Protocol B7461001

Phase 1/2 Study of PF-06463922 (an ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations

Statistical Analysis Plan
(SAP)

Version: **6.0**

Date: **15-MAR-2019**

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7461001 is based on the Protocol Amendment 6, dated 15 July 2016.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	List major changes: - Endpoints - Analysis Sets - Hypothesis and decision rules - Analyses on all efficacy endpoints - Added analysis according to Investigator Assessment and Independent Central Review - Detailed analyses to be performed pooling patients in different subgroups - Added descriptions of analyses to be performed on EXP-1 patients continuing treatment with crizotinib - Updated PK sections - Updated TO sections - Updated PRO section	Updated SAP to match changes in study design and analysis as detailed in Protocol Amendment 3 and 4, with particular emphasis on analysis of Phase 2 part of the trial.

SAP Version	Change	Rationale
3	List major changes: - revised analyses related to Investigator Assessment and Independent Central Review - revised Analysis Sets used for efficacy analyses - added definition of Intent-To-Treat Analysis Sets - excluded from the Evaluable for Response Per Protocol Analysis Sets those patients missing data on ALK or ROS1 rearrangement - added Spider Plots - added pooling of patients in subgroup EXP-4:EXP-5 as recommended by the FDA - detailed analyses to be performed pooling patients in different subgroups - added analysis of Cumulative Incidence of CNS/Non CNS/Deaths and removed analysis of IC-TTP and EC-TTP - added analysis of TTP for prior therapies - detailed analysis on Japanese Lead-In Cohort - added details on Relative Dose calculations	Need to integrate efficacy analysis due to feedback received from the FDA about possible registration strategy Added details/clarifications/ algorithms

SAP Version	Change	Rationale
4	List major changes: - addition of Drug-Drug interaction (DDI) and Holter Monitoring in parallel with the ongoing Phase 2 part of the study - Study Endpoints, Study Objectives, and the Statistical Analysis section updated to support the DDI and Holter monitoring - adjustment in the sample sizes of ALK-positive patient subgroups being studied in Phase 2 - added pooling of patients in subgroup EXP-2:EXP-3 - increase in overall sample size in Phase 2 and overall sample size in the study - added details about analysis of Probability of first event being a CNS progression, non CNS progression, or death - added analysis of IC-TTP - added eDISH plots - changes to the algorithm to define Adequate Baseline Tumor Assessments-added details to algorithm to determine ALK or ROS1 rearrangement status - other minor clarifications throughout the document	Updated SAP to match changes in study design and analysis in Phase 2 part of the trial as detailed in Protocol Amendment 6.

SAP Version	Change	Rationale
5	List major changes: - Removed Evaluable for Response analyses for phase 1 and phase 2 - Included patient receiving only Day -7 in ITT -added Per Protocol Analysis Set definition - added efficacy analyses on subgroups EXP-3A:3B - added analysis of DCR at 24 weeks - added details in Pharmacokinetic analysis and Biomarker analysis - added Concordance assessment between ROS1+ local test result and central test result - updated details on Relative Dose calculations in Appendix 4 Added details and clarifications through the document	
6	List major changes: - Revised ITT definition - removed pooling of patients in subgroups EXP-1:EXP-5 and EXP-2:EXP-3 and added pooling of patients in subgroup EXP-2:EXP-3A and EXP-3B:EXP-5 - added description of analyses to be conducted on DDI substudy - Added clarifications on the evaluation of Disease Control Rate at 12 and 24 weeks.	Updated SAP to match changes detailed in Protocol Amendment 8 and to provide clarification for additional analyses in patient subsets and DDI substudy.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7461001.

2.1. Study Objectives

Phase 1

Primary Objective:

- To assess safety and tolerability of PF-06463922 as a single agent at increasing dose levels in patients with advanced ALK+ or advanced ROS1+ NSCLC in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary objectives:

- To evaluate the overall safety and tolerability of PF-06463922.
- To evaluate the single- and multiple-dose PK profiles of single-agent PF-06463922.
- To detect early signs of cognitive dysfunction.
- To evaluate patient reported outcomes (PRO) of global Quality of Life (QOL) functioning, and the impact of PF-06463922 on disease/treatment-related symptoms of lung cancer.
- To evaluate the potential of single-agent PF-06463922 to cause CYP3A inhibition/induction using midazolam as a probe.
- To characterize the effects of single-agent PF-06463922 on the QTc interval.
- To evaluate tumor and blood-based molecular markers of response and resistance to single-agent PF-06463922.
- To characterize the effect of food on PF-06463922.
- To evaluate preliminary anti-tumor activity of single-agent PF-06463922 in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC
- To evaluate response to prior therapies

Exploratory objectives:

- To explore the brain penetration of single-agent PF-06463922.

Phase 2

Primary Objective:

- To evaluate overall (intra- and extracranial) and intracranial anti-tumor activity of single-agent PF-06463922 at RP2D in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC.

Secondary Objectives:

- To confirm the safety and tolerability of single-agent PF-06463922 at the RP2D.
- To confirm single- and multiple-dose PK profiles of single-agent PF-06463922 at the RP2D.
- To assess secondary measures of clinical efficacy.
- To detect early signs of changes in mood, cognitive function, or suicidal ideation and behavior (SIB).
- To evaluate patient reported outcomes (PRO) of global QOL, functioning and the impact of PF-06463922 on disease/treatment-related symptoms of lung cancer at the RP2D.
- To further evaluate the effects of single-agent PF-06463922 at the RP2D on the QTc interval.
- To further evaluate tumor and blood-based molecular markers of response and resistance to single-agent PF-06463922 at the RP2D.
- To evaluate the safety and efficacy of single-agent crizotinib following PF-06463922 in treatment-naïve patients with advanced ALK+ NSCLC.
- To evaluate response to prior therapies.

Exploratory objectives:

- To explore the brain penetration of single-agent PF-06463922 at the RP2D.

Japanese Patient Only Lead-In Cohort (LIC)

- To evaluate the safety and tolerability of PF-06463922 in Japanese Patients before starting enrollment of Japanese Patients in Phase 2 portion of the study.

Drug-drug Interaction (DDI)/Holter Monitoring Study

- To evaluate the potential of PF-06463922 to inhibit/induce CYP2B6, CYP2C9, P-gp, and select Glucuronosyltransferases (UGT) isoforms.
- To characterize the effects of PF-06463922 on Electrocardiogram (ECG) endpoints.

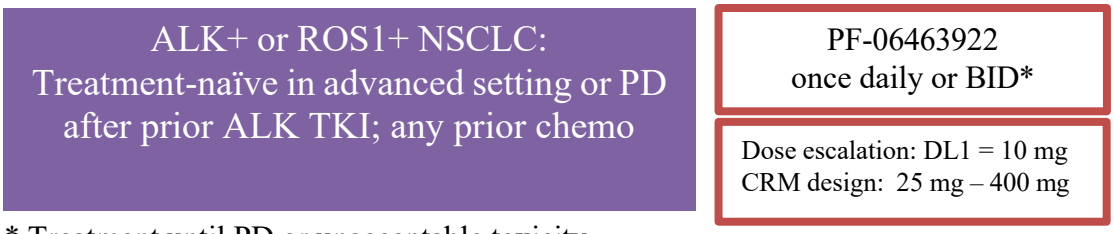
- To characterize the safety and efficacy of PF-06463922 of patients entering the DDI/Holter monitoring study.

2.2. Study Design

This is a Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, PD and anti-cancer efficacy exploration study of PF-06463922 as a single agent in patients with advanced ALK+ or advanced ROS1+ NSCLC. This clinical study will consist of 2 parts, Phase 1 and Phase 2.

Figure 1. Study Schema

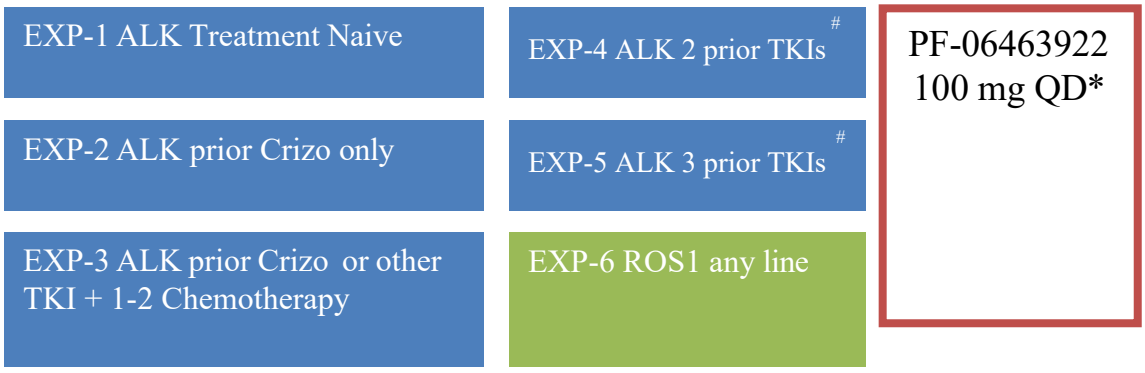
Phase 1:



* Treatment until PD or unacceptable toxicity

The dose of 100 mg was the RP2D defined from the Phase 1 portion of the study.

Phase 2:



- Asymptomatic brain metastases allowed in all cohorts.
- Preplanned analysis for Phase 2 ALK+ NSCLC patients with brain metastases.

* Treatment until PD or unacceptable toxicity

In EXP-4/EXP-5 Prior 2 or 3 TKIs refers to **line** of therapy. For example, if the same TKI were given twice, that would be considered as 2 prior lines of treatment. Any number of lines of prior chemotherapy is allowed.

The Phase 1 portion of the study will estimate the MTD for single-agent PF-06463922 in dose escalation cohorts in patients with advanced ALK+ or advanced ROS1+ NSCLC with or without asymptomatic CNS metastases, and will enroll approximately 36 patients (depending on toxicities observed). Additional patients (approximately 15) beyond 36 may

be enrolled to better characterize RP2D, which could include safety, PK, alternative dosing schedules (if applicable), food effect, etc.

To understand the single-dose pharmacokinetics (PK) of PF-06463922, a lead-in period preceding the continuous daily dosing will be conducted. A single lead-in dose of PF-06463922 will be given on Day -7. No trial drug will be administered during the interval between the lead-in single dose and Day 1 of the first cycle.

The Phase 2 will evaluate the anti-cancer activity of single-agent PF-06463922 in multiple subpopulations of patients with advanced ALK+ NSCLC and patients with advanced ROS1+ NSCLC and will allow to better define the safety, PK and pharmacodynamic profiles of single-agent PF-06463922 at the RP2D. Additionally, at the discretion of the treating investigator and if clinically indicated, patients who are ALK inhibitor treatment naïve at baseline (ie, part of EXP-1 subpopulation) and who discontinue PF-06463922 due to reasons other than withdrawal of consent may be eligible to receive single-agent crizotinib. At the time of PF-06463922 discontinuation, patients who are eligible to receive crizotinib will undergo a brief Screening period to ensure inclusion and exclusion criteria are met and required assessments are performed.
The Phase 2 will enroll approximately 260 patients and will include patients from the following subpopulations:

- EXP-1: Treatment-naïve patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases. (targeting 30 patients). No prior chemotherapy is allowed in the metastatic setting. In those countries where standard of care does not allow for treatment-naïve ALK+ NSCLC patients to receive PF-06463922 in the first-line treatment setting, patients will not be enrolled into EXP-1 subgroup. EXP-1 patients may be eligible to receive single-agent crizotinib following treatment with PF-06463922 if allowed per local guidelines and appropriate per investigator discretion.

- EXP-2: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after only crizotinib therapy. (targeting 80 patients between EXP-2 and EXP-3A-EXP-3B combined). No prior chemotherapy is allowed in the metastatic setting.

- EXP-3: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after crizotinib therapy and 1 or 2 prior regimens of chemotherapy given before or after crizotinib therapy [EXP-3A] **OR** patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor therapy other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting [EXP-3B] (as above, targeting 80 patients between EXP-2 and EXP-3 A -EXP-3B combined).

- EXP-4: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 2 prior lines of ALK inhibitor therapies. (targeting 70 patients). Patients may have had any number of prior chemotherapy regimens in any disease setting.

- EXP-5: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 3 prior lines of ALK inhibitor therapies. (targeting 40 patients). Patients may have had any number of prior chemotherapy regimens in any disease setting.

- EXP-6: Patients with advanced ROS1+ NSCLC who are treatment naïve or have had any number of prior cancer therapies. (targeting approximately 40 patients). Patients may or may not have asymptomatic CNS metastases In those countries where standard of care does not allow for treatment-naïve ROS1+ NSCLC patients to receive PF-06463922 in the first-line treatment setting, patients will not be enrolled into EXP-6 treatment-naïve subgroup.

Approximately 340 patients (Phase 1, Phase 2, and DDI and Holter monitoring study) are expected to be enrolled in the study overall.

After the collection of data for the evaluation of primary objective is completed, and most of the secondary endpoints characterized, data recording will be limited to adverse events, with the purpose of performing long term safety assessments and overall survival. At the end of treatment the biological samples will be collected for translational analysis.

The Independent Central Radiology review will be stopped with implementation of Protocol Amendment 8, as the data collection required for the primary and secondary endpoints is deemed sufficient.

To evaluate the safety and tolerability of PF-06463922 in Japanese patients, a Japanese patient only lead-in cohort (LIC) will be enrolled to evaluate PF-06463922 safety and PK in Japanese patients treated at a previously tested dose in Phase 1. The LIC will be conducted at Japanese sites concurrently with the Phase 2 portion of the study but will be considered separate from Phase 2 enrollment. A minimum of 3 Japanese patients will be enrolled into the LIC. Japan will participate in Phase 2 after completion (DLT evaluation) of LIC. Patients enrolled into the LIC will follow the same eligibility criteria, study procedures (unless otherwise specified), and patient withdrawal criteria as outlined in Phase 2. The PF-06463922 starting dose for the LIC will be communicated by letters to the investigators after identification of the RP2D in Phase 1. Following 1 cycle of dosing, a safety review will be performed. If, based on the safety profile in the first cycle of treatment, PF-06463922 is shown to be tolerable in Japanese patients, then Japan sites will join the Phase 2 portion of the study.

To evaluate the potential interaction between PF-06463922 and drugs that are metabolized or transported via pathways that include CYP2B6, CYP2C9, P-gp, and select UGT isoforms, a drug-drug interaction (DDI) study will be conducted in approximately 30 (to get at least 6 PK evaluable patients for each of the 4 probe substrates) patients who meet the prior treatment requirements of EXP groups 2-6. Additionally, within this study, an evaluation of the effects of PF-06463922 on the PR interval will be conducted via continuous Holter telemetry. A time matched comparison will be done for the PR interval at baseline (approximately 10 time points) to the PR intervals following a single dose of PF-06463922 and the PR interval following multiple dosing. In addition, arrhythmia analysis will be performed using Holter

Monitoring data from these patients. This study will be analyzed separately from Phase 1 and Phase 2 data.

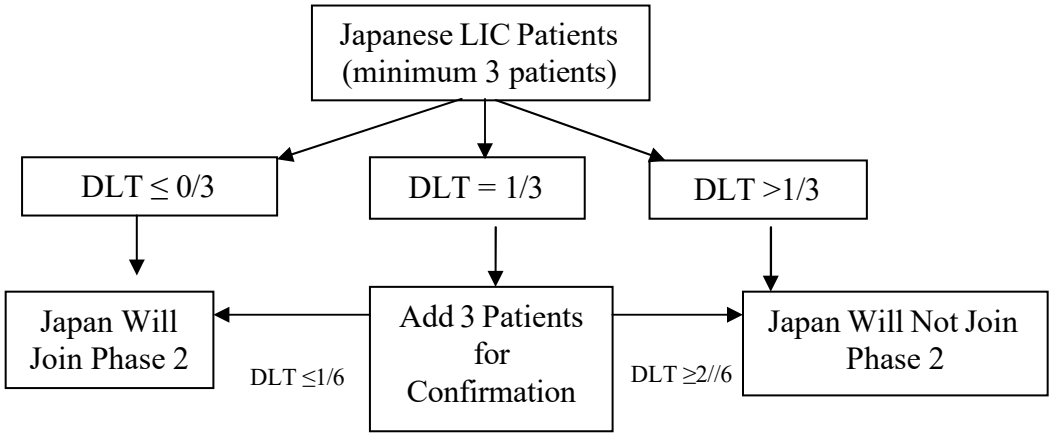
In all study parts, PF-06463922 will be administered orally once daily (QD) (or twice daily [BID] dosing in Phase 1) continuously in 21-day cycles. When BID dosing is used, the choice of BID dose levels will be evaluated based on emerging safety and PK data. Patients will self-administer PF-06463922 in the outpatient setting. On the days of PK sample collections, PF-06463922 will be administered in the clinic. The PF-06463922 starting dose in Phase 1 will be 10 mg.

