# Protocol *B7461010*

## *A PHASE 1, SINGLE DOSE OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS OF LORLATINIB IN SUBJECTS WITH IMPAIRED RENAL FUNCTION*

# Statistical Analysis Plan (SAP)

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## Revision History

| Version | Date | Author(s) | Summary of Changes/Comments |
|---|---|---|---|
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## APPENDICES

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

## 2. INTRODUCTION

*In this study, the PK of lorlatinib after a single oral dose of lorlatinib will be evaluated in non-cancer subjects with normal renal function, mild renal impairment (defined as $CL_{cr}$ ≥60 mL/min and $CL_{cr}$ <90 mL/min), moderate renal impairment (defined as $CL_{cr}$ ≥30 mL/min and $CL_{cr}$ <60 mL/min), and severe renal impairment (defined as $CL_{cr}$ <30 mL/min not requiring dialysis) who are otherwise healthy. Data from this study would allow for the estimation of any changes in lorlatinib plasma exposure with varying extent of renal impairment.*

### 2.1. Study Design

*This will be a Phase 1, open-label, multi-center, single treatment study in subjects with normal renal function and varying degrees of renal impairment. Each subject will receive a single oral dose of lorlatinib administered in the fasted state.*

*This study is aimed toward enrolling approximately 32 evaluable subjects who complete the PK assessments. Subjects with the following renal function will be enrolled (Table 1).*

**Table 1. Group Assignment Based on Creatinine Clearance Estimates**

| *Group* | *Description* | *Estimated eGFR* |
|---|---|---|
| *A (n=8)* | *Normal* | *≥90 mL/min* |
| *B (n=8)* | *Mild Renal Impairment* | *≥60- <90 mL/min* |
| *C (n=8)* | *Moderate Renal Impairment* | *≥30- <60 mL/min* |
| *D (n=8)* | *Severe Renal Impairment* | *<30 mL/min and not requiring dialysis* |

*Subjects who do not complete all PK collections may be replaced to ensure 8 evaluable subjects in Groups A, B, and C and at least 4 evaluable subjects in Group D.*

*Estimated glomerular filtration rate (eGFR) will be calculated using the MDRD equation as follows:*

$$eGFR\ (mL/min/1.73m^2) = 175 \times (S_{cr,\ std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$$

*where $S_{cr, std}$ denotes serum creatinine measured with a standardized assay for serum creatinine. Note that the value of eGFR, which is directly obtained from the lab or calculated using the equation above, is generally normalized to an average body size of 1.73 $m^2$ for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtrated drugs (including secreted drugs), renal elimination capacity is related to absolute glomerular filtration rate (GFR) in mL/min. The MDRD-derived, body surface area (BSA)-adjusted value of eGFR used to obtain absolute GFR (mL/min) for renal disease classification or subject assignment into different renal disease groups should be multiplied by the individual subject's normalized body surface area (ie, measured BSA/1.73 $m^2$). The BSA of an individual will be calculated by the following formula as described below:*

$$BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$$

*In addition $CL_{cr}$ will be calculated using the Cockcroft-Gault equation as follows:*

$$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times total\ body\ weight\ (kg) \times (0.85\ for\ females)}{72 \times serum\ creatinine\ (mg/dL)}$$

*Subjects will need to demonstrate stable renal function during the screening period within approximately a 2-week timeframe prior to dosing. Stable renal function is defined as 2 eGFR values obtained at least 3 days but not more than 14 days apart being within 25% of each other. The average value of the 2 eGFR values will be used for study enrollment and initial renal function stratification. The eGFR value within 24 hours prior to lorlatinib dosing will be the value used for final subject stratification, group assignment, and PK analysis. The $CL_{cr}$ value will be recorded at the same time eGFR is determined. The $CL_{cr}$ value on Day -1 (calculated by Cockcroft-Gault equation) will be calculated and recorded.*

*In order to safeguard subject safety, this study will enroll subjects with renal impairment in a staggered fashion. A single oral dose of 100 mg lorlatinib will be administered first to subjects with mild renal impairment (Group B). After single 100 mg oral dose of lorlatinib is tolerated in at least 3 subjects with mild renal impairment, subjects with moderate renal impairment (Group C) will be enrolled one at a time and administered a single oral dose of lorlatinib. There will be an observation period of at least 1 week after dosing of the first 3 subjects to evaluate safety and tolerability. Based on the safety and tolerability of the first 3 subjects in Group B, a dose lower than 100 mg of lorlatinib may be considered for Group C, as determined by the Sponsor. After dosing of 3 moderate renal impairment subjects, the PK, safety, and tolerability will be evaluated during an observation period of at least 1 week to confirm whether the selected dose is appropriate. If yes, the remaining subjects in Group C and the subjects in severe group (Group D) will be enrolled and dosed at the same dose. If not, a new, lower dose will be proposed for the remaining subjects in Group C and all subjects in Group D based on available information.*

