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

Compound:	PF-06463922
Compound Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	118,296
European Clinical Trial Database (EudraCT) Number:	2013-002620-17
Protocol Number:	B7461001
Phase:	1/2

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 8	23 January 2019	Since the primary endpoint of the study has been met and secondary endpoints characterized, the main purpose of the amendment is to fulfill the obligation to provide drug supply and standard of care to the patients still receiving a benefit from the study drug. Therefore, a reduced Schedule of Assessments is introduced allowing to perform most study procedures per standard of care or clinical judgment of treating physician. Data recording will be limited to adverse events, with the purpose of performing long term safety assessments and overall survival. Further clarification on dose modifications section (5.2.7) and management of toxicities guidelines. Update to Section 5.2, PF-06463922 will not be supplied anymore as 5 mg tablets. Revision to Concomitant Treatments section 5.3 to align with the PF-06463922 approved label. Hormonal contraceptives not listed anymore as a highly effective method because they are metabolized by CYP3A, which may be induced by PF-06463922. Pregnancy test assessments frequency increased by adding every cycle monitoring during the study treatment, and at first follow-up visit. Contraceptive check frequency increased by adding every cycle monitoring during the study treatment and subsequent follow-up. Changes to Analysis Set definitions, to match SAP V5.0 finalized after Protocol Amendment 6 removing the Evaluable for Response Analysis Sets and to incorporate regulatory recommendation on ITT definition. Added clarifications on pooled/subgroup

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		analyses. Added clarifications on the evaluation of Disease Control Rate at 12 and 24 weeks. Added details on analysis of DDI cohort. End of trial definition updated.
Amendment 7	23 March 2018	Clarification to Section 1.3.5, Section 4.1, and Section 4.3.1 regarding the requirement for all sexually active men to use a condom through 97 days after the last dose of PF-06463922 to prevent any transfer and exposure of study drug to the partner given the known embroyonic and fetal toxicity risk. Additonal monitoring (Transthoractic Echocardiogram) for patients enrolled in France and Germany per the request of Health Authorities in those countries. Table 5, Footnote 16, updated to remove 9 hour PK timepoint as this is a typo. Also removed from Section 7.2.8. Added Appendix 13, which is required for sites in France only.
Amendment 6	15 July 2016	Addition of Drug-Drug interaction (DDI) and Holter Monitoring in parallel with the ongoing Phase 2 part of the study. Added language in applicable sections to include this study. Study Endpoints, Study Objectives, and the Statistical Analysis section updated to support the DDI and Holter monitoring and the Statistical Analysis Plan. Addition of exclusion criteria and clarification of inclusion criteria for patients participating in the DDI and Holter monitoring in Phase 2. Clarification to Exclusion Criteria 4; patients

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		who experience clinically significant tumor flare may begin treatment with a shortened prior systemic washout period, after discussion with the sponsor. Removal of some required assessments in Phase 1, Phase 2, and Japanese Patient Only Lead-In Cohort (LIC), and reduction of frequency in some assessments in Phase 1, Phase 2, and Japanese LIC. Allowance of Fine Needle Aspiration (FNA) samples as a substitute for De Novo biopsies in both Phase 1 and Phase 2 only if De Novo biopsy is not safe or feasible. Adjustment in the sample sizes of ALK-positive patient subgroups being studied in Phase 2. Updated Statistical Analysis Section to correlate with this change. Increase in overall sample size in Phase 2 and overall sample size in the study. Revised Dose Modification Guideline for patients who experience first-degree, second-degree or complete heart block. Removed food and beverage restriction as it relates to PF-06463922 dosing requirements. Removal of restriction for taking proton pump inhibitors (PPI) concomitantly with PF-06463922. Minor other clarifications throughout.
Amendment 5	11 March 2016	Updated the Background sections to include new data in animals relating to the association of lorlatinib and teratogenicity. Minor related changes made to the Contraception section without changes made to contraception guidance. Updated the Background sections to include

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		new information on PR interval prolongation as seen in a healthy volunteer study and in Study B7461001. Updated Exclusion Criterion 9 to exclude patients with a PR interval >220 msec, or 2nd- or 3rd-degree AV block within 3 months prior to study entry and to align with other ongoing and planned Pfizer-sponsored clinical trials with PF-06463922. Added a dose modification guideline for patients with PR interval prolongation in Section 5.2.7. Added Appendix 12 which provides examples of drugs known to prolong PR interval. Minor administrative edits made to the Adverse Event and Reporting and Publication of Study Results sections.
Amendment 4	22 July 2015	Identification and justification of Recommended Phase 2 Dose (RP2D), including available safety, pharmacokinetics, and efficacy data from Phase 1. Alignment of Phase 1 and Phase 2 Study Objectives and Endpoints. Update to the type and allocation of patients in the subgroup categories (EXP) in Phase 2. Increase in Phase 2 sample size. Revisions of Patient Inclusion Criteria; clarification of patient population entry criteria relating to prior treatment, modification of serum total amylase requirement and removal of alkaline phosphatase requirement. Additionally, removal of requirement for negative pregnancy test at baseline visit. Revision of Patient Exclusion Criteria;

