to evaluate dose per day factoring in dose reductions or interruptions.
Overall RD (%) = 100 × [overall actual total dose] / [intended total dose per day × number of days from C1D1 to last dose of PF-06463922].

Note:

- The Intended total daily dose of PF-06463922 remains constant; the intended dose level is fixed at the start of treatment for each hepatic group;
- What is described above remains the same for the calculations even if the intended dose level changes, per protocol, during the study.

Appendix 2. SAS Code for Analyses

An example of the PROC MIXED code for PK parameter analysis is provided below:

```
proc mixed data=tab.pk;
 class group;
 model l&var=group/s cl alpha=0.1 ddfm=KR;
 lsmeans group;
 estimate 'Moderate vs Normal' group 0 -1 0 1 /cl alpha=0.1;
 estimate 'Mild   vs Normal' group  -1 0 1 0 /cl alpha=0.1;
 ods output lsmeans=lms;
 ods output solutionf=fixedcoef;

run;

/* Letter assignments for group within the estimate statement above are as follows;

Group A1 = Normal (Reference)
Group B = Mild (Test)
Group A2 = Normal (Reference)
Group C = Moderate (Test)

Note: Group B (Test) will be compared to Group A1 (Reference) and Group C (Test) will be
compared with Group A2 (Reference)

  */;
```