*Subjects with normal renal function (Group A) will be matched to the subjects with renal impairment (Groups B, C, and D) and will receive a single oral lorlatinib dose corresponding to the dose level(s) administered in this study with respect to demographically pooled average age (±10 years), weight (±20 kg), and gender (ratio 1:1, ±2 patients per gender). Therefore, enrollment of Group A will begin after all subjects from Groups B, C, and D have completed the PK collection. If a reduced lorlatinib dose is necessary for any renal impaired group(s), an additional control group will be added to match the reduced dose using the same match criteria of average age, weight, and gender.*

### 2.2. Study Objectives

**Primary Objective**

- *To evaluate the effect of renal impairment on the single dose pharmacokinetics of lorlatinib on otherwise healthy subjects.*

**Secondary Objective**

- *To evaluate the safety and tolerability of a single dose of lorlatinib in healthy subjects and subjects with renal impairment.*

**Tertiary Objective**

- *To evaluate the pharmacokinetics of lorlatinib metabolite(s) in healthy subjects and subjects with renal impairment who are otherwise healthy.*

**Exploratory Objective**

- CCI [redacted]

## 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis will be conducted for this study. Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

No hypotheses are required.

### 4.2. Statistical Decision Rules

No decision rules are required.

# 5. ANALYSIS SETS

## 5.1. Pharmacokinetic (PK) Analysis Set

### 5.1.1. Concentration Analysis Set

*The PK concentration population is defined as all subjects enrolled and treated and who have at least 1 lorlatinib plasma concentration.*

### 5.1.2. Parameter Analysis Set

*The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest.*

## 5.2. Pharmacodynamic Analysis Set

None.

## 5.3. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

## 5.4. Other Analysis Sets

None.

## 5.5. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are allocated but not treated.

## 5.6. 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.

### 5.6.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

### 5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

# 6. ENDPOINTS AND COVARIATES

## 6.1. Efficacy Endpoint(s)

None.

## 6.2. Safety Endpoints

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events;*
- *laboratory data;*
- *vital signs data;*
- *ECG results.*

## 6.3. Other Endpoints

### 6.3.1. PK Endpoints

Blood and urine samples for PK analysis of PF-06463922 (and its metabolite) will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06463922 and the PF-06895751 metabolite (if possible) from the concentration-time data using standard noncompartmental methods:

**Table 2. Noncompartmental PK Parameters**

| Matrix | PK Parameter | Analysis Scale | PF-06463922 | PF-06895751 |
|---|---|---|---|---|
| Plasma | $AUC_{inf}$* | ln | A, D | D |
| | $AUC_{last}$ | ln | A, D | D |
| | $C_{max}$ | ln | A, D | D |
| | $MRAUC_{inf}$* | ln | NA | D |
| | $MRAUC_{last}$ | ln | NA | D |
| | $MRC_{max}$ | ln | NA | D |
| | $T_{max}$ | R | D | D |
| | $t_{1/2}$* | R | D | D |
| | $CL/F$* | ln | A, D | D |
| | $V_Z/F$* | ln | D | D |
| Urine | $CL_R$ | ln | A, D | NA |
| | Ae | R | D | NA |
| | Ae(%) | R | D | NA |

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, MR=Metabolite (PF-06895751) to parent ratio of,ln=natural-log transformed, R=raw (untransformed), *=if data permits.

### 6.3.2. PD Endpoints

None.

### 6.4. Covariates

None.

## 7. HANDLING OF MISSING VALUES

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

### 7.1. 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.)

### 7.2. 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.

### 7.3. 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 be presented for a particular renal function group with ≥3 evaluable measurements. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

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 compound is adequately 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.

## 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 8.1. Statistical Methods

The relationship between PK parameters and renal function (eGFR) will be determined by a linear regression model.

The effect of the renal impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (renally impaired groups) and the Reference (normal renal function group) using a one-way ANOVA model based on natural log transformed data.

### 8.2. Statistical Analyses

*Analysis of variance (ANOVA) will be used to compare the natural log transformed $AUC_{inf}$ (if data permit), $AUC_{last}$ and $C_{max}$ between the normal renal function group and each of the renal impairment groups.* If a mixture of doses are used within the study, then the previous analysis will utilize dose normalized PK parameters instead. *Point estimates and associated 90% confidence intervals (CIs) for the difference of each comparison will be estimated and exponentiated to provide geometric mean ratios and associated 90% CIs.*

*Regression analysis will be conducted to characterize the relationship between renal function and PK parameters CL/F and $CL_R$. Both eGFR obtained from the MDRD equation and $CL_{cr}$ calculated from the C-G formula on Day -1 will be used in regression analysis. Analysis results will include estimates of parameters for the chosen model as well as measures of precision such as CI or standard errors. PK parameters $AUC_{inf}$, $C_{max}$, $AUC_{last}$, time for $C_{max}$ ($T_{max}$), terminal plasma elimination half-life ($t_{½}$), CL/F, $CL_R$, $V_z$/F, cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose (Ae), cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose, expressed as fraction of administered dose (Ae%), will be summarized descriptively by analyte (eg, lorlatinib and its metabolite(s)) and renal function group.*