For each dose level in Phase 1, patients will be enrolled in cohorts of minimum 3 patients (unless 2 DLTs are observed in the first 2 patients tested at that dose level). If toxicity is observed at the first dose level, then a lower dose level (Dose Level -1) may be tested.

2.2.1. Japanese Patient Lead-In Cohort (Japan Sites Only)

To date, there is no documented experience with PF-06463922 in Japanese patients. Therefore, to evaluate the safety and tolerability of PF-06463922 in Japanese patients, this study will include a Japanese patient lead-in cohort (LIC) to evaluate PF-06463922 safety and PK of in Japanese patients treated at a previously tested dose in Phase 1. The LIC will be conducted at Japanese sites concurrently with the Phase 2 portion of the study but will be considered separate from Phase 2 enrollment. Japan will participate in Phase 2 after completion (DLT evaluation) of LIC. Patients enrolled into the LIC will follow the same eligibility criteria, study procedures (unless otherwise specified), and patient withdrawal criteria as outlined in Phase 2. Initially up to 3 patients will be enrolled and treated. If a DLT is observed in 1 of the initial 3 treated patients, then 3 additional patients will be enrolled and treated. Patients who discontinue treatment before completing Cycle 1 (ie, the DLT observation period) or receive less than 16 of the planned 21 PF--06463922 doses for reasons other than treatment-related toxicity (eg, missed appointments, misplaced study drug supplies, development of coexisting medical condition rendering the patient unable to swallow medication, development of rapidly progressing disease) will be replaced for DLT evaluation but will remain in the overall safety and efficacy analyses. If ≤33% patients experience DLT (0/3 or 1/6), then the tested dose would be considered tolerable in Japanese patients, and the Phase 2 portion of the study will be opened to Japan sites. If >33% patients experience DLT, then Japan sites will not join the Phase 2 study and a lower dose cohort may be explored if deemed necessary. Additional patients may be included for further safety and tolerability assessments in the LIC as appropriate.

Figure 2. Japanese Patient-Only Lead-In Cohort Schema

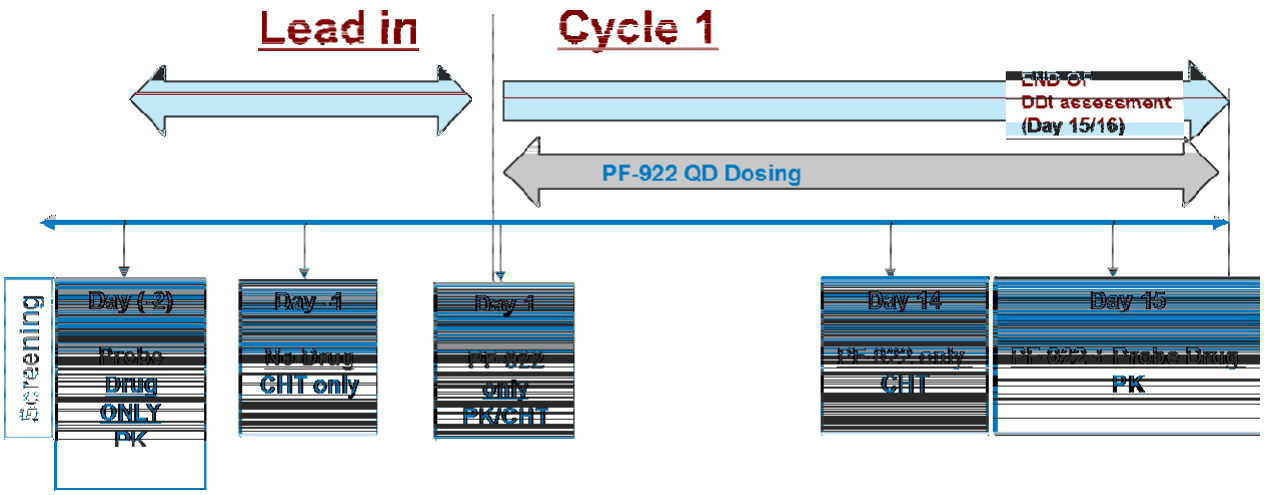


2.2.2. Drug-Drug Interaction (DDI) and Holter Monitoring Study

For evaluation of the drug interaction potential of PF-06463922, approximately 30 patients (to obtain at least 6 PK evaluable patients for each of the 4 drug probes) will be administered a single dose of the probe substrate alone on Day -2 to determine the exposure of the probe substrate when given without PF-06463922. Starting on Cycle 1 Day 1, patients will begin

daily dosing of 100 mg PF-06463922 QD. On Cycle 1 Day 15, another single dose of the probe substrate will be administered concurrently with PF-06463922.

In consultation with the sponsor and based on the co-medications the patients is expected to use concurrently with the probe substrate during the DDI portion (or within 2 weeks prior to first dose of probe substrate); at least 6 patients will be assigned to take each of the probe substrates listed below. Subjects who withdraw prior to completion of the Cycle 1 Day 15 DDI assessment or have inadequate assessments for DDI evaluation for any probe substrate may be replaced at the sponsor's discretion (up to a maximum of two).



PF-922= PF-06463922
CHT= continuous holter monitoring

Probe Drugs

Enzyme/ Transporter	Suggested Probe
CYP2B6	Bupropion (100-mg single dose)
CYP2C9	Tolbutamide (500-mg single dose)
UGT	Acetaminophen (500-mg single dose)
Pgp	Fexofenadine (60-mg single dose)

Additionally, continuous Holter telemetry of subjects enrolled in this study will be used to evaluate the effect of PF-06463922 on the PR interval by comparing the patient's pre-drug baseline with PR interval observations associated with exposure of PF-06463922 following a single dose and at steady state. Twenty-four hour Holter monitoring will be conducted on Day -1 through Cycle 1 Day 1, and again on Cycle 1 Day 14. On Day -1, the 24-hour Holter monitoring will begin approximately 24 hours after probe substrate administration on Day -2. On Cycle 1 Day 14, 24-hour Holter monitoring will begin immediately prior to PF-06463922 administration. It is assumed that any inhibition as well as induction of metabolic enzymes/transporters due to PF-06463922 will be completed within 15 days of continuous dosing of PF-06463922.

This study will be conducted in approximately 10 participating Phase 2 sites and will begin and conclude upon official notification by the sponsor via letter or email. At the time of registration, sites will inform Pfizer what concomitant medications a patient is receiving and what drug probe is suggested. Patients in the DDI and Holter monitoring study will meet the same inclusion and exclusion criteria as required for the main study, with some additional criteria specified specifically in the B7461001 Protocol, Section 4.2. Additionally, patients will only be eligible to participate if they meet the prior treatment requirements of EXP groups 2-6.

The results of this study will be presented in the Final CSR, separately from Phase 1 and Phase 2.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Phase 1 Primary Endpoint:

- Cycle 1 Dose-Limiting Toxicities (DLTs).

Phase 2 Primary Endpoint:

- Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. In patients with asymptomatic CNS metastases, up to five (5) intracranial target lesions in addition to the five (5) extracranial target lesions will be assessed.

3.2. Secondary Endpoint

All patients unless otherwise indicated:

- Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy.
- Laboratory abnormalities as characterized by type, frequency and severity (as graded by NCI CTCAE v.4.03).
- Left Ventricular Ejection Fraction (LVEF).
- Vital Signs (heart rate, blood pressure).
- Total Mini-Mental State Examination Score [Phase 1 only].
- Mood assessment, Cognitive Function assessment, Suicidal Ideation and Behavior assessment [Phase 2 only].
- Pharmacokinetic parameters of PF-06463922: Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and Vz/F and $t_{1/2}$, AUC_{inf} as data permit. Multiple Dose (assuming

steady-state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, Vz/F, Rac ($AUC_{ss,\tau}/AUC_{sd,\tau}$) and Rss ($AUC_{ss,\tau}/AUC_{sd,inf}$) as data permit. Phase 1 only: urine PK parameters (Ae%, and CLR) of PF-06463922 from MDZ and food effect substudy.

- Pharmacokinetic parameters of midazolam: C_{max}, T_{max}, AUC_{last}, CL/F, and Vz/F and $t_{1/2}$, AUC_{inf} as data permit [Phase 1 only].
- Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL.
- QTc interval.
- Disease Control Rate (DCR) at 12 and 24 weeks defined as the percent of patients with a confirmed complete response (CR), confirmed partial response (PR) or stable disease (SD) according to RECIST 1.1 at 12 and 24 weeks.
- Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 [Phase 1 only – primary endpoint in Phase 2]. In patients with asymptomatic CNS metastases, up to 5 intracranial target lesions in addition to the 5 extracranial target lesions will be assessed.
- Time-to-event endpoints: Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DR), and Time to Tumor Response (TTR).
- Probability of first event being a Central Nervous System (CNS) progression, non CNS progression, or death.
- Time to Progression (TTP) [Phase 2 only].
- Response to prior systemic therapies
- Selected molecular profiling of tumor tissue, e.g., ALK kinase domain mutations and circulating nucleic acid (CNA), e.g., ALK kinase domain mutations.

Phase 2 patients with ALK+ NSCLC receiving single-agent crizotinib following first-line treatment with PF-06463922:

- Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy.
- Laboratory abnormalities as characterized by type, frequency, and severity (as graded by NCI CTCAE v.4.03).
- Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1, and time-to-event endpoints including PFS, DR, TTR and OS.

3.3. Other Endpoints

Phase 1 Exploratory Endpoints:

- Time to Progression (TTP)

Phase 1 and 2 Exploratory Endpoints:

- Cerebral Spinal Fluid (CSF) concentration of PF-06463922.

Endpoints for Japanese Patient Only Lead-in Cohort (LIC)

- Cycle 1 Dose Limiting Toxicities (DLTs).

Endpoints for Drug-drug Interaction (DDI)/Holter Monitoring Study

- Pharmacokinetic parameters (as data permit) for probe substrate after single oral administration with or without PF-06463922: Plasma AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, CL/F, V_z/F and $t_{1/2}$.

- Pharmacokinetic parameters (as data permit) for relevant probe substrate metabolite(s) and PF-06463922 metabolite(s): Plasma and AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$, MRC_{max}, $MRAUC_{inf}$, and $MRAUC_{last}$.

- PR and other ECG measurements with PF-06463922 treatment.

3.4. Baseline Variables

For Phase 1 the main baseline variables will be

- ALK or ROS1 rearrangement status (derivation details provided in Appendix 3.1).

- number of prior ALK/ROS1-TKI (none, 1, at least 2)

In Phase 2, patients will be attributed to specific subgroups (EXP-1:EXP-6) based on prior treatment received, and analyzed accordingly.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (Day -7 for the patient receiving lead-in dose in Phase 1 or Phase 2, C1D1 for all other patients), or

- the event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. An infinite lag will be used for the study.

An exception to infinite lag is adopted for adverse events occurring during treatment with PF-06463922 on the EXP-1 patients who then receive crizotinib following PF-06463922. In that case the lag stops on date of start of treatment with crizotinib. However, for SAEs deemed related to lorlatinib by the investigator the timeframe for collection remains 28 days after discontinuing lorlatinib independently from start of crizotinib, allowing to attribute causality to both drugs.

3.5.2. Laboratory Data

Lab assessments performed on or prior to first dose of treatment (Day -7 for patients receiving Day -7 Lead-in dose, Cycle 1 day 1 for the other patients) will be attributed to baseline. All other assessments will be considered as occurred on treatment.

4. ANALYSIS SETS

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

4.1. Full Analysis Set

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

4.2. Intention-To-Treat Analysis Set (ITT)

The ITT analysis set includes all enrolled patients with an ALK or ROS1 rearrangement as per local test results and who received at least one dose of study medication (including Day-7 Lead-in dose).

4.3. Per Protocol Analysis Sets

Patients with CNS metastases based on Investigator Assessment

Subset of the ITT analysis set including only patients with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to Investigator Assessment

Patients with CNS metastases based on Independent Central Review

Subset of the ITT analysis set including only patients with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to Independent Central Review

Phase 1

Evaluable for MTD

All enrolled patients who receive at least 75% of the planned PF-06463922 doses in the first cycle (ie 16 dosing days). Patients who receive less than 75% of the planned PF-06463922 doses in the first cycle due to DLT are also considered evaluable for MTD.

4.4. Safety Analysis Set (SA)

The safety analysis set includes all enrolled patients who receive at least one dose of PF-06463922 (including Lead-in dose).

In the Japanese Patients Lead-in Cohort of Phase 2 the Safety Analysis Set is a Subset of Safety Analysis Set including only Japanese Patients entered in the Lead-In Cohort described in Study Protocol section 3.2. (Japanese patients enrolled into the LIC will be analyzed separately from patients enrolled in the main part of the study.)

4.5. Other Analysis Sets

4.5.1. PK Concentration Analysis Set

4.5.1.1. PF-06463922

The PK concentration analysis set of PF-06463922 is defined as all patients treated (including Day -7 dose) who have at least 1 concentration of PF-06463922.

4.5.1.2. Midazolam (Phase 1 only)

The PK concentration analysis set of midazolam is defined as all patients treated with midazolam (including Day - 7 dose) who have at least 1 concentration of midazolam.

4.5.1.3. DDI Probe Substrates

The PK concentration analysis set of the DDI probe substrates (bupropion, tolbutamide, acetaminophen, or fexofenadine) is defined as all patients treated with the probe substrate (on lead-in Day -2 and Cycle 1 Day 15) who have at least 1 concentration of the probe substrate or relevant probe substrate metabolite(s).

4.5.2. PK Parameter Analysis Set

4.5.2.1. PF-06463922

The PK parameter analysis set is defined as all enrolled patients who receive at least one dose of PF-06463922 (including Day -7 dose) and have sufficient information to estimate at least 1 of the PK parameters of interest (C_{max} or AUC) for PF-06463922.

4.5.2.2. Midazolam (Phase 1 only)

The midazolam analysis set includes patients who have received at least one dose of midazolam and for which at least 1 midazolam PK parameter of interest (C_{max} or AUC) is available.

4.5.2.3. DDI Probe Substrates

The PK parameter analysis set of the DDI probe substrates is defined as all enrolled patients who receive at least one dose of the probe substrate (bupropion, tolbutamide, acetaminophen, or fexofenadine) and have sufficient information to estimate at least 1 of the PK parameters of interest (C_{max} or AUC) for the probe substrate and probe substrate metabolite(s).

4.5.3. CNA Peripheral Blood Analysis Set

The circulating nucleic acid (CNA) Peripheral Blood Analysis Set is defined as all patients of the ITT analysis set who have at least one molecular biomarker (analyte mutation) assayed.

4.5.4. Paired CNA Peripheral Blood Analysis Set

The Paired CNA Peripheral Blood Analysis Set is defined as all patients in the ITT analysis set who have valid paired results from at least one molecular biomarker (analyte mutation) assayed at Screening and post-treatment (ie, end of treatment for Phase 1, C3D1 and/or end of treatment for Phase 2).

4.5.5. Tumor Tissue Analysis Set

The Tumor Tissue analysis set is defined as all patients in the ITT analysis set who have at least one molecular tumor biomarker assayed from either the screening archival or screening de novo tumor biopsy sample (or both).