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		removal of patients who are in the locally advanced disease setting, exclusion of patients who have had prior treatment with antibody therapy or drugs specifically targeting T-cell co-stimulation or immune checkpoint pathways, removal of exclusion criteria relating to contraindication to midazolam (MDZ) administration as this substudy is no longer required in Phase 2, exclusion of patients requiring drugs that are strong CYP2C19 and/or CYP2C8 inhibitors, exclusion of patients requiring drugs that are known P-gp substrates with a narrow therapeutic index, and exclusion of pregnant women or breastfeeding women per country requirement. Additional clarification that patients with bradycardia are not excluded if otherwise healthy (eg, runners, etc.). Addition of optional crizotinib treatment after PF-06463922 in Phase 2 for ALK+ NSCLC patients who were treatment naïve prior to receiving PF-06463922. Added Safety Reference Documents for crizotinib. Removal of some required assessments in Phase 2 including Midazolam substudy, Food Effect substudy, some PK requirements, Urine Sample for 6 beta-Hydroxycortisol/ Cortisol (6β-OHC/C) Ratio, Blood for beta-Hydroxycholesterol/Cholesterol, Mini Mental State Examination, and Blood Specimen for Circulating Tumor Cell (CTC) enrichment. Revisions to the PK requirements, including timepoints, in Phase 2. Addition of some required assessments in Phase 2 including assessments of Cognition, Mood and Suicidal Ideation and Behavior (SIB) and Contraceptive check (as appropriate). Added the requirement for a rater at each site to administer the assessments of Mood and Suicidal Ideation and Behavior

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		(SIB). Change in sample size of patients receiving Lead-In Dose in Phase 2 from 30 patients to approximately 10 Non-Japanese patients and 3 Japanese patients. Revision to the timepoint requirements in Phase 2 for Electrocardiogram (ECG) collection and PK collection. Clarification that some of the required laboratory assessments in Phase 2 (chemistry, hematology, coagulation, lipids, and urinalysis) may be performed within 72 hours of the next cycle start. Clarification that Cerebrospinal Fluid (CSF) in Phase 2 will only be collected at Screening for those patients who have suspected or confirmed Leptomeningeal Carcinomatosis not visualised on MRI. After Screening, CSF collection is not required. Clarification that for patients in Phase 2 who have not had prior systemic therapy in the locally advanced or metastatic disease setting, a de novo biopsy sample is not required unless the previous sample was collected >4 months after the first PF-06463922 dose. Additional clarification that tumor tissue slides are acceptable if country regulations prevent sending core biopsy sample. Revision of Dose Modification Tables for Phase 1 and Phase 2 including the addition of specific Dose Modifications for Non-Hematologic toxicities, Hematologic toxicities, Lipid Elevations, and Central Nervous System (CNS) effects. Added a Dose Reduction Table for Phase 2. Added requirement for submission of radiographic images to a Central Core

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		Imaging Laboratory in Phase 1 (retrospectively) and Phase 2 (prospectively). Updated PF-06463922 drug packaging and tablet strength information in Phase 2. Revision to Concomitant Treatment and Medication Section; added data available from Phase 1, added a table for suggested Lipid-Lowering agents, and added information around caution of using drugs that are considered proton pump inhibitors. Updated Statistical Analysis Section to align with modifications/additions to Protocol Amendment 4, including sample size determination, planned analyses across Phase 2 subgroups. Revised Appendix 9 to align with changes made to the Schedule of Activities table in Phase 2. Revised Appendix 10 per modifications made to Phase 2 Schedule of Activities table. Added Appendix 11 for ALK+ NSCLC patients who were treatment-naïve prior to receiving PF-06463922 and go on to receive crizotinib. Adverse Event Reporting and Communication of Results by Pfizer language updated to align with Pfizer protocol template. Minor editorial and clarifications for consistency throughout.
Amendment 3	29 October 2014	Clarified that additional doses in Phase 1 may be explored outside of the continual reassessment method (CRM) model recommendations to optimize recommended Phase 2 dose (RP2D) determination. Increased Phase 1 and Phase 2 sample size. Updated Statistical Analysis section to reflect