*Metabolite(s) to parent ratio for $C_{max}$ ($MRC_{max}$), metabolite(s) to parent ratio for $AUC_{last}$ ($MRAUC_{last}$), and metabolite(s) to parent ratio for $AUC_{inf}$ ($MRAUC_{inf}$) will also be summarized descriptively by renal function group.*

*For $AUC_{inf}$, $AUC_{last}$ and $C_{max}$, box-whisker plots of the parameters will be plotted by analyte and renal function group and overlaid with geometric means. Individual concentrations will be listed and summarized descriptively by group and PK sampling time. Individual subject and summary profiles (means and medians) of the concentration-time data will be plotted across different groups.*

*For summary statistics and summary plots by renal function group and sampling time, the nominal PK sampling time will be used; for individual subject plots by time, the actual PK sampling time will be used.*

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 by renal function group:

**Table 3. PK Parameters to be Summarized Descriptively by Group**

| Parameter | Summary Statistics |
|---|---|
| $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $MRAUC_{last}$, $MRAUC_{inf}$, $MRC_{max}$, $CL_R$, CL/F and $V_Z$/F | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |
| $t_{1/2}$, Ae, Ae(%) | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum. |

Supporting data from the estimation of $t_{½}$ and $AUC_{inf}$ will be listed by analyte and group: terminal phase rate constant ($k_{el}$); goodness of fit statistic from the log-linear regression ($r^2$); the percent of $AUC_{inf}$ based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of $k_{el}$. This data may be included in the clinical study report.

Presentations for PF-06463922 concentrations and any metabolite(s) will include:

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

- a summary of concentrations by renal function group and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by renal function group (all renal function groups on the same plot per scale, based on the summary of concentrations by renal function group and time postdose).

- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by renal function group (all renal function groups on the same plot per scale, based on the summary of concentrations by renal function group and time postdose).

- individual concentration time plots by renal function group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each renal function group per scale).

- a listing of all urine concentration interval sorted by renal function group (present in heading), subject ID and nominal collection duration postdose.

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.

### 8.3. Safety Analysis

A set of summary tables split by renal function group will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06463922.

#### 8.3.1. Treatment and Disposition of Subjects

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

Data will be reported in accordance with the sponsor reporting standards.

#### 8.3.2. Demographic and Clinical Examination Data

A break-down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

#### 8.3.3. Discontinuation(s)

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

Data will be reported in accordance with the sponsor reporting standards.

#### 8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by renal function group.

#### 8.3.5. Laboratory Data

The baseline measurement is the last planned pre-dose measurement.

For each planned time point, baseline values and change from baseline values within each treatment group will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

#### 8.3.6. Vital Signs Data

Supine blood pressure and pulse rate will be measured at the time points as per the schedule of activities mentioned in the protocol.

The baseline measurement is the last predose measurement.

For each planned time point, baseline values and change from baseline values within each renal function group will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

### 8.3.7. ECG Data

The baseline measurement is the last planned predose triplicate measurement.

The average of the replicate readings collected at each assessment time will be calculated prior to summarizing the data across subjects.

Baseline values and *changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by treatment group and time.*

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

| | ***Borderline (msec)*** | ***Polonged (msec)*** |
|---|---|---|
| *Absolute value* | *--* | *≥480* |
| *Absolute change* | *30-<60* | *≥60* |

*In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.*

*The number (%) of subjects with maximum post-dose PR interval values, maximum increases from baseline and second degree atrioventricular block (AVB) type 2 or higher in the following categories will be tabulated by renal function group as below:*

| | ***Msec*** |
|---|---|
| *Absolute Value* | *≥200 - <220* |
| | *≥220 - <240* |
| | *≥240 - <260* |
| | *≥260* |
| *Absolute Change* | *40 - <60* |
| | *60 - <80* |
| | *≥80* |
| *Relative Change from baaseline* | *>25%* |
| *Second-degree AVB type 2 or higher*[a] | |

[a]*: Second degree block type 2 or higher would be determined by the ECG machine and confirmed by a physician.*

These data will be listed in accordance with the sponsor reporting standards.

### 8.3.8. Other Safety Data

*Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be reported* in the Clinical study report.

### 8.3.9. Concomitant Treatments

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

### 8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, serum or urine B-hCG for all females of childbearing potential, urine or blood cotinine concentration, HIV, HepBsAg, HepBcAb, and HCVAb testing will be obtained at Screening.

These data will not be brought in-house, and therefore will not be listed.

### 8.3.11. Analysis of Other Endpoints

Pharmacogenomic and biomarker data will be collected and retained for future analyses, but will not be analyzed or reported for this study.

## 9. REFERENCES

1. FDA Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. 05/98.

2. PF-06463922 Investigator's Brochure 2016.

# 10. APPENDICES

## Appendix 1. SAS CODE FOR ANALYSES

CCI