4.5.6. De Novo Tumor Tissue Analysis Set

The De Novo Tumor Tissue analysis set is defined as all patients in the ITT analysis set who have at least one molecular tumor biomarker assayed from the screening de novo tumor biopsy sample.

4.5.7. Paired Tumor De Novo Analysis Set

The Paired Tumor De Novo analysis set is defined as all patients in the ITT analysis set who have both
a) either archival tumor tissue or de novo biopsy at Screening, and
b) an End of treatment de novo biopsy
with at least one molecular tumor biomarker assayed.

4.5.8. PRO Evaluable Analysis Set

The PRO-evaluable analysis set is defined as all patients in the Safety analysis set who completed a baseline (last PRO assessment prior to first dose of PF-06463922, which could be day -7 or C1D1) and at least one post-baseline PRO assessment. The PRO-evaluable analysis set will be the primary population for the analysis of change from baseline

4.5.9. MMSE(Mini Mental State Examination)/Mood/Cognitive/SIB assessment Evaluable Analysis set

The evaluable analysis set for MMSE – Phase 1 only is defined as all patients in the Safety analysis set who completed a baseline (last assessment prior to first dose of PF-06463922, which could be day -7 or C1D1) and at least one post-baseline assessment.

4.5.10. Crizotinib Post PF-06463922 Analysis Set

The crizotinib Post PF-06463922 analysis set includes all patients enrolled in EXP-1 subgroup who discontinue PF-06463922 due to reasons other than withdrawal of consent and receive at least one dose of single agent crizotinib within this study, as detailed in Protocol Appendix 11.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis of objective tumor response based on Independent Central Review (ICR) assessment will be performed when, for each subgroup, all of the treated patients have reached at least three tumor assessments on treatment or have otherwise progressed, died, withdrawn from treatment or withdrawn consent.

The final analysis of the study will be performed when, for each subgroup, at least 2/3 of OS events (deaths) have occurred.

In the phase 2 part, subjects will be mapped to the EXP-group as indicated in the Enrollment Form. Each case will be reviewed for consistency with Prior Systemic Therapies collected in the eCRF and, in case of misallocation noted during data review, the patient will be allocated to the appropriate/closest EXP-group (e.g. Patients receiving 4 Prior ALK TKI will be attributed to EXP-5).

In the DDI/Holter part of the study, efficacy endpoints will be described only in tabular format with listings, paged by groups mapping patients to the EXP-groups as they have been defined in the phase 2 part.

Safety results of the DDI/Holter patients will be analyzed for the whole group of DDI/Holter patients, separately from phase 2. All safety analyses as defined for the phase 2 part will be performed for the DDI/Holter patients.

5.1. Hypotheses and Decision Rules

Phase 1

No formal statistical hypothesis testing is planned.

Phase 2

For subpopulations EXP-1:EXP-5 the goal of the primary analysis of objective response will be to estimate the Objective Response Rates (ORR) and their exact 95% confidence intervals. No statistical hypothesis testing is planned and no decision rule is in place.

The table below shows possible estimated ORR and 95% CIs for different level of responses in populations of 30, 40 patients, 70 and 80 patients.

Table 2 Estimated ORRs and Related 95% Confidence Intervals

Responses/Cohort Sample Size	ORR (Estimated 95% CI)
21/30	**70% (50.6-85.3)**
23/30	**77% (57.7-90.1)**
25/30	**83% (65.3-94.4)**
16/40	**40% (24.9-56.7)**
20/40	**50% (33.8-66.2)**
24/40	**60% (43.3-75.1)**
24/70	**34% (23.4-46.6)**
28/70	**40% (28.5-52.4)**
32/70	**45% (33.7-58.1)**
32/80	**40% (29.2-51.6)**
40/80	**50% (38.6-61.4)**
48/80	**60% (48.4-70.8)**

For subpopulation EXP-6 the group-sequential two-stage design using an O'Brien-Fleming non-binding stopping boundary for futility to test the null hypothesis that the response rate $P \leq 0.30$ versus the alternative that $P \geq 0.50$ has an expected sample size of 31 and a probability of early termination of 0.40 under the null hypothesis. This is based on a target 1-sided type I error rate of 0.10 and power of 0.90. After testing the drug on 20 patients in the first stage, the trial in this subpopulation will be terminated if ≤5 patients respond (based on Confirmed Responses according to Investigator Assessment). If the trial proceeds to the second stage, a total of 39 patients will be studied. If the total number of responding patients for this subpopulation is ≥16 (based on Confirmed Responses according to Investigator Assessment), then the null hypothesis will be rejected based on these data.

5.2. General Methods

5.2.1. Analyses for Binary Data

Binary endpoints will be summarized by percentage rates along with the 95% confidence intervals using an exact method.

5.2.2. Analyses for Continuous Data

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

5.2.3. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables. Missing data for a variable will be included in the denominator and a row will be included for the number and percent with missing values.

5.2.4. Analyses for Time to Event Data

For each endpoint the median, quartiles and for TTP, IC-TTP, PFS and OS the probabilities at one year and 18 months will be estimated using the method of Kaplan and Meier. Confidence intervals for the median and quartiles will be generated by the method of Brookmeyer and Crowley. Two-sided 95% confidence intervals for the 1-year and 18 month survival probability will be calculated for the log [-log(1-year (18-month) survival probability)] using a normal approximation and then back transformed to give a confidence interval for the 1-year (18 month) survival probability itself.

5.3. Methods to Manage Missing Data

5.3.1. Conventions for Missing or Derived Dates

Missing or Partial Death Dates

If there is a record for death, but the date is missing or is partial, it will be imputed based on the last contact date.

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
    - 1st day of the month and year of death, if day of death is missing OR
    - January 1st of the year of death, if both the day and month of death are missing.

Date of Last Dose of Study Drug

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cutoff date for the analysis as the last dosing date. Note: teams should confirm that the patient is actively receiving dose at the time of the data cutoff.
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is

- completely missing then it will be ignored in the imputations below
- partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
- partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy

- For patients who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is:

a) Only year (YYYY) for start of anti-cancer therapy is available

IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 01JANYYYY

b) Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

IF

Year = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

Month < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY ;

ELSE IF

Year = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

Month = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (day part of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]) MMM YYYY ;

ELSE IF

Year = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

Month > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY ;

ELSE IF

Year < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY ;

ELSE IF

Year > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

Other Missing or Partial Dates

In compliance with Pfizer standards, imputation methods generally apply to partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

These rules are used unless the calculations result in negative time durations (e.g., date of resolution cannot be prior to date of onset). In this case, the resolution and onset dates will be the same and the duration will be set to 1 day.

This standard will be modified for the computation of TTP of the last prior treatment regimen prior to PF-06463922. In particular, if the day of the month for the progression is missing the 1st of the month will be used, as above. However, if both month and day are missing and

the year is equal to the year of the end date for the last prior treatment regimen, the end date for the last prior treatment regimen will be used

For time to event endpoints, non-event observations will be censored as defined in Section 6.1.

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.

If less than half of the constituent items on the QLQ-C30 and QLQ-LC13 have been answered for a multi-item subscale, that subscale will be considered missing. Single-item subscales will be considered missing if the constituent item is incomplete.

5.3.2. Pharmacokinetics

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.)

Deviations, missing concentrations and anomalous values

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

- A concentration has been reported as ND (i.e., not done) or NS (i.e., no sample)
- Deviation in sampling time greater than 20% of the nominal time
- Pre-dose samples intended to be taken prior to dose but sampled after dose

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

Pharmacokinetic parameters

Actual PK sampling times will be used in the derivation of PK parameters. Nominal PK sampling times may be used if the actual PK times are not recorded or missing.

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

In summary tables, statistics will not be presented for a particular analyte and state (fed, fast) if more than 50% of the data are NC. For statistical analyses (i.e., analysis of variance), PK parameters coded as NC will also be set to missing.

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

5.3.3. 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.

5.3.4. Biomarkers and Pharmacodynamics

No missing biomarkers will be imputed.

No duplicate results for biomarker or pharmacodynamic markers are expected. However, if more than one record is received for a particular time point, the duplicate records will be averaged. All data (original duplicate records and averaged value) will be listed. If two sets of data for the same timepoint are received and they are not true duplicates, the study team will meet to discuss handling of these data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Dose Limiting Toxicity (DLT) – Phase 1 only

DLT definition is provided in Appendix 7. DLT is tabulated based on the specific Dose Limiting Toxicity page.

Summaries and analyses of DLT will be based on the per protocol analysis set: Evaluable for MTD (Phase 1).

DLTs will be listed by Dose Level, including Patient ID and DLT details (source: the Dose Limiting Toxicity CRF page)

The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the study protocol (section 3.4).

6.1.2. Objective Tumor Response

Objective Tumor Response is the Primary Endpoint for Phase 2 and a Secondary Endpoint for Phase 1. As most of the details in the analysis are the same, the two are detailed only once, in this section.

Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. In patients with asymptomatic CNS metastases, up to five (5) intracranial target lesions in addition to the five (5) extracranial target lesions will be assessed (as in the Long et al paper).

The following analyses of response will be performed according to ICR assessment and derived investigator assessment, respectively. The analyses based on the ICR assessment will be considered primary.

The tumor assessments obtained on study will be independently reviewed by an external vendor for determination of response or progression. This will consist of both a determination of overall response and of both intracranial and extracranial response per the rules outlined in their Charter. For tumor assessments reported by ICR data will be used as transferred from ICR and no derivation of response or date of response will be performed, unless subsequent anticancer therapy was given to the patient. In this case, programming will account for anticancer therapy to re-derive the best overall response (BOR) (based on ICR time point by time point assessment) and time of response, as appropriate.

For each patient BOR and Best Intracranial Response will be determined (details provided in Appendix 1).

Best Overall Response is defined as the best response recorded from the start of the treatment (C1D1) until Progression or start of new anti-tumor therapy (see Appendix 1 for details on how to define subsequent anti-tumor therapy), whichever occur earlier.

Intracranial Response will be analyzed for Patients with CNS metastases at study entry (a subset obtained selecting only the patients with Target and/or Non Target Lesions having Disease Site=Brain at study entry).

Best Intracranial Response is defined as the best response recorded from the start of the treatment until patient has a Progression in Brain lesions or initiates new anti-tumor therapy without documented progression, whichever occur earlier.

Confirmation of response will be required at least 4 weeks after initial response is observed. For a patient to be called having a Best Overall Response of Stable Disease (SD), he/she must maintain the status of stable disease for at least 6 weeks (42 days) after treatment start.

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

- Do not have a confirmed CR or PR while on study, or
- Do not have a post-baseline tumor evaluation (at final analysis)
- Receive anti-tumor treatment other than the study medication prior to reaching a confirmed CR or PR, or
- Die, progress, or drop out for any reason prior to reaching a confirmed CR or PR,

will be counted as non-responders in the assessment of ORR.

6.1.2.1. Analysis of ORR

ORR is defined as the percent of patients with Best Overall Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) according to RECIST version 1.1 relative to the analysis sets/subgroups described in Appendix 2, and will be provided along with the corresponding 95% confidence interval.
The primary analysis will be based on the Intention-To-Treat Analysis Set with tumor scans as assessed by the ICR.

Waterfall plots displaying the best percentage change from baseline in tumor size will be presented. The best percent change from baseline will be calculated from start of study treatment up to first visit with disease progression or to the last visit available prior to the start of new anti-tumor therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis).

A spider plot displaying the % change from baseline across visits in tumor size will be presented. The % change from baseline will be calculated from start of study treatment to each visit up to first visit with disease progression or to the last visit available prior to the start of new anti-tumor therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis).

6.1.2.2. Analysis of Intracranial ORR

Intracranial ORR is defined as the percent of patients with intracranial response (i.e. Best Overall Intracranial Response as confirmed CR or confirmed PR considering only the Lesions having Disease Site=Brain) relative to patients with Brain lesions at study entry in the analysis sets/subgroups as specified in Appendix 2, and will be provided along with the corresponding 95% confidence interval. This includes patients for whom the brain lesions have been choosen as RECIST target lesions or not.

Waterfall plots corresponding to IC lesions will be presented. The best percent change of sum of IC lesions from baseline will be calculated from start of study treatment up to first visit with IC disease progression or to the last visit available prior to the start of new anti-tumor therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis).

Spider plots displaying the % change of sum of IC lesions from baseline across visits in tumor size by best overall response will also be presented. The % change from baseline of sum of IC lesions will be calculated from start of study treatment to each visit up to first visit with disease progression or to the last visit available prior to the start of new anti-tumor therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis).

6.1.2.3. Pooled and subgroup ORR and Intracranial ORR

Different Pooled ORRs/IC-ORR will be calculated on the groups resulting from pooling ITT analysis set of the following subpopulations:

- EXP-2:5 (for PF-06463922 treatment after at least one prior ALK TKI)
- EXP-2:3A (for PF-06463922 treatment after prior crizotinib)
- EXP-3B (for PF-06463922 treatment after one prior ALK TKI different from crizotinib)
- EXP-3B:5 (for PF-06463922 treatment after at least one prior 2nd generation ALK TKI)
- EXP-4:5 (for PF-06463922 treatment after at least two prior ALK TKIs)

Waterfall plots and Spider plots will also be provided for each pooled analysis set.

In addition to summarizations per study phase, a pooled set of ALK+ patients receiving 100 mg QD between Phase 1, Phase 2 and Japan LIC may be used in support of regulatory submissions.

6.1.2.4. Analysis of Disagreement in Response Assessment

The Disagreement Rate between the Response Assessments (either Best Overall Response or IC Best Overall Response) based on the ICR assessments and the derived Investigator Assessment of tumor data will be calculated.

Definitions used to determine Disagreement Rate in Response

	Derived Investigator Assessment	Independent Central Review	Variable name
Agreement	Response	Response	a
	No Response	No Response	b
Disagreement	Response	No Response	c
	No Response	Response	d

Definitions used to determine Disagreement Rate in IC Response

	Derived Investigator Assessment	Independent Central Review	Variable name
Agreement	IC Response	IC Response	a_{IC}
	No IC Response	No IC Response	b_{IC}
Disagreement	IC Response	No IC Response	c_{IC}
	No IC Response	IC Response	d_{IC}

$N = (a + b + c + d)$

$N_{IC} = (a_{IC} + b_{IC} + c_{IC} + d_{IC})$

The Disagreement Rate measures the proportion of patients for whom there is a discrepancy between the assessment of derived Best Overall Response according to Investigator and to ICR.

Disagreement Rate = $[(c+d) / N] \times 100\%$.

IC-Disagreement Rate = $[(c_{IC}+d_{IC}) / N_{IC}] \times 100\%$.

For both Response and IC Response, the analysis will be for the following groups:

- For Phase 1 patients, pooling patients from all of the dose escalation cohorts.

- For Phase 2 patients, separately for each of the sub-populations EXP-1 to EXP-6 described in the Study Design section as well as for pooled/subgroup analysis sets EXP-2:5, EXP-2:3, EXP-4:5, and EXP-3A/EXP-3B separately.

Each Disagreement Rate (on Phase 1 and Phase 2) will be provided on the ITT Analysis Set.

6.2. Secondary Endpoints

All the analyses of efficacy endpoints but OS will be made according to both ICR assessment and derived Investigator assessment, respectively. The ICR assessments will be considered primary.
In Phase 1, endpoints will be calculated by ALK+ or ROS1+ status pooling the populations from all of the dose escalation cohorts.
In Phase 2, estimates of efficacy endpoints will be calculated separately for subgroups EXP-1:6; in addition, pooled and subgroup estimates will be calculated on the groups resulting from pooling/subgroup ITT analysis set of the following subpopulations:

- EXP-2:5 (for PF-06463922 treatment after at least one prior ALK TKI)
- EXP-2:3A (for PF-06463922 treatment after prior crizotinib)
- EXP-3B (for PF-06463922 treatment after one prior ALK TKI different from crizotinib)
- EXP-3B:5 (for PF-06463922 treatment after at least one prior 2nd generation ALK TKI)
- EXP-4:5 (for PF-06463922 treatment after at least two prior ALK TKIs)

In addition to summarizations per study phase, a pooled set of ALK+ patients receiving 100 mg QD between Phase 1, Phase 2 and Japan LIC may be used in support of regulatory submissions.