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		increase in Phase 1 and Phase 2 sample size and cover exploration of doses outside of CRM model recommendations. Added lipid testing to Phase 1 and Phase 2 to further evaluate the effect of PF-06463922 on cholesterol and triglyceride levels. Added a Food Effect Substudy in Phase 1 (up to 6 patients) and a corresponding Phase 1 study objective and endpoint to assess the impact of food on PF-06463922 safety and pharmacokinetics (PK). Added the requirement for a neurological assessment in at least 12 Phase 1 patients at baseline (and thereafter if clinically indicated) to better understand and characterize some of the CNS effects observed to date in Phase 1. Added that twice daily (BID) dosing will be tested in Phase 1 to further characterize and evaluate the safety and PK of PF-06463922. Changed the requirement from bone scans required in all patients at Screening and every 12 weeks thereafter to bone scans required at Screening for all patients and only thereafter if bone disease was identified at baseline. Additionally, clarified that for patients with documented disease progression who are still receiving PF-06463922, tumor assessments may be done as per standard of care. Added a Japanese patient-only Lead-In Cohort (LIC) to investigate the safety and PK of PF-06463922 in Japanese patients. Updated Inclusion Criterion #2 in Phase 1 only to additionally allow patients to enter the study who have had more than 2 prior ALK or ROS inhibitors. Updated Inclusion Criterion #14 for Japan sites only to further define patients not of childbearing potential.

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		Removed Exclusion Criterion #11 to avoid contradiction to Exclusion Criterion #4. Clarified that in those countries where the standard of care does not allow for treatment-naïve patients to receive PF-06463922 in the first-line treatment setting, those patients will be excluded from EXP-1 and EXP-4 subgroups in Phase 2. Added a Cycle 3 Day 1 time point for Blood Specimens for Circulating Nucleic Acid (CNA) to Phase 2. Aligned Study Objectives in Phase 1 and Phase 2 with Study Endpoints. Removed Screening Blood Metabolite Profiling sample collection in Table 4. Minor editorial changes made throughout.
Amendment 2	28 March 2014	**Minor clarifications and corrections made throughout** Updated Schedule of Activities table in Part 1 and Part 2, including PK and PD tables, to align with protocol text and study objectives, endpoints, and applicable appendices. Updated Part 2 Study Endpoints to clarify efficacy analyses to be performed in Phase 1 and Phase 2 to allow an in-depth characterization of the efficacy profile in the different subpopulations. Added the source for the reference document being used for midazolam. Revised Study Inclusion and Exclusion criteria. Updated Dose-Limiting Toxicity (DLT) definition to clarify that Grade ≥3 laboratory abnormalities do not immediately constitute a

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		DLT, and clarified the criteria for intrapatient dose escalation. Clarified that midazolam may be evaluated with fewer than 3 to 4 dose levels depending on emerging PK results from previous dose levels evaluated. Added new Medication Error section, and updated Hospitalization, Exposure During Pregnancy, Occupational Exposure and Serious Adverse Event Reporting Requirements to align with Pfizer's policy on Adverse Event monitoring. Updated Communication of Results section to align with Pfizer's policy of Public Disclosure.
Amendment 1	17 September 2013	**Minor editorial changes made throughout** **<u>Reason for amendment</u>**: • Per US FDA review of the IND, an assessment of left ventricular ejection fraction (LVEF) was added to ensure safety monitoring of any potential LVEF dysfunction, and a specific exclusion criterion as well as specific DLT definition and instructions for dose modification in case of toxicity were added to the protocol. • In addition, the measurement of secondary measures of efficacy were added to objectives and the endpoints list was modified accordingly. • Finally, minor editorial changes were made throughout the protocol to fix some inconsistencies. **Schedule of Activities in Phase 1, Table 1** • *Added* "LVEF (Echocardiogram or MUGA) Assessment at Screening, before dosing at Day 1 Cycle 2, before dosing at Day

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		1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.), and at the End of Treatment visit (±2 days time window applicable at the discretion of the investigator)." **Schedule of Activities in Phase 2, Table 3** • *Added* "LVEF (Echocardiogram or MUGA) Assessment at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.), and at the End of Treatment visit (±2 days time window applicable at the discretion of the investigator)." • Footnote #24, Banked biospecimen: *Reduced* blood volume collected from "6 mL" to "4 ml", as this is the actual volume that will be collected. **Schedule of Pharmacokinetic Activities in Phase 2, Table 4** • To be consistent with the text in the protocol, a row was *added* to the "MDZ Substudy" to include "Blood sample for PF-06463922 metabolite profiling" to be collected at screening, and at steady-state Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs post dose. **Schedule of Pharmacokinetic Activities in Phase 1 and Phase 2** • *Updated* the Table 2 and Table 4 to match Footnote #4 and #7 respectively, to indicate the urine sample for all patients will be collected at Day 1 Cycle 2. **Section 1.3.4, Safety Considerations in the**