6.2.1. Disease Control Rate (DCR) at 12/24 Weeks (Phase 1 and Phase 2)

For DCR the protocol endpoint planned to evaluate it only at 12 weeks. In addition to that, DCR at 24 weeks has been evaluated as well.

A patient is considered as being in Disease Control at 12/24 weeks if:

- at least 1 time-point assessment being CR/PR/SD at day 84/168 or later and there is no PD before this CR/PR/SD time-point assessment

- Last Actual Dosing date at day > 84 days/168

DCR at 12/24 weeks is defined as the percent of patients with Disease Control at 12/24 weeks (i.e. having at week 12/24 or later a status of response (CR or PR) or of SD, relative to the analysis sets/subgroups described in Appendix 2.

IC-DCR at 12/24 weeks is defined as the percent of patients with Disease Control of brain lesions at 12/24 weeks (i.e. having at week 12/24 or later a status of IC-response (CR or PR) or of IC SD in brain lesions, relative to the analysis populations/subgroups described in Appendix 2.

DCRs and IC-DCRs will be provided along with the corresponding 95% confidence interval.

For the EXP-3A/EXP-3B the DCR will be calculated also at 24 weeks (ie 168 days).

6.2.2. PFS (Phase 1 and Phase 2)

PFS is defined as the time from first dose (C1D1) to first documentation of objective disease progression or to death on study due to any cause, whichever comes first. If tumor progression data include more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event date/censoring date – date of C1D1 dose+1)/30.44. For patients whose treatment is discontinued without documented disease progression, if the tumor scans are performed without large gaps (<2 consecutive [≤14 weeks] missed tumor assessments) to follow for disease progression, the actual date of progression will be used as an un-censored value in the analysis of PFS.

Patients with inadequate baseline assessments will have their event time censored on the date of treatment start (definition for adequate baseline tumor assessment is provided in Appendix 1: Evaluation of RECIST tumor assessment Criteria).
Patients receiving only Day -7 dose will be attributed PFS duration of 1 day and censored.
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).
Patients lacking an evaluation of tumor response after treatment start and who are however given an anti-tumor treatment will have their event time censored on the date of treatment start (C1D1).

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 and progression free at the time of the analysis;
- Who are given anti-tumor treatment (see Appendix 1 for details on how to define subsequent anti-tumor therapy) 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. One exception to this rule is for patients who have documented PD or death within (and including) 14 days of anti-tumor systemic therapy, the PD or death will be considered an event.

For patients who have at least 1 on-study disease assessment and who have documentation of disease progression or death on study on or prior to cycle 25 (18 months) for Phase 1 or cycle

38 (30 months) for Phase 2 and after ≥2, consecutive missed tumor assessments (i.e., >14 weeks after last on-study tumor assessment), the date of censoring will be the last assessment prior to the missed assessments.

For patients who have disease assessment after cycle 25 (18 months) for Phase 1 and cycle 38 (30 months) for Phase 2, and who have documentation of disease progression or death on study after these time points and >13 weeks after the last on study tumor assessment (representing ≥ 1 missed tumor assessment) the date of censoring will be the last assessment prior to the missed assessment.

Estimates of the time-to-event curves using the Kaplan-Meier method will be presented relative to the analysis sets/subgroups described in Appendix 2. This method will be applied to derive the median event time and a confidence interval for the median. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods. Two-sided 95% confidence intervals for the 1-year and 18 month progression-free survival probability will be calculated for the log [-log(1-year (18-month) progression-free survival probability)] using a normal approximation and then back transformed to give a confidence interval for the 1-year (18 month) progression-free survival.

A listing will be provided for the patients whose PFS is censored due to missing visits, discontinued without an event, and inadequate baseline tumor assessment.

6.2.3. OS (Phase 1 and Phase 2)

OS is defined as the time from first dose (C1D1) to the date of death due to any cause. OS (in months) will be calculated as (date of death/last contact − date of C1D1 dose +1)/30.44. For patients still alive at the time of analysis, the OS time will be censored on the last date the patients were known to be alive. Patients lacking data beyond the date of C1D1 dose will have their OS censored at the date of the C1D1 dose. Patients receiving only Day -7 dose will have OS calculated from Day -7.

Last date patient was known to be alive is determined as the last date among the following ones:

1) Date Last Known To Be Alive in Survival Follow-up CRF.
2) Last dosing date in Dosing Record CRF.
3) Subject Enrollment Date in Subject Enrollment CRF.
4) Date of decision to discontinue treatment in Subject Summary - End of Treatment CRF if d/c reason was not Subject died or Lost to follow-up.
5) Collect date in Subject Summary - End of Study CRF if d/c reason was not Subject died or Lost to follow-up.
6) The most recent Collection Date in Laboratory Data CRF.
7) The most recent AE onset/stop date in Adverse Event Reports CRF if CTC Grade <5.
8) The most recent Systemic Therapy Start Date in Follow-up Systemic Therapy for Primary Diagnosis CRF.

9) The most recent Date of Assessment in ECOG Performance Status CRF if ECOG Performance Status is not 5.
10) Vital signs date from Vital Signs CRF.
11) Stop date from Follow-up radiation therapy CRF.
12) Date of surgery from Follow-up surgery for primary diagnosis CRF.
13) Evaluation date from Target/Non-Target CRF
14) Date of tumor assessment from Investigator Overall Objective Tumor Assessment CRF

Estimates of the time-to-event curves using the Kaplan-Meier method will be presented relative to the analysis sets/subgroups described in Appendix 2. This method will be applied to derive the median event time and a confidence interval for the median. Two-sided 95% confidence intervals for the 1-year and 18 month survival probability will be calculated for the log [-log(1-year (18-month) survival probability)] using a normal approximation and then back transformed to give a confidence interval for the 1-year (18 month) survival probability itself.

6.2.4. Duration of Response (Phase 1 and Phase 2)

DR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or death due to any cause, whichever occurs first. For patients whose Response proceeds from PR to CR, the onset of PR is taken as the onset of response. DR (in months) is calculated as (first date of PD or death/censoring − first date of CR or PR that is subsequently confirmed +1)/ 30.44. Censoring for DR is identical to the censoring rules presented for PFS.

DR will be summarized in the populations of patients with a confirmed CR or PR relative to the analysis sets/subgroups described in Appendix 2 based on both ICR and derived investigator assessments using the Kaplan-Meier method and will be displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median will be provided.

All the analyses will be repeated also for IC-DR (Duration of Intracranial Response) considering patients with intracranial response (i.e. Best Overall Intracranial Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) considering only the Lesions having Disease Site=Brain).

In case the number of patients with Progressive Disease after a confirmed CR or PR is small, the use of Kaplan-Meier method may be limited so the DR and IC-DR will be summarized using Number (%) of Subjects Censored with DR less than 6 months, ≥6 - <9 , ≥9-<12, ≥12-<15, ≥15-<18, ≥18-<21, ≥21-<24, >=24 months.

6.2.5. Time to Tumor Response (Phase 1 and Phase 2)

TTR is defined as the time from first dose (C1D1) to first documentation of objective tumor response (CR or PR) that is subsequently confirmed. For patients whose objective response proceeds from PR to CR, the onset of PR is taken as the onset of response. If lesion

assessment data include more than 1 date, the date of the last assessment that confirmed objective response will be used. TTR will be calculated as (first event date − Cycle 1 Day 1 dose date +1)/30.44. TTR will only be calculated for the subgroup of patients with a confirmed objective tumor response relative to the analysis sets/subgroups described in Appendix 2.

TTR will be summarized based on both ICR and derived investigator assessments using descriptive statistics. In addition, the number and percent of patients with TTR in the following time intervals may be provided: 0 to <2 months, 2 to < 4 months, 4 to < 6 months, ≥ 6 months.

All the analyses will be repeated also for IC-TTR (Time To Intracranial Response) considering patients with intracranial response (i.e. Best Overall Intracranial Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) considering only the Lesions having Disease Site=Brain).

6.2.6. Time to Tumor Progression (Phase 2 Only)

TTP is defined as the time from first dose (C1D1) to the date of the first documentation of objective tumor progression. If tumor progression data include more than 1 date, the first date will be used. TTP (in months) will be calculated as (first event date/censoring − treatment start date +1)/30.44. For patients whose treatment is discontinued without documented disease progression, if the tumor scans are performed without large gaps (<2 consecutive [≤14 weeks] missed tumor assessments) to follow for disease progression, the actual date of progression will be used as an un-censored value in the analysis of TTP.

Patients with inadequate baseline assessments will have their event time censored on the date of treatment start (definition for adequate baseline tumor assessment is provided in Appendix 1: Evaluation of RECIST tumor assessment Criteria).
Patients receiving only Day -7 dose will be attributed TTP duration of 1 day and censored.
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.

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

- Who are progression free at the time of the analysis;
- Who died without documented disease progression;
- Who are given other anti-tumor treatment (see Appendix 1 for details on how to define subsequent anti-tumor therapy) prior to documented disease progression on study. 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 within (and including) 14 days of anti-tumor treatment, in which case, the PD will be considered an event.

For patients who have at least 1 on-study disease assessment and who have documentation of disease progression on study on or prior to cycle 25 (18 months) for Phase 1 or cycle 38 (30 months) for Phase 2 and after ≥2, consecutive missed tumor assessments (i.e., >14 weeks after last on-study tumor assessment), the date of censoring will be the last assessment prior to the missed assessments.

For patients who have disease assessment after cycle 25 (18 months) for Phase 1 and cycle 38 (30 months) for Phase 2, and who have documentation of disease progression on study after these time points and >13 weeks after the last on study tumor assessment (representing ≥ 1 missed tumor assessment) the date of censoring will be the last assessment prior to the missed assessment.

Estimates of TTP curve using the Kaplan-Meier method will be presented relative to the analysis sets/subgroups described in Appendix 2. This method will be applied to derive the median event time and a confidence interval for the median. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods. Two-sided 95% confidence intervals for the 1-year and 18 month TTP probability will be calculated for the log [-log(1-year (18-month) TTP probability)] using a normal approximation and then back transformed to give a confidence interval for the 1-year (18 month) TTP probability.

Intracranial Time to Progression

In addition to the TTP endpoint defined in the protocol, Intracranial Time To Progression (IC-TTP) has been evaluated as well.

IC-TTP is defined as the time from first dose (C1D1) to the date of the first documentation of objective progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases.

IC-TTP will be calculated for the ITT set and for subgroups of patients with and without brain metastases at baseline based on both ICR and derived Investigator Assessments. For the subgroup of patients without brain metastases at baseline only the new brain metastases will be considered events.

For IC-TTP the same censoring rules described above for TTP will be implemented with the following exception:

- patients without brain metastases at baseline will not be considered as having inadequate baseline assessments, and thus will not have their event time censored on the date of treatment start.
- patients will not be censored in case of surgery or radiotherapy as described in section 6.2.6, if surgery or radiotherapy involve an extracranial lesion.

For patients having no brain lesion at baseline and no brain lesion at following assessments IC-TTP will be censored on the date of the last evaluable tumor assessment documenting absence of progressive brain disease (with censoring reason “progression free at the time of the analysis”).

IC-TTP will be summarized using the Kaplan Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported.

6.2.7. Probability of first event being a CNS progression, non CNS progression, or death.

The probability of first event being a CNS progression, a non CNS progression, or Death will be evaluated with a Competing Risk approach by estimating Cumulative Incidence Functions relative to the analysis sets/subgroups described in Appendix 2 based on both ICR and derived Investigator Assessments.

All the analyses will be repeated also on patients with Brain lesions at study entry in the analysis sets/subgroups as specified in Appendix 2 (i.e. considering only those having at least one Baseline Lesion having Disease Site=Brain).

The time to first event being a Competing Event (either "CNS progression" or "non CNS progression" or "Death") is defined as time from first dose (C1D1) until the date of that specific event. Patients not known to have any of the Competing Events are censored on the date they were last assessed for disease status for PFS.

Patients who presented one type of event are counted as a competing cause of failure for the analysis of other type of events. For example, in the estimation of time to first event being CNS progression, the patients having a non CNS progression (or those dying before the CNS progression occurs) are counted as competitive cause of failure.

6.3. Other Endpoint(s)

6.3.1. Time to Tumor Progression (Phase 1 Only)

For patients in Phase 1, TTP, will be evaluated using the definition provided in section 6.2.6 as exploratory endpoints as detailed in Appendix 2.

Estimates of the time-to-event curves using the Kaplan-Meier method will be presented. This method will be applied to derive the median event time and a confidence interval for the median. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods.

6.3.2. Response to prior therapies

TTP of the last prior treatment regimen before PF-06463922
In each of the EXP-2:EXP-5 subgroups of phase 2 the TTP (in months) will be calculated for

- the last prior Systemic Therapy before PF-06463922 and
- the last prior ALK TKI treatment before PF-06463922 and
- the last prior Systemic Therapy other than ALK TKI treatment before PF-06463922

from the first dose date of the last prior treatment regimen to the date of progression: (progression date − first dose date +1)/30.44. Patients without a progression date will be censored to the end date of the last prior treatment regimen. If there are multiple drugs in the prior regimen, the earliest start date and latest end date will be used. TTP will be calculated for patients in the ITT analysis set with at least 1 prior anticancer regimen for advanced/metastatic disease. The median event time (and other quartiles) and 2-sided 95% CI for the median will be provided.

Recurrent event analysis within-patient TTP

In each of the EXP-2:EXP-5 subgroups of phase 2 the TTP with PF-06463922 will be compared with the TTP on

- the last prior Systemic Therapy before PF-06463922 and
- the last prior ALK TKI treatment before PF-06463922 and
- the last prior Systemic Therapy other than ALK TKI treatment before PF-06463922

for patients having both evaluations using the recurrent event analysis. The hazard ratio, the 2-sided 95% CI, and the associated p-value will be provided. The robust sandwich covariance matrix estimate of the parameter estimator will be used to account for dependence of the multiple event times.

6.3.3. Pharmacokinetic Analyses

6.3.3.1. PF-06463922 and Metabolite (PF-06895751) PK Analysis

For PF-06463922 and its major metabolite (PF-06895751) concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady-state). For individual patient plots by time, the actual PK sampling time will be used. For summary statistics and mean/median plots by sampling time, the nominal PK sampling time will be used. Mean and median profiles will be presented on both linear-linear and log-linear scales.

Presentations for concentrations will include but not be limited to:

- Listing of all concentrations of PF-06463922 and its M8 metabolite PF-06895751 sorted by dose, day of assessment, patient ID and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- Summary of concentrations by dose, day of assessment and nominal time post dose, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV and the number of concentrations above the lower limit of quantification.
- Phase 2 sparse sampling patients will additionally have summary of concentrations by EXP group, day of assessment, and nominal time post dose

- Linear and semi-log plots of median/mean /SD concentrations against nominal time post dose by dose and day of assessment (based on the summary of concentrations by dose, day of assessment and time post dose). For the 25 and 100 mg QD cohorts, C1D1 and C1D15 data will be used for plotting; for the remaining cohorts the Day -7 and C1D15 data will be used.
- Linear and semi-log plots of individual concentrations against actual time post dose by day of assessment (there will be separate plots for each dose). For the 25 and 100 mg QD cohorts, C1D1 and C1D15 data will be used for plotting; for the remaining cohorts the Day -7 and C1D15 data will be used.
- Listing of trough concentrations by dose, day of assessment, and patient ID.
- Summary of trough concentrations by dose and day of assessment, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV and the number of concentrations above the lower limit of quantification.
- Trough concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

6.3.3.2. PF-06463922 and Metabolite (PF-06895751) Pharmacokinetic Parameters

PK parameters will be estimated using non-compartmental analysis. Actual PK sampling times will be used in the derivation of PK parameters. Missing values will be handled as detailed in Section 5.3.2. All calculations will follow the Pfizer Clinical Pharmacology Guidance "Pharmacokinetic Data Handling and Non-Compartmental Analysis Conventions".

Plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC_{last}) for PF-06463922 and its major metabolite PF-06895751 will be estimated using non-compartmental analysis. Standard urine pharmacokinetic parameters will be estimated including renal clearance (CLr), cumulative amount of drug recovered unchanged in the urine (Ae) and cumulative total amount of drug recovered unchanged in the urine, expressed as fraction of administered dose (Ae%). If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity (AUC_{inf}) area under the plasma concentration versus time curve during the dosing interval (AUC_{tau}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F), apparent volume of distribution (V_z/F), accumulation ratio (R_{ac}) and linearity ratio (R_{ss}) will be also estimated. The single dose and steady-state PK parameters will be summarized descriptively by dose, cycle and day. Each PK parameter will be listed and summarized by dose and by visit (For the 25 and 100 mg QD cohorts, C1D1 and C1D15; for the remaining cohorts, Day -7 and C1D15) and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC_{last}, AUC_{inf}*, AUC_{tau}, C_{max}, C_{trough}, CL/F*, V/F*,	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric cv%.
T_{max}	N, median, minimum, maximum.

$t_{1/2}$, Rac*, Rss*, Ae and Ae (%)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

* if data permits

Dose normalized and non –dose normalized AUC_{inf} if data permits (AUC_{τ} at steady state), AUC_{last} and C_{max} will be plotted against dose (using linear and logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. A footnote will be added to the plots to indicate that geometric means are presented. These plots will be used to help understand the relationship between the PK parameters and dose.

The observed accumulation ratio and the linearity ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

6.3.3.3. Effect of PF-06463922 on Midazolam Pharmacokinetics

Individual and descriptive statistics of midazolam plasma concentrations at each nominal time point by midazolam alone and in presence of PF-06463922 will be listed and plotted.

Plasma concentration-time data of MDZ in the absence and presence of PF-06463922 will be analyzed using non-compartmental methods to estimate the following PK parameters in individual patient: C_{max}, T_{max}, $AUC_{0\text{-}last}$, and, if data permit, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL/F and V_d/F. Descriptive statistics will be provided for these PK parameters in tabular form.

The pharmacokinetic parameter $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ (if data permit) and C_{max} will be utilized to estimate the effect of multiple doses of PF-06463922 on MDZ PK.

Natural log transformed MDZ AUC0-last, AUC0-∞ (if data permit) and Cmax values will be analyzed using appropriate statistical models accounting for sequence, dose and treatment (with PF-06463922, test, and without PF-06463922, reference) effects. Estimates of the adjusted mean differences (with PF-06463922 and without PF-06463922) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (with PF-06463922 and without PF-06463922) and 90% confidence intervals for the ratios.

Presentations for concentrations will include but not be limited to :

- Summary of concentrations by visit, nominal time post dose, and PF-06463922 dose cohort, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV and the number of concentrations above the lower limit of quantification.

Individual and summary statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf} (if data permits) will be provided in tabular form by midazolam alone and in presence of PF-06463922.

Box plots of PK parameters $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ (if data permit) and C_{max} will be provided by midazolam alone and in presence of PF-06463922 (individual values will also be presented)

6.3.3.4. Effect of Food on PF-06463922 Pharmacokinetics

For the evaluation of the food effect, PF-06463922 plasma concentration-time data will be compared on Day -7 to Cycle 1/Day 1. Natural log transformed AUC0-last, AUC24 (if data permit) and Cmax values will be analyzed using an appropriate statistical model accounting for sequence and treatment (fed, fast) effects. Estimates of the adjusted mean differences (Fed-Fasted) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (Fed/Fasted) and 90% confidence intervals for the ratios.

Presentations for concentrations will include but not be limited to :

- Summary of concentrations by visit, nominal time post dose, and fed vs. fasted, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV and the number of concentrations above the lower limit of quantification.
- Linear and semi-log plots of median/mean/SD concentrations against nominal time post dose by visit, and fed vs. fasted
- Linear and semi-log plots of individual concentrations against actual time post dose by visit and fed vs. fasted

In addition, summary statistics of PF-06463922 plasma concentrations at each nominal time point will be reported by fed and fasted state.

Individual and summary statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf} (if data permits) will be provided in tabular form by fed and fasted state.

Box plots of PK parameters $AUC_{0\text{-}last}$, AUC_{24} and C_{max} of PF-06463922 will be provided by fed and fasted state (individual values will also be presented)

6.3.3.5. Japanese (Patients from Japanese Sites) and Asian Patients

Japanese patients enrolled at Japanese sites (including the LIC) will be summarized separately from, and will be compared to the patients enrolled in the main part of the study . Additionally, Asian patients will be summarized separately from, and will be compared to the patients enrolled in the main part of the study.

Concentration presentations for PF-06463922 and its metabolite will include but not be limited to:

- Listing of all concentrations sorted by day of assessment, patient ID and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.
- Summary of concentrations by day of assessment and nominal time post dose, where the set of statistics will include n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV and the number of concentrations above the lower limit of quantification.
- Linear and semi-log plots of median/mean/SD concentrations against nominal time post dose by day of assessment.
- Linear and semi-log plots of individual concentrations against actual time post dose by day of assessment.
- Trough concentrations will be plotted using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

Comparisons between the Japanese patients vs. the non-Japanese patients from the main part of the study, and Asian patients vs. the non-Asian patients from the main part of the study, will be done. Natural log transformed AUC0-last, AUC0-∞ (if data permit) and Cmax values will be analyzed using a an appropriate statistical model accounting for sequence, dose, and Japanese vs. Non-Japanese or Asian vs. non-Asian effects. Estimates of the adjusted mean differences (with Japanese vs. non-Japanese, Asian vs. non-Asian) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (with Japanese vs. non-Japanese, Asian vs. non-Asian) and 90% confidence intervals for the ratios.

Individual and summary statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf} (if data permits) will be provided in tabular form by Japanese vs. non-Japanese and Asian vs. non-Asian.

Box plots of PK parameters $AUC_{0\text{-}last}$, AUC_{inf} (if data permit) and C_{max} of PF-06463922 will be provided for Japanese vs. non-Japanese and Asian vs. non-Asian. (individual values will also be presented)

6.3.3.6. Drug Drug Interaction and Holter Monitoring Study (Phase 2)

For the evaluation of the DDI effect (potential effect of PF 06463922 on the plasma exposure of probe substrates), a minimum of 6 evaluable patients for each probe substrate have been empirically chosen. A sample size of 6 subjects will provide 90% CI for the difference between treatments of ± 0.5338 on the natural logarithm scale for C_{max}, with 80% coverage probability.

Efficacy in patients entering the DDI and Holter monitoring study will be analyzed separately from the Phase 2 efficacy population.

For patients participating in the DDI substudy, plasma concentration time data for probe substrates (bupropion, tolbutamide, acetaminophen, or fexofenadine, and their relevant metabolites) in the absence of PF 06463922 on Lead-in Day -2 (probe substrate alone) will be compared to Cycle 1 Day 15 (probe substrate in the presence of steady state PF

06463922). Natural log transformed AUC24, AUC_{inf} (if data permits), and C_{max} for the probe substrates and their relevant metabolites will be analyzed using an appropriate statistical model accounting for the treatment effect. Estimates of the adjusted mean differences (Test Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratios of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The probe substrate alone on Day 2 (Treatment A) will be the Reference treatment, and the probe substrate co administered with PF 06463922 on Cycle 1 Day 15 (Treatment B) will be the Test treatment.

Plasma PK parameters AUC_{24}, AUC_{last}, AUC_{inf} (if data permits), C_{max}, T_{max}, CL/F, V_z/F and $t_{1/2}$ for the probe substrates and PF 06463922, and AUC_{24}, AUC_{last}, AUC_{inf} (if data permits), C_{max}, T_{max}, $t_{1/2}$, MRC_{max}, $MRAUC_{24}$, $MRAUC_{inf}$, and $MRAUC_{last}$ for relevant metabolite(s) of the probe substrates as well as PF 06463922 metabolite(s) will be listed and summarized descriptively by visit. Box whisker plots for PK parameters AUC_{24}, AUC_{inf} (if data permits) and C_{max}, for the probe substrates (and their relevant metabolites) will be plotted by treatment. Corresponding matchstick plots will also be created. Plasma concentrations for the probe substrates, their metabolites (as appropriate), PF 06463922 and it's metabolite will be listed and summarized descriptively by PK sampling time and treatment/visit. Individual subject and summary profiles (median and means) of the probe substrate concentration time data will be plotted by treatment/visit.

For summary statistics and summary 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. An evaluation of the effects of PF 06463922 on the PR interval will be conducted via continuous Holter telemetry comparing the subject's time matched PR interval (approximately 10 timepoints) with exposure of PF 06463922 following a single dose and again at steady state. In addition, arrhythmia analysis will be performed using Holter Monitoring data from these patients.

Continuous 24-hour Holter Monitoring data will be analyzed according to the Statistical Analysis Plan from iCardiac (the vendor supplying the Holter Monitor). In addition, with Holter data brought in house, time-matched summary tables for PR interval by visit will be generated using extractions at time points corresponding to the PK collections. Box plots overlaid on individual data points and matchstick plots will also be created for the PR interval at each extracted time-point . For drug-drug interaction assessment in the Holter Monitoring patients, the PK parameters for the probe substrates will be compared on Lead-In Day -2 and Cycle 1 Day 15. Statistical evaluation for the comparison will be conducted and box plots for the C_{max} and AUC will be generated.

6.3.3.7. Urine 6 beta-Hydroxycortisol/Cortisol (6β-OHC/C) Ratio Analysis

Urine 6 beta-Hydroxycortisol/Cortisol (6β-OHC/C) Ratio data will be summarized using graphical methods and descriptive statistics in tabular form, as appropriate. The ratios will be listed as well as summarized. The change in the ratios from the baseline (Day -7) to values on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 1 will be summarized, analyzed (ANOVA will be used to compare the ratios of 6 beta-Hydroxycortisol/Cortisol

(6β-OHC/C) by lorlatinib dosing group, with the RP2D of 100 mg QD as the reference, across study visits) as well as plotted as Box-Whisker plots.

6.3.3.8. Serum 4 beta-Hydroxycholesterol/Cholesterol Ratio Analysis

Serum 4 beta-Hydroxycholesterol/Cholesterol Ratio data will be summarized using graphical methods and descriptive statistics in tabular form, as appropriate. The ratios will be listed as well as summarized. The change in the ratios from the baseline (Day -7) to values on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day1 and Cycle 5 Day 1 will be summarized, analyzed (ANOVA will be used to compare the ratios of 4 beta-Hydroxycholesterol/Cholesterol by lorlatinib dosing group, with the RP2D of 100 mg QD as the reference, across study visits) as well as plotted as Box-Whisker plots

6.3.3.9. Population Pharmacokinetic Analysis or PK/PD Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-06463922 exposure and biomarkers or significant safety endpoints. The results of these analyses, will be described in a separate Population Pharmacokinetic Modeling Analysis Report (PMAR).

6.3.3.10. Metabolite Profiling

Plasma metabolite profiling will be summarized in a separate report and not included in the clinical study report (CSR).

6.3.3.11. CSF Analysis

CSF concentrations of PF-0646392 will be listed along with corresponding bound and unbound plasma concentrations of PF-06463922 if available.

6.3.4. Statistical Analysis of Biomarker Endpoint

Biomarkers will be assessed separately for blood and tumor biopsy tissue samples. In each case, summaries of baseline levels and changes from baseline will be reported. .

The statistical approach may examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

Due to the exploratory nature of the proposed biomarkers, the data analysis will be conducted with the goal of identifying biomarkers with the strongest concordance to clinical outcome, encompassing both safety and efficacy. Candidate biomarkers will be validated in subsequent trials.

6.3.4.1. CNA Mutations

Analyses of CNA Mutations will be based on the CNA Peripheral Blood analysis set.

CNA mutations are measured at Screening, and EOT in Phase1 and at Screening, C3D1 and EOT in Phase 2. For phase 1, patients are expected to have none or one or more of the twelve to seventeen possible ALK or three possible ROS1 mutations included in the panel (digital PCR analysis at Inostics), and patients may have a change in mutation after treatment. For Phase2, patients are expected to have none or one or more mutations (no panel restriction, NGS panel analysis, G360 at Guardant Health), and patients may have a change in mutation while on treatment (C3D1) or at EOT.

Phase 1 will be summarized separately by ALK+ or ROS1+ status. A frequency table will be provided for each timepoint for all mutations, and a table of none vs ≥ 1 mutation will be provided for all dosing cohorts and overall. All data will be listed.

Phase 2 will be summarized separately by EXP-group 1-6, 2-3A combined, 4-5 combined, 3B-4-5 combined and separately EXP-3A and EXP-3B. The additional patients enrolled in the DDI/Holter monitoring substudy will be mapped to the treatment groups as defined in the phase 2 part. A frequency table will be provided for each timepoint for all ALK-kinase mutations. A frequency table of none vs ≥ 1 mutation will be provided. All data will be listed.
For the six EXP groups and the combined , EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B, frequency tables of the mutations at Screening vs. disease control at 12 and 24 weeks (yes=disease control, and no=no disease control), BOR (yes=objective response, and no=no objective response) will be provided. For EXP-2:EXP-3A, and EXP-3B:EXP-4:EXP-5, a summary table of the type of mutations at Screening will be provided.

PFS and OS analyses will be described by kinase domain mutational status (ie, none vs. ≥ 1 mutation at screening) and overall using Kaplan-Meier curves with appropriate summary statistics including median time and associated two-sided 95% CIs. Kaplan-Meier estimates with two-sided 95% CIs at specific time points (6 months, 12 months and 18 months) will be summarized as well. All analyses will be run on each of the six EXP groups, and then on the combined EXP-2:EXP-3A, EXP-3B:EXP-4:EXP-5, and EXP-4:EXP-5, and separately EXP-3A and EXP-3B.

6.3.4.2. Tumor Tissue Analysis

Analyses of Tumor Tissues will be based on the Tumor Tissue Analysis Set.

DNA mutations in tumor tissue (archival or de novo) are measured at screening. Patients are expected to have none or one or more of nine possible mutations.

Phase 1 will be summarized separately by ALK+ or ROS1+ status, using patients in the tumor tissue analysis set for Phase 1 (Section 4.5.5). A frequency table of mutations and none vs. ≥ 1 mutation will be provided. All data will be listed.

Phase 2 will be summarized separately by EXP-groups 1-6 and, EXP-2:EXP-3A combined, EXP-4:EXP-5 combined, EXP-3B:EXP-4:EXP-5 combined, and separately EXP-3A and EXP-3B, using patients in the tumor tissue analysis set for Phase 2. The additional patients

enrolled in the DDI/Holter monitoring substudy will be mapped to the expansion cohorts as defined in the phase 2 part. A frequency table of mutations at screening and none vs. ≥ 1 mutation will be provided. All data will be listed.

For the six EXP groups and the combined EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B, frequency tables of the mutations at Screening vs. disease control at 12 and 24 weeks (yes=disease control, and no=no disease control), BOR, and OR (yes=objective response, and no=no objective response), and one vs > 1 mutation will be provided. For EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B, a summary table of the type of mutations at Screening will be provided.

PFS and OS analyses will be described by mutational status (ie, none vs >=1 mutation at Screening, and by 1 vs >1 mutation at Screening) and will be run for the following subgroups: six EXP groups, and combined EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B.

6.3.4.3. Tumor De Novo Analysis

Analyses of Tumor De Novo will be based on the Paired Tumor De Novo Analysis Set.

DNA mutations are measured at screening and optionally at end of treatment.

Phase 1 will be summarized separately by dosing cohort and overall, using patients in the paired tumor de novo analysis set for Phase 1 (Section 5.5.4). A frequency table will be provided for each timepoint for all mutations, as well as a frequency table of none vs. ≥ 1 mutation,. All data will be listed.

Phase 2 will be summarized separately by EXP-groups 1-6 and combined EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B, using patients in the paired tumor de novo analysis set or the de novo tumor analysis set . A frequency table will be provided for each timepoint for all mutations, as well as a frequency table of none vs. ≥ 1 mutation, and a frequency table of 1 vs. >1 mutation. All data will be listed.

6.3.4.4. Tumor vs. Blood Analyses

Mutations will be measured in both blood and tumor for all patients. For Phase 1 (all dosing cohorts combined) and Phase 2 (by EXP-groups 1-6, and combined EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B) separately, a listing of CNA mutations vs. DNA mutations in de novo tumors (or if not available, archival sample) at screening will be provided (each patient is a row in the listing.) Also, a tabulation of the number of patients with the same number of mutations in both blood and tumor, and a different number of mutations in blood and tumor will be provided for Phase 1 and Phase 2 separately.

6.3.5. Concordance assessment between ROS1+ local test result and central test result

For the ROS1 cohort the Agreement Rate between the Local and Central Test Result will be presented relative to the Full Analysis Set. Local test is defined as any protocol allowed ROS1 test that was performed at the enrolling site. Central test is defined as the ThermoFisher NGS test performed at a central lab.

		Central Test Result	
		ROS1+	ROS1-
Local Test Result	ROS1+	a	B
	ROS1-	c	D

N = (a + b + c + d)

The following Agreement Rates will be calculated :

Overall Percent Agreement (OPA)= [(a+d) / N] x 100%.
Positive Percent Agreement (PPA): [a/(a+c)] x 100%
Negative Percent Agreement (NPA): [d/(d+b)] x 100%

Patients with Indeterminate or invalid test results will be excluded from the analysis.

The results of analysis will be included in a specific ROS1 biomarker report that will be appended to the final CSR.

6.4. Subset Analyses

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Summaries of Baseline Variables, Patient Characteristics and Prior anti-cancer treatments will be provided on the Safety Analysis set.

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

will be summarized by category (number and percent).

Age (continuous), height (cm), weight (kg), Body Mass Index (BMI) (kg/m2), will be summarized with descriptive statistics (mean, standard deviation, minimum, and maximum).

BMI (kg/m2) 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.

Prior anti-cancer treatments include systemic therapy, radiation, and surgery. The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one prior anti-cancer surgery;
- Patients with at least one prior anti-cancer radiotherapy;
- Patients with at least one prior systemic therapy;

For both Phase 1 and Phase 2 Prior systemic therapies will be summarized as follows based on the number and percentage of patients:

- Number of prior systemic therapy regimens: 0 / 1 / 2 / 3 / ≥4;
- Number of prior ALK or ROS1 TKI regimens: 0 / 1 / 2 / 3 / ≥4;

6.5.2. Study Conduct and Patient Disposition

For both Phase 1 and Phase 2 the Study Protocol consists of two different epochs: Study and Treatment

6.5.2.1. Patient Disposition

Discontinuation for each epoch will be summarized separately.
Discontinuation from Study will be summarized using Full Analysis Set.
Discontinuation from Study Treatment will be summarized using the 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.

6.5.2.2. Protocol Deviations

Protocol Deviations will be compiled prior to database closure. Categories will be assigned by the study Clinician. Potentially Important PDs with non-missing sub-categories will be summarized by category (n(%)) for the full analysis set.

In both phase 1 and phase 2, failure to document ALK or ROS1 gene rearrangement constitutes a violation of the first protocol inclusion criteria, defining the disease to be treated (Evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, AJCC v7.0) that carries an ALK gene rearrangement, as determined by the Food and Drug Administration (FDA)-approved FISH assay (Abbott Molecular Inc) or by Immunohistochemistry (IHC) (Ventana Inc), or a ROS1 gene rearrangement as determined by FISH or RT-PCR or Next Generation Sequencing (NGS) via a local diagnostic test (LDT).

In the phase 2 part, failure to meet disease requirement of any of the Subgroups Exp-1 to Exp-6 constitutes a violation of the second protocol inclusion criteria defining the Disease Status Requirement.

Such deviations will be reviewed on a case by case basis, each case will be attributed during data review to the closest EXP- group (e.g. Patients receiving 4 Prior ALK TKIs will be attributed to EXP-5) and tabulated as Protocol Deviation in a specific listing.

6.5.3. 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

providing mean, median and range of months of administration, Overall Relative Dose of PF-06463922. Details for calculation of Relative Dose are provided in Appendix 4.

For patients receiving only Day -7 dose the Treatment Duration is defined as 1 day.

The same approach will be adopted to describe Duration of treatment with PF-06463922 beyond progression from derived Investigator Assessment (For patients with progression from derived Investigator Assessment before last actual dosing date, not during follow-up period), with Duration of Treatment in months calculated as (End of Treatment Date – PD date + 1)/ 30.44.

Duration of Treatment will also be analyzed adopting a Time to event approach, thus censoring the time of patients still on treatment.

Number of patients having dose reductions / dose delays will be provided separately for Dose Levels in phase 1 and subgroups EXP-1:6 in phase 2.

"Swimmer plots" describing treatment duration will be provided. The plots will show for every patient the entire treatment duration and the actual number of days on/off drug (in phase 1 two versions will be provided, one using different colors for the different dose levels and accounting dose breaks and another one with no colors and not showing breaks but only the overall duration).

Duration of Follow up will be summarized as described by Schemper et al (1996) reversing the censoring and event indicators and estimating follow-up time with the method of Kaplan and Meier (referred to as the "reversed Kaplan-Meier method")

6.5.4. Concomitant Medications, Non-Drug Treatments and Follow-up Radiotherapy/Systemic Therapy

All medications received from screening onwards will be considered as concomitant medications and will be coded by the World Health Organization (WHO) medical dictionary. Data for concomitant medications and non-drug treatments will be summarized and listed. Follow-up systemic therapy for primary diagnosis will be listed for each patient. If any concurrent or follow-up surgery or radiation therapy is given these data will be listed for each patient as well.

6.6. Safety Summaries and Analyses

Analysis of safety for patients in the phase 1 part, the Phase 2 part, Japan Lead-In cohort and the DDI/Holter substudy will be based on the Safety Analysis Set. For all safety analyses, only descriptive methods will be used without any formal statistical testing.

In addition to summarizations per study phase, a pooled set of patients receiving 100 mg QD between Phase 1, Phase 2 and Japan LIC may be used in support of regulatory submissions.

Baseline is defined as the last evaluation on or prior to the first dose of study drug (i.e. including day -7 for patients in phase 1 or receiving Lead-in dose in phase 2 or Cycle 1 Day 1 for other subjects).

For the EXP-1 patients who then receive crizotinib following PF-06463922, the period of observation and possible attribution of causality to PF-06463922 ends at Start of treatment with crizotinib. For SAEs deemed related to lorlatinib by the investigator the timeframe for collection remains 28 days after end of loraltinib treatment, independently from start of crizotinib, allowing to attribute causality to both drugs.

6.6.1. Adverse Events

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 present AEs on the entire study.

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.

Treatment – emergent SAEs and treatment-related SAEs will be summarized by MedDRA SOC and preferred term. Patients who experienced a SAE during the SAE reporting period will be listed for all the patients in the Safety Analysis set. The number and percentage of patients who experienced any serious treatment – emergent SAE will be summarized for all cycles. 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.

6.6.2. 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.

Coagulation assays (collected at Screening, End of Treatment and as needed) will be summarized in a listing by visit reporting the value and the CTC grade for each visit.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

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.

6.6.3. 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 (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) between 10% and 20%
	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
	Maximum Change from baseline (increase) ≥ 30 bpm
	Maximum Change from baseline (decrease) ≥ 30 bpm

In addition, the baseline and the change from baseline in blood pressure, weight and pulse rate will be summarized using descriptive statistics by visit.

6.6.4. Electrocardiogram

The analysis of ECG results will be based on Safety Analysis set patients with baseline and on-treatment ECG data. 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.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (i.e., Bazett's, Fridericia's and possibly a study specific factor). The study specific correction factor estimates the correction factor (β) for the population using only the baseline non-averaged triplicate or singlet data. The adequacy of the correction method will be assessed graphically (plots of QT and QTc versus RR) and supplementary transformations may be considered, as appropriate. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF, and QTcB by cycle, day and dose. Individual QTc (all evaluated corrections) intervals will be listed by time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by, cycle, day, dose and by time point. A similar analysis will be provided also for Heart Rate.

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum post dose QTc (QTcB, QTcF, or study specific) 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:

PR interval

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. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on QTc change (and PR interval) from baseline will be explored graphically. Additional concentration-QTc analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

6.6.5. Physical Examination

Individual patient data will be listed.

6.6.6. Urinalysis

Individual urinalysis patient data will be listed together with other Lab values.

6.6.7. Concomitant medication to lower Cholesterol or Triglycerides

For Total Cholesterol and Triglycerides abnormalities, in addition to the summary tables included in the set produced for the biochemistry assays, the n, mean, std, median, min, max time to start of medication will be presented for the medications included in the lists provided in Appendix 5.1.

Time to start of medication to lower Cholesterol or Triglycerides will be calculated (only for patients starting the listed medications) from Cycle 1 Day 1 (or Day -7 if it is the first dose) to the start of a medication to lower Cholesterol and/or Triglycerides.

If a patient takes medication in more than one timeframe, the start date of first timeframe is used for calculation

6.6.8. Pregnancy Test

Individual patient pregnancy test results will be listed together with other Lab tests.

6.6.9. Left Ventricular Ejection Fraction

For patients with MUGA scans or echocardiograms, individual LVEF (left ventricular ejection fraction [%]) and its changes from baseline will be summarized by time point (changes from baseline should only be calculated for the on treatment evaluation using the same method used for baseline). *The number of patients and the percentage whose maximum relative decrease from baseline in LVEF is greater than 20% will be calculated.*

6.6.10. Patient Reported Outcomes

The PRO-Evaluable analysis set will be the primary population for the analyses of change from baseline in phase 1 and phase 2. In phase 2, PRO analyses will be performed by the EXP sub-groups, EXP-1: EXP- 6 and on the groups pooling EXP-1:EXP-6, EXP-2:EXP-3A, EXP-4:EXP-5, EXP-3B:EXP-4:EXP-5 and separately EXP-3A and EXP-3B

Visit windows as defined in Appendix 6 will be applied for the analysis of the PRO endpoints.

Patient reported outcomes of global QOL, functioning and lung cancer specific disease/treatment related symptoms, will be assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, Version 3.0), and its corresponding module for lung cancer (QLQ-LC13, Version 3.0).

Specifically, the EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), global quality of life, disease/treatment related symptoms (fatigue, pain, nausea/vomiting, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhoea), and the perceived financial impact of disease. (Aaronson et al.) The QLQ-LC13 module includes questions specific to the disease associated symptoms (dyspnea, cough, haemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy, and alopecia), and analgesic use of lung cancer patients. (Bergman et al.)

PRO Scoring Procedure

The subscales of the EORTC QLQ-C30 and the QLQ-LC13 will be scored based on the EORTC scoring manual. (Fayers et al). In summary, each scale of the EORTC QLQ-C30 and the QLQ-LC13 will be transformed so that scale scores will range from 0 to 100. The transformation will proceed in 2 steps. First, the average of the items contributing to a subscale will be calculated to compute the raw score of the scale. Next, a linear transformation will be applied to ‘standardize’ the raw score. After scores are transformed, higher scores on the EORTC QLQ-C30 will represent higher (“better”) levels of functioning

and/or a higher ("worse") level of symptoms. Higher scores on the EORTC QLQ-LC13 will represent higher ("worse") level of symptoms. (Fayers et al)

Patient Reported Outcomes
As measures of instrument compliance rates, at each time point, the number and percentage of patients who complete the QLQ-C30 and QLQ-LC13 will be summarized in a table, as will the reasons for non-completion of these measures. Summarization will be based on the Safety Analysis Set. For Phase 1 the summary will be presented combining dosing cohorts, while for Phase 2 for each subgroup separately.

Tables will be used to summarize, the mean (and SD), and median (and range) of absolute scores and change from baseline of the QLQ-C30 and QLQ-LC13 multiple-item and single-item scale scores. The mean change of absolute scores from baseline will also be assessed using confidence intervals. Line charts depicting the means (SE) and mean change from baseline (SE) of scales over time will be provided.

The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QOL, and single items of the EORTC QLQ-C30 and the QLQ-LC-13 will be summarized by dosing cohort/subgroup.

A change of at least 10 points would be considered clinically relevant (Osoba et al).
An average for each patient will be calculated across cycles of the mean change from baseline in the symptom scales, in the functioning scales, and in the global QOL scale. For the symptom scales, improvement is defined as a decrease of at least 10 points in the average change from baseline. For the functioning and global QOL scales, improvement is defined as an increase of at least 10 points in the average change from baseline. For the symptom scales, worsening is defined as an increase of at least 10 points in the average change from baseline. For the functioning scale and global QOL scales, worsening is defined as a decrease of at least 10 points in the average change from baseline. Global QOL, functioning scales and symptom scales that have not improved nor worsened will be considered stable.

6.6.11. Mini Mental State Examination. [Phase 1 only]

Changes of the Total Mini Mental State Examination Score will be described across cycles.

6.6.12. Cognitive, Mood and Suicidal Ideation and Behavior Analyses

Analysis of Cognitive, Mood and Suicidal Ideation and Behavior data will be described in a specific SAP prepared by COGSTATE company and analyzed in a separate report prepared by COSTATE after data base release.

6.6.13. ECOG Performance Status

A shift table of baseline ECOG PS by maximum post-baseline ECOG PS will be presented. Individual patient data will be listed.

6.7. Analyses on Patients Receiving Crizotinib after PF-06463922 in EXP-1

All analyses on Patients Receiving crizotinib after PF-06463922 in EXP-1 will be based on the crizotinib Post PF-06463922 analysis set and will be provided if there is at least one patient receiving crizotinib after PF-06463922. The efficacy of this group of patients will not be subject to ICR.

The analysis of data on patients receiving crizotinib after PF-06463922 will focus on

- the efficacy endpoints ORR, PFS, DR, TTR, OS,
- patient characteristics
- AEs and Laboratory assessments
- Duration of Treatment

Efficacy Endpoints definition follow the definition of same endpoints already provided in for EXP-1 through EXP-6, with the following caveats:

- Response evaluation will only be based on Derived Investigator assessment
- For tumor assessments, the baseline assessment will be the re-baselined assessment as described in Protocol Appendix 11
- The starting date for the calculation of PFS, TTR, and OS will be the treatment start date of crizotinib

AEs and laboratory endpoint definitions follow the definition of the same endpoints already provided for adverse events and laboratory data, with the following caveats:

- The first dose of study medication will be defined as the treatment start date of crizotinib.
- The AEs relative to this part of the study will be identified as those with Study Treatment Name=crizotinib in the AE CRF module. SAEs within 28 days from last Lorlatinib dose should be reported for both drugs.

Patient characteristics such as patient age, gender, height, weight, race, will be taken as a subset of patients enrolled to EXP-1 and summarized in frequency tables, and descriptive statistics will be provided for quantitative variables. Age will be recalculated based on the date of start of treatment with crizotinib.

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

Drug administration of crizotinib will be described in terms of treatment duration in months starting from new Cycle 1 Day 1, total number of cycles administered, the median (range) of cycles administered.

6.8. Analysis on Japanese Lead-In Cohort patients

Upon completion of the DLT observation period the following data listings will be provided for safety review:

- Demographic characteristics
- Administration schedule
- Prior therapies
- Concomitant therapies (Surgery/Systemic Therapy/Radiation Therapy)
- Adverse events
- Lab data
- Vital Signs
- ECG
- SAEs
- Deaths

At the Final Analysis the complete set of data will be listed separately from those of Phase 2 patients, including efficacy listings based on Derived Investigator Assessment and ICR and listings for ALK or ROS1 rearrangement status.

7. INTERIM ANALYSES

7.1. Introduction

7.2. Interim Analyses and Summaries

This is an open label, single arm trial for which no formal interim analysis is planned for the Phase 1 part and for the Phase 2 part for subgroup EXP-1 to EXP-5.

Phase 2 – Subgroup EXP-6

This is an open label, single arm cohort for which one interim evaluation is planned. The final analysis will be performed after the last subject last visit.

A group sequential two-stage sub-study will be conducted, using an O'Brien-Fleming stopping boundary for futility to test the null hypothesis on Overall Response Rate.

Accrual will be paused after testing the drug on 20 patients of the first stage. The cohort will be terminated if ≤5 patients respond. If at least 6 confirmed responses (CR or PR) according to Investigator Assessment are observed, accrual will be restarted and cohort will proceed to the second stage, and a total of 39 patients will be studied. If the total number of responding patients according to Investigator Assessment is ≥16 for this subpopulation, then the null hypothesis will be rejected.

The objectives of the interim analysis in EXP-6 group (i.e. only ROS1 Patients) are to:

- Assess the safety of the study treatment in ROS1 patients, and
- Stop the enrollment in the cohort early in the EXP-6 subpopulation due to futility if warranted.

8. REFERENCES

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9. APPENDICES

Appendix 1. Evaluation of RECIST tumor assessment Criteria

The details in evaluation of RECIST 1.1 criteria with modification to include assessment of CNS metastases adopted in the study are provided in Protocol Appendix 3.

The primary efficacy analysis for this study will be based on ICR and interpretation of tumor assessment scans from study sites (details of this process are described in the study specific ICR charter). Analyses based on ICR will use data as transferred from ICR without any further derivation except to account for censoring. Further details are provided in the Programming Plan.

This appendix describes:

- the rules used for programmatic derivation of tumor response and progression using RECIST version 1.1 based on Investigator Assessment of tumor data as recorded on the electronic case report forms (eCRF).

The first dose is defined as Cycle 1, Day 1 dose.

General Basis for the Rules

The tumor response criteria are based on RECIST 1.1 (Eisenhauer et al., 2009), with modification to account for intracranial tumor response (as described in Long et al, 2012).

"On-Study" Period for Response/PFS:

- is defined as the time from the date of first dose until progression, death, withdrawal of consent or loss to follow-up, whichever occurs first. However, deaths will be included in the PFS analysis if they occur within 14 weeks (2 tumor assessment timeframes + 2 weeks allowance) from the last tumor assessment on study.

Subsequent Anti-tumor Therapy:

- Includes any systemic anticancer therapy, radiation therapy (other than Palliative RT), and surgery

Methods of Tumor Assessment:

- The following are considered "interchangeable" methods:
  - bone lesions can be evaluated by:
    - CT – any type
    - MRI
    - Xray
    - Bone scan.

- Brain can be evaluated by:
    - CT – any type
    - MRI
- Lesions different from bone and brain can be evaluated by any of these methods.

Appendix 1.1. Overall Response

Adequate Baseline (for Investigator Assessment only)

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

- All lesions recorded at baseline must have an associated status recorded on the eCRF (e.g. if 3 target lesion sites of disease are recorded at baseline but only 2 have associated measurements, then the sum of longest dimensions cannot be calculated);
- Baseline lesions must be assessed with an acceptable method of tumor assessment that includes: Conventional CT Scan, Spiral CT Scan, X-ray, MRI, Physical Exam, Bone Scan, CT with contrast, CT without contrast, PET, and Other.
- For patients having only Lymph nodes as Target Lesions, the short axis of the Lymph nodes must be ≥15 mm when assessed by CT

Evaluation of Target Lesions for Each Visit:

Notes:

- The sum of lesion dimensions (SLD) is only considered if the methods of assessments are consistent with baseline. The "interchangeable" methods noted above are all considered consistent methods.

In the SLD, the longest diameter will be used for non-nodal lesions and the short axis dimension will be used for each lymph node included in the sum.

- Complete Response (CR) is defined by the disappearance of all non-lymph node target lesions (where all target lesions are recorded with a length of 0 mm on the "Target Lesions" eCRF). Any pathological lymph nodes (recorded as target lesion) must have reduction in short axis to < 10 mm. Note: the SLD may not be zero if lymph nodes are included as target lesions.
- Partial Response (PR) is defined by a 30% or more decrease in SLD of target lesions, taking as reference the baseline SLD.
- Progressive Disease (PD) is defined by a 20% or more increase in the SLD of target lesions relative to baseline or the smallest SLD (nadir) recorded since the first dose. In addition to the relative increase of 20%, SLD must also demonstrate an absolute increase of at least 5 mm (≥ 5 mm) relative to baseline or the smallest SLD (nadir) recorded since the first dose.
- Stable Disease (SD) is assigned when neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD is observed, taking as reference the smallest sum diameters while on study.
- No Target Lesion at Baseline (NB) is assigned if "No Target Lesion" is checked, on the "Target Lesions" eCRF.
- Indeterminate (IND) is assigned if any individual target lesion is evaluated as "Indeterminate" (if "Indeterminate" is checked on the "Target Lesions" eCRF), or

if inconsistent methods are used for post-baseline lesion assessment for any lesion, or if one or more target lesions are not assessed.

Note: if not all lesions identified at baseline are assessed or if some are IND but the SLD from the ones that are assessed confirm PD, then the target lesion response is PD.

Determination of target lesion response in case of reappearance of one or more target lesion(s) that have previously disappeared:

- If the previous target lesion response was CR, and a non-lymph node target lesion reappears, then the response is always PD.
- If the previous target lesion response was CR, and a lymph node target lesion reappears, then the response (whether CR or PD) is assessed based on PD criteria noted above. The response will be PD only if SLD criterion for PD is met and if the lymph node returns to pathologic size (≥ 10 mm) and meets the absolute requirement of 5 mm increase over nadir for the reappearing lesion. Otherwise, the response is CR.
- If the previous target lesion response was PR, then the response should be evaluated based on the SLD.

Evaluation of Non-Target Lesions for Each Visit:

Notes:

- The lesions assessed are only considered for CR, Non-CR / Non-PD and PD if the methods of assessments are consistent with baseline. The "interchangeable" methods noted above are all considered consistent methods.
    - CR is defined by the disappearance of all non-target lesions (where all non-target lesions are marked 'Absent' on the "Non-Target Lesion" eCRF). All lymph nodes must be non-pathological in size (< 10 mm in short axis).
    - Non-CR / Non-PD is defined if all non-target lesions are marked 'Present/Not Increased' on the "Non-Target Lesion" eCRF.
    - No Non-Target Lesion at Baseline (NB) is assigned if "No Non-Target Lesions" is marked on the "Non-Target Lesions" eCRF.
    - IND is assigned if any individual non-target lesion is evaluated as "Indeterminate" (marked as "Indeterminate" on the "Non-Target Lesions" eCRF), or if inconsistent methods are used for post-baseline lesion assessment for any lesion, or if one or more non-target lesions are not assessed.
    - PD is assigned if any non-target lesion is marked "Increased" on the "Non-Target Lesion" eCRF. However, in an effort to programmatically define "unequivocal progression" of non-target lesions, the derived non-target lesion response will also take into account the "Non-Target Lesions" assessment

from the IOTA eCRF (for non-target lesions) as noted in the following below:

Non-Target Lesion Assessment Status	"Non-Target Lesions" Assessment Status on IOTA eCRF	Derived Non-Target Lesion Response
PD ("Increased" is marked for ≥ 1 lesion)	PD	**PD**
	Non-CR/Non-PD	**Non-CR/Non-PD**
	CR	**Non-CR/Non-PD**
	Not Assessed (NA)	**PD**
	No Baseline (NB)	**PD**
	Indeterminate (IND)	**IND**
	Missing	**PD**

Note: Relevant discrepancies between the non-target lesion assessment status and information on the IOTA page will be queried.

New Lesion: is defined by the appearance of 1 or more new lesions (where any lesion is marked 'New' on the "New Lesions" eCRF). Note: the requirement for consistent methods of assessment with baseline, obviously, does not apply on new lesions.

Overall Response Evaluation for Each Visit:

- Overall response is determined from the derived target and non-target lesion data using conventions in the table below under the assumption that there are no new lesions identified at the visit.
- If there are any new lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.

The rules for derived overall response for each visit are presented in the table below.

Target Lesion Response	Non-Target Lesion Response	Overall Response
CR	CR	CR
CR	Non-CR/Non-PD	PR
CR	PD	PD
CR	IND	PR
PR	CR	PR
PR	Non-CR/Non-PD	PR
PR	PD	PD
PR	IND	PR
SD	CR	SD
SD	Non-CR/Non-PD	SD
SD	PD	PD
SD	IND	SD
PD	Any Response	PD

IND	PD	PD
IND	Non-PD	IND
Not Collected at Baseline	CR/(Non-CR/Non-PD)/PD/IND	CR/ (Non-CR/Non-PD) /PD/IND
CR/PR/SD/PD/IND	Not Collected at Baseline	CR/PR/SD/PD/IND
CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, IND=Indeterminate. Note: If non-target (or target) lesions are not collected at baseline, then the overall response is equivalent to the target (or non-target) lesions response.		

Best Overall Response Evaluation for Each Patient:

- The best overall response is the best response (CR, PR, SD, Non-CR/Non-PD ,PD or IND) derived during the "on-study" period for each study.
- Best overall response is derived from the sequence of derived objective responses at every visit.
- Assessments done after PD or after "anti-tumor treatment" but prior to PD will not be considered for evaluation of best overall response.
- For a patient to qualify for a best response of SD, the overall response evaluation must have met the stable disease criteria at least once since date of the first dose at a minimum interval of 6 weeks (42 days).
- unconfirmed CR and PR will be classified as a best response of SD provided it meets the 42 days requirement.
- Indeterminate (IND) is assigned for a patient who has only a baseline assessment, or a response assessment of CR/PR/SD at an interval less than 6 weeks and has no subsequent disease evaluation, or has all overall response evaluations assessed as IND.
- If a patient's first overall response other than IND is PD (documented within 14 weeks of first dose), then the patient's best overall response is PD. If the first response of CR/PR/SD at < 42 days is followed by a PD then the best overall response is PD.

The primary efficacy endpoint for phase 2 is objective response rate (both Overall and Intracranial). As such, confirmation of response with at least 4 weeks (28 days) between 2 assessments is required for this study. These 2 assessments need to evaluate all sites of disease that have been followed since baseline (i.e., all target and non-target lesions).

Note: Two PRs separated by one or more SD or IND assessment can be considered a confirmed response (i.e. confirmed PR) as long as the two PRs are ≥ 4 weeks (28 days) apart.

The table below presents derivation of best overall response status for specific cases

Week 6	**Week 12**	**Week 18**	**Week 24**	**Best Overall Response**
CR	CR	PD		CR

CR	IND	CR	PD	CR
CR	PR			SD if CR documented at 6 weeks; otherwise it is PD.
CR	PD			SD*
PR	CR	CR	PD	CR
PR	CR	PD		PR
PR	PR	PD		PR
PR	SD/IND	PR	PD	PR
PR	PR	CR	PD	PR
PR	PD			SD*
SD/IND	CR	PD		SD
SD/IND	PR	PD		SD
SD	PD			SD*
SD	IND			SD**
PD				PD
IND	PD			PD
IND	SD	PD		SD
IND	IND	PD		IND

* If SD was documented < 42 days following the date of first dose, the best overall response will be PD.
** If SD was documented < 42 days following the date of first dose, the best overall response will be IND.

Appendix 1.2. Overall Intracranial Response

Intracranial Response will be analyzed for Patients with CNS metastases at study entry (a subset obtained selecting only the patients with Target and/or Non Target Lesions having Disease Site=Brain at study entry).

Adequate Baseline for Intracranial Response (for Investigator Assessment only)

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

- All Brain lesions recorded at baseline must have an associated status recorded on the eCRF (e.g. if 3 target lesions are recorded at baseline but only 2 have associated measurements, then the sum of longest dimensions cannot be calculated);
- Baseline Brain lesions must be assessed with an acceptable method of tumor assessment that includes: Conventional CT scan, Spiral CT scan, CT without contrast, CT with contrast, MRI.

Evaluation of Target Lesions for Intracranial Response for Each Visit:

Notes:

- The sum of Brain lesion dimensions (SLD) is only considered if the methods of assessments are consistent with baseline. The "interchangeable" methods noted above are all considered consistent methods.

In the SLD, the longest diameter will be used for Brain lesions included in the sum.

- Complete Response (CR) is defined by the disappearance of all Brain target lesions (where all target lesions are recorded with a length of 0 mm on the "Target Lesions" eCRF).
- Partial Response (PR) is defined by a 30% or more decrease in SLD of target Brain lesions, taking as reference the baseline SLD.
- Progressive Disease (PD) is defined by a 20% or more increase in the SLD of target Brain lesions relative to baseline or the smallest SLD (nadir) recorded since the first dose. In addition to the relative increase of 20%, SLD must also demonstrate an absolute increase of at least 5 mm ($\geq$ 5 mm) relative to baseline or the smallest SLD (nadir) recorded since the first dose.
- Stable Disease (SD) is assigned when neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD is observed, taking as reference the smallest sum diameters while on study.
- Indeterminate (IND) is assigned if any individual target brain lesion is evaluated as "Indeterminate" (if "Indeterminate" is checked on the "Target Lesions" eCRF), or if inconsistent methods are used for post-baseline lesion assessment for any lesion, or if one or more target lesions are not assessed.

Note: if not all Brain lesions identified at baseline are assessed or if some are IND but the SLD from the ones that are assessed confirm PD, then the target lesion response is PD.

Determination of target lesion response in case of reappearance of one or more target lesion(s) that have previously disappeared:

- If the previous target lesion response was CR, and a target brain lesion reappears, then the response is always PD.
- If the previous target lesion response was PR, then the response should be evaluated based on the SLD.

Evaluation of Non-Target Lesions for Intracranial Response at Each Visit:

Notes:

- The Brain lesions assessed are only considered for CR, Non-CR / Non-PD and PD if the methods of assessments are consistent with baseline. The "interchangeable" methods noted above are all considered consistent methods.
    - CR is defined by the disappearance of all non-target Brain lesions (where all non-target lesions are marked 'Absent' on the "Non-Target Lesion" eCRF).
    - Non-CR / Non-PD is defined if all non-target Brain lesions are marked 'Present/Not Increased' on the "Non-Target Lesion" eCRF.
    - IND is assigned if any individual non-target Brain lesion is evaluated as "Indeterminate" (marked as "Indeterminate" on the "Non-Target Lesions" eCRF), or if inconsistent methods are used for post-baseline lesion assessment for any lesion, or if one or more non-target lesions are not assessed.
    - PD is assigned if any non-target Brain lesion is marked "Increased" on the "Non-Target Lesion" eCRF.

New Lesion: is defined by the appearance of 1 or more new Brain lesions (where any Brain lesion is marked 'New' on the "New Lesions" eCRF). Note: the requirement for consistent methods of assessment with baseline, obviously, does not apply on new lesions.

Overall Intracranial Response Evaluation for Each Visit:

- Overall Intracranial response is determined from the derived target and non-target brain lesion data using conventions in the table below under the assumption that there are no new Brain lesions identified at the visit.
- If there are any new Brain lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.

The rules for derived overall Intracranial Response for each visit are presented in the table below.

Target Brain Lesion	Non-Target Brain Lesion	

Response	Response	Overall Intracranial Response
CR	CR	CR
CR	Non-CR/Non-PD	PR
CR	PD	PD
CR	IND	PR
PR	CR	PR
PR	Non-CR/Non-PD	PR
PR	PD	PD
PR	IND	PR
SD	CR	SD
SD	Non-CR/Non-PD	SD
SD	PD	PD
SD	IND	SD
PD	Any Response	PD
IND	PD	PD
IND	Non-PD	IND
Not Collected at Baseline	CR/(Non-CR/Non-PD)/PD/IND	CR/(Non-CR/Non-PD)/PD/IND
CR/PR/SD/PD/IND	Not Collected at Baseline	CR/PR/SD/PD/IND
CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, IND=Indeterminate. Note: If non-target (or target) lesions are not collected at baseline, then the overall response is equivalent to the target (or non-target) lesions response.		

Best Overall Intracranial Response Evaluation for Each Patient:

- The best overall Intracranial Response is the best response (CR, PR, SD, PD or IND) recorded during the "on-study" period for each study.
- Best overall Intracranial Response is derived from the sequence of objective responses.
- Assessments done after PD or after "anti-tumor treatment" but prior to PD will not be considered for evaluation of best overall response.
- For a patient to qualify for a best Intracranial Response of SD, the overall Intracranial response evaluation must have met the stable disease criteria at least once since date of the first dose at a minimum interval of 6 weeks (42 days).
- unconfirmed Intracranial CR and PR will be classified as a best response of SD provided it meets the 42 days requirement.
- Indeterminate (IND) is assigned for a patient who has only a baseline assessment, or a Intracranial Response assessment of CR/PR/SD at an interval less than 6 weeks and has no subsequent disease evaluation, or has all overall response evaluations assessed as IND.

- If a patient's first overall Intracranial Response other than IND is PD (documented within 14 weeks of first dose), then the patient's best overall Intracranial Response is PD. If the first response of CR/PR/SD at < 42 days is followed by a PD then the best overall Intracranial Response is PD.

The primary efficacy endpoint for phase 2 is objective response rate (both Overall and Intracranial). As such, confirmation of Intracranial Response with at least 4 weeks (28 days) between 2 assessments is required for this study. These 2 assessments need to evaluate all sites of disease that have been followed since baseline (i.e., all target and non-target lesions).

Note: Two Intracranial PRs separated by one or more SD or IND assessment can be considered a confirmed response (i.e. confirmed PR) as long as the two PRs are ≥ 4 weeks (28 days) apart.

The table below presents derivation of best overall Intracranial Response status for specific cases

Week 6	**Week 12**	**Week 18**	**Week 24**	**Best Overall Intracranial Response**
CR	CR	PD		CR
CR	IND	CR	PD	CR
CR	PR			SD if CR documented at 6 weeks; otherwise it is PD.
CR	PD			SD*
PR	CR	CR	PD	CR
PR	CR	PD		PR
PR	PR	PD		PR
PR	SD/IND	PR	PD	PR
PR	PR	CR	PD	PR
PR	PD			SD*
SD/IND	CR	PD		SD
SD/IND	PR	PD		SD
SD	PD			SD*
SD	IND			SD**
PD				PD
IND	PD			PD
IND	SD	PD		SD
IND	IND	PD		IND

* If SD was documented < 42 days following the date of first dose, the best overall Intracranial Response will be PD.
** If SD was documented < 42 days following the date of first dose, the best overall Intracranial Response will be IND.

Appendix 2. Summary of efficacy analyses

PHASE 1			Patients from all of the dose escalation cohorts will be pooled Each set of outputs will be presented by ALK+/ROS1+ rearrangement
Endpoint	**Analysis Set**	**Purpose/Timing**	**Statistical Methods**
ORR	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	Point estimate of Rate of confirmed responses and related corresponding exact 95% CI; Waterfall plot and Spider Plot on ITT-ICR (See 6.1.2.1)
DR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
TTR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	Descriptive analysis (See 6.2.5)
DCR at 12/24 Weeks	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	Point estimate corresponding exact 95% CI (See 6.2.1)
IC-ORR	- CNS-ICR - CNS-IA	Subgroup analysis of secondary endpoint	Point estimate of Rate of confirmed responses and related corresponding exact 95% CI; Waterfall plot and Spider Plot on CNS-ICR (See 6.1.2.2)
IC-DR	Responding Patients in - CNS-ICR - CNS-IA	Subgroup analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
IC-TTR	Responding Patients in - CNS-ICR - CNS-IA	Subgroup analysis of secondary endpoint	Descriptive analysis (See 6.2.5)
IC-DCR at 12/24 Weeks	- CNS-ICR - CNS-IA	Analysis of secondary endpoint	Point estimate corresponding exact 95% CI (See 6.2.1)
PFS	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (median and 95% CI, 1 year and 18 months progression free survival probability and 95% CI) (See 6.2.2)
TTP		Analysis of exploratory endpoints	K-M method (median and 95% CI, 1 year and 18 months Survival probability and 95% CI) (See 6.3.1)
OS	- ITT	Analysis of secondary endpoint	K-M method (median and 95% CI, 1 year and 18 months Survival probability and 95% CI) (See 6.2.3)

Abbreviations:
ITT-ICR: Intention-To-Treat Analysis Set, Independent Central Review
ITT-IA: Intention-To-Treat Analysis Set, Investigator Assessment

CNS-ICR: Patients with CNS metastases based on Independent Central Review
CNS-IA: Patients with CNS metastases based on Investigator Assessment

PHASE 2			
Endpoint	**Analysis Set**	**Purpose/Timing**	**Statistical Methods**
	EXP-1:EXP-6		
ORR	- ITT-ICR - ITT-IA	Analysis of **primary endpoint**	Point estimate of Rate of confirmed responses and related exact 95% CI; Waterfall plot and Spider Plot on ITT-ICR) (See 6.1.2.1)
DR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
TTR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	Descriptive analysis (See 6.2.5)
DCR at 12/24 Weeks	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	Point estimate exact corresponding 95% CI (See 6.2.1)
IC-ORR	- CNS-ICR - CNS-IA	Subgroup analysis **of primary endpoint**	Point estimate of Rate of confirmed responses and related exact 95% CI; Waterfall plot and Spider Plot on CNS-ICR) (See 6.1.2.2)
IC-DR	Responding Patients in - CNS-ICR - CNS-IA	Analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
IC-TTR	Responding Patients in - CNS-ICR - CNS-IA	Analysis of secondary endpoint	Descriptive analysis (See 6.2.5)
IC-DCR at 12/24 Weeks	- CNS-ICR - CNS-IA	Analysis of secondary endpoint	Point estimate corresponding exact 95% CI (See 6.2.1)
PFS	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months progression-free survival probability and 95% CI and median and 95% CI) (See 6.2.2)
TTP	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.6)
OS	- ITT	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.3)
IC-TTP	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.6)
IC-TTP	- CNS-ICR - CNS-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.6)

PHASE 2			
Endpoint	**Analysis Set**	**Purpose/Timing**	**Statistical Methods**
IC-TTP	Pts with no CNS-Mets - ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.6)
Pts receiving prior ALK TKIs **Pts receiving prior crizotinib** **Pts receiving one prior ALK TKI different from crizotinib** **Pts receiving at least one prior 2nd generation ALK TKI** **Pts receiving at least 2 prior ALK TKIs**	**Pooled EXP-2:EXP-5,** **Pooled EXP-2: EXP-3A** **EXP-3B** **Pooled EXP-3B: EXP-5** **Pooled EXP-4:EXP-5**		
ORR	- ITT-ICR - ITT-IA	Analysis of **primary endpoint**	Point estimate of Rate of confirmed responses and related exact 95% CI; Waterfall plot on ITT-ICR (See 6.1.2.1)
DR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
TTR	Responding Patients in - ITT-ICR - ITT-IA	Analysis of secondary endpoint	Descriptive analysis (See 6.2.5)
DCR at 12/24 Weeks	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	Point estimate corresponding exact 95% CI (See 6.2.1)
IC-ORR	- CNS-ICR - CNS-IA	Subgroup analysis **of primary endpoint**	Point estimate of Rate of confirmed responses and related exact 95% CI; Waterfall plot on CNS-ICR (See 6.1.2.2)
IC-DR	Responding Patients in - CNS-ICR - CNS-IA	Analysis of secondary endpoint	K-M method (median and 95% CI) (See 6.2.4)
IC-TTR	Responding Patients in - CNS-ICR - CNS-IA	Analysis of secondary endpoint	Descriptive analysis (See 6.2.5)

PHASE 2			
Endpoint	**Analysis Set**	**Purpose/Timing**	**Statistical Methods**
PFS	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.2)
OS	- ITT	Analysis of secondary endpoint	K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.3)
CI-CNS prog CI-Non CNS Prog CI Death	- ITT-ICR - ITT-IA	Analysis of secondary endpoint	Cumulative Incidence curve (all three CIs in the same graph (See 6.2.7)
CI-CNS prog CI non CNS prog CI Death	- CNS-ICR - CNS-IA	Analysis of secondary endpoint	Cumulative Incidence curve (all three CIs in the same graph (See 6.2.7)
	EXP-1 only		
ORR	crizotinib Post PF-06463922 analysis set	Analysis of secondary endpoint	Point estimate of Rate of confirmed responses and related exact 95% CI; Waterfall plot (See 6.1.2.1)
PFS			K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.2)
DR			K-M method (median and 95% CI) (See 6.2.4)
TTR			Descriptive analysis (See 6.2.5)
OS			K-M method (1 year and 18 months Survival probability and 95% CI and median and 95% CI) (See 6.2.3)

Abbreviations:
ITT-ICR: Intention-To-Treat Analysis Set, Independent Central Review
ITT-IA: Intention-To-Treat Analysis Set, Investigator Assessment
CNS-ICR: Patients with CNS metastases based on Independent Central Review
CNS-IA: Patients with CNS metastases based on Investigator Assessment
EXP-3A Patients relapsing after with prior crizotinib therapy and prior regimens of chemotherapy.
EXP-3B Patients with 1 prior non-crizotinib ALK TKI therapy +/- prior regimens of chemotherapy

Appendix 3. Data Derivation Details

Appendix 3.1. ALK or ROS1 rearrangement status

The ALK rearrangement status will be derived from the CRF pages MOLECULAR BIOLOGY OF DISEASE 1, 2 and 4 (forms MBIA_G_DL_1 / MBIA_G_DL_2 / MBIA_G_DL_4)

If the value in the "QUALITATIVE RESULT" is "POSITIVE" in the Page MBIA_G_DL_1, or the value is "POSITIVE" or "2+" or "3+" in the Page MBIA_G_DL_2, or in the Page MBIA_G_DL_4, response to either of following question is "YES": "the Specific Gene Alteration-POSITIVE (SPECIFIC ALTERATION UNKNOWN):"; "Specific Gene Alteration-EML4-ALK.V1 (E13; A20):"; "Specific Gene Alteration-EML4-ALK.V3A/B (E6; A20):"; "Specific Gene Alteration-EML4-ALK.V2 (E20; A20):"; "Specific Gene Alteration-EML4-ALK.V7 (E14; A20):"; "Specific Gene Alteration-EML4-ALK.V4 (E15; A20):"; "Specific Gene Alteration-EML4- ALK.V5A/B (E2; A20):"; "Specific Gene Alteration-KIF5B-ALK:"; "Specific Gene Alteration-TFG-ALK:" , then the status is ALK rearrangement positive

The ROS1 rearrangement status will be derived from the CRF pages MOLECULAR BIOLOGY OF DISEASE 5, 6 and 7 (forms MBIA_G_DL_5 to MBIA_G_DL7)

If the value in the "QUALITATIVE RESULT" is "POSITIVE" in the Pages MBIA_G_DL_5 or MBIA_G_DL_6, or the value in the "QUALITATIVE RESULT" is either "POSITIVE" or "2+" or "3+" in the Page MBIA_G_DL_7, then the status is ROS1 rearrangement positive.

Appendix 4. 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
- What is described above remains the same for the calculations even if the intended dose level changes, per protocol, during the study.

Appendix 5. List of terms grouped for specific analyses

Appendix 5.1. Medications to lower Cholesterol and/or Triglycerides

ATORVASTATIN
ATORVASTATIN CALCIUM
BEZAFIBRATE
EZETIMIBE
FENOFIBRATE
FISH OIL
GEMFIBROZIL
INEGY
LOVASTATIN
NICOTINIC ACID
OMEGA-3 TRIGLYCERIDES
OMEGA-3-ACID ETHYL ESTER
PITAVASTATIN
PITAVASTATIN CALCIUM
PRAVASTATIN
PRAVASTATIN SODIUM
ROSUVASTATIN
ROSUVASTATIN CALCIUM
SIMVASTATIN

Appendix 6. Definition and Use of Visit Windows in PRO Reporting

The following visit label and visit windows will be applied for the analysis of PRO endpoints.

A Questionnaire is considered complete if at least one question is answered regardless of whether DONE/ NOT DONE is checked for the variable: EFND (i.e., efficacy not done).

In the case of multiple records for a patient within a particular visit window, then use the assessment which is closest to the target day. In the unlikely event that both (or all) the records are equidistant from the target day then use the patient's last assessment within that visit window.

Visit Label	Visit Window (inclusive)	Target Day	Width (days)
Lead-in Day -7	-10 to -7	-7	
Cycle 1 Day 1	-6 to 1	1	
Cycle 2	12 to 32	22	21
Cycle 3	33 to 53	43	21
Cycle 4	54 to 74	64	21
Cycle 5	75 to 95	85	21
Cycle 6	96 to 116	106	21
Cycle 7	117 to 137	127	21
Cycle 8	138 to 158	148	21
Cycle 9	159 to 179	169	21
Cycle 10	180 to 200	190	21
Cycle 11	201 to 221	211	21
Cycle 12	222 to 242	232	21
Cycle 13	243 to 263	253	21
Cycle 14	264 to 284	274	21
……			
……			
End of Treatment	Visit window applicable to subject's end of treatment visit		

Appendix 7. DLT Definition (Phase 1)

Severity of adverse events will be graded according to NCI CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring in the first cycle of treatment (21 days) which are attributable to PF-06463922.

Hematologic:

- Grade 4 neutropenia lasting >7 days.
- Febrile neutropenia (defined as ANC <1000/mm^3 with a single temperature of ≥38.3°C (≥(101°F) or a sustained temperature of ≥38°C (≥100.4°F) for >1 hour).
- Grade ≥3 neutropenic infection.
- Grade ≥3 thrombocytopenia with bleeding.
- Grade 4 thrombocytopenia.

Non-Hematologic:

- Grade ≥3 pancreatitis.
- Grade ≥3 toxicities (excluding Grade ≥3 laboratory abnormalities not requiring dose modifications) persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals).
- Symptomatic Grade ≥3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs), or asymptomatic Grade ≥3 QTc prolongation that has been confirmed by repeat testing and re-evaluation by a qualified person, and persists after correction of reversible causes such as electrolyte abnormalities or hypoxia.
- ≥20% decrease in Left Ventricular Ejection Fraction (LVEF) compared to baseline echocardiogram or Multi Gated Acquisition Scan (MUGA) using the same method.

Other:

- Failure to deliver at least 16 out of the 21 prescribed daily total doses (approx. 75% planned dose for Cycle 1) due to toxicities attributable to study drug.
- Failure to restart dosing after 21 days (1 cycle) delay due to toxicities attributable to study drug.

Appendix 8. Programming specifications

Appendix 8.1. TTP of the last prior treatment regimen before PF-06463922

Assume that the dataset *xx* has 2 records for each patient (*subjid*) and following other variables:

- *treat*, the treatment (PF-06463922 or last prior treatment regimen, identified in the code below as "last line treatment")
- *ttp_strt*, the start time in days of TTP (set to 0 for last prior treatment regimen and set to [PF-06463922 start date - prior start date + 1] for the PF-06463922 treatment)
- *ttp_end* the stop time in days of TTP (for each *treat*, set to [{end date - start date + 1}+*ttp_strt*])
- *ttpcens,* the censoring flag (0=not censored, 1=censored)

With this dataset, the following SAS code will generate the hazard ratio, the 95% CI and the p-value.

```
proc phreg data=xx covs(aggregate) covm;
  class treat  (ref='last line treatment')  ;
  model (ttp_strt, ttp_end)*ttpcens(1) = treat /ties=efron rl;
  ods output parameterestimates=param;
id subjid;
run;
```

Note that: patients having only 1 record will not contribute to the results; prior to running PROC PHREG; the dataset should be sorted by *treat* and *subjid*, with the stop date on the first record ≤ the start date on the second record; the assignment of 1/0 values for the censoring/progression flags values can be reversed as long as the model statement is changed accordingly; the value of *treat* must be the same for all prior records (eg, assign a value such as "last line treatment" for all patients rather than the specifics of the prior treatment given for the patient) and the value of *treat* must be the same for all PF-06463922 records (eg, a value such as "PF-06463922")