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		Clinical Trial • *Added* "changes in left ventricular ejection fraction" to the list of safety observations that would be monitored in the study. **Section 2.1, Study Objectives and Section 2.2. Endpoints** • *Added* "To assess secondary measures of clinical efficacy" as a Secondary Objectives in the Phase 2 objectives. **Section 2.1, Study Objectives and Section 2.2. Endpoints** • *Added* "Left Ventricular Ejection Fraction" to the list of Secondary Endpoints. • *Added* "Disease Control Rate (DCR) at 6 and 12 weeks" to the list of Secondary Endpoints in Phase 2 of the study. DCR is defined as the percent of patients with a confirmed complete response (CR), partial response (PR) or stable disease (SD) according to RECIST 1.1, at 6 and 12 weeks, respectively. **Section 4.2, Exclusion Criteria** • *Added* Criteria #22: "Patients presenting with abnormal Left Ventricular Ejection Fraction (LVEF) by echocardiogram or Multi Gated Acquisition Scan (MUGA) according to institutional lower limits." **Section 3.2 DLT definition (Phase 1)** *Added* to "Non Hematologic": • A ≥20% decrease in Left Ventricular Ejection Fraction (LVEF) compared to baseline echocardiogram or Multi Gated Acquisition Scan (MUGA). **Section 5.2.1, Formulation and Packaging**

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		• *Removed* "commercially available" from how Midazolam will be supplied, as Midazolam will be supplied by the Sponsor. • *Clarified* that the prescribed dose of Midazolam will be "2 mg/mL". **Section 5.2.7, Table 6: PF-06463922 Dose Modifications for PF-06463922-Related Toxicity** • *Added* "LVEF dysfunction" dose modification criteria. **Section 7.1 and Section 7.1.7, Safety Assessments** • *Added* "In order to monitor potential left ventricular ejection fraction dysfunction, an echocardiogram or Multi Gated Acquisition Scan (MUGA) will be performed at the time points described in the Schedule of Activities. • *Changed* "patient reported outcomes" to "mini mental state examination (MMSE)" in the list of safety assessments that will be monitored in the study. **Section 7.5.1, Markers of Drug Response** • *Reduced* blood volume collected for the blood biospecimen from "6 mL" to "4 mL", as this is the actual volume that will be collected. **Section 9.3, Sample Size Determination, Phase 2** • For clarification of the Phase 2 sample size determination, *added* "If the total number of responding patients is equal to or greater than 20 for each subpopulation, then the null hypothesis will be rejected." **Section 9.4.2, Analysis of Secondary**

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		Endpoints • *Added* "Disease Control Rate (DCR) at 6 and 12 weeks" to the list of secondary endpoints to be analyzed. Specifically, "Disease Control Rate (DCR) is defined as the percent of patients with a confirmed complete response (CR), partial response (PR) or stable disease (SD) according to RECIST 1.1, at 6 and 12 weeks, respectively. DCR at weeks 6 and 12 will be analyzed in the same subpopulations described in Section 9.4.1 for ORR." **Section 9.6.2, Analysis of Secondary Safety Endpoints for Both Phase 1 and Phase 2** *Added* "Left Ventricular Ejection Fraction" to the list of secondary endpoints to be analyzed. Specifically, "For patients with MUGA scans or echocardiograms, individual LVEF (left ventricular ejection fraction) proportion (%) and its changes from baseline will be summarized by time point. The number of patients and the percentage whose maximum decrease from baseline in LVEF is equal or greater than 20% will be calculated."
Original protocol	28 June 2013	N/A

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

PROTOCOL SUMMARY

INDICATION

Anaplastic Lymphoma Kinase (ALK)-positive (ALK+) or ROS oncogene 1 (ROS1)-positive (ROS1+) advanced non-small cell lung cancer (NSCLC).

BACKGROUND AND RATIONALE

PF-06463922 is a selective, ATP competitive small molecule tyrosine kinase inhibitor (TKI) of the ALK and ROS1 receptor tyrosine kinases (RTK) that also potently inhibits ALK kinase domain mutations responsible for resistance to crizotinib. Oncogenic fusions of ALK and ROS1 define two distinct subsets of human lung adenocarcinoma patients and play essential roles in regulation of tumor cell survival, growth and metastasis.

In vitro, PF-06463922 demonstrated potent, concentration-dependent inhibition in catalytic activities of ALK, ALK mutants and ROS1 kinases in recombinant enzyme and cell based assays. PF-06463922 also inhibited ALK and ROS1 dependent oncogenic functions in human NSCLC cell lines, and demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting either non mutant ALK and ROS1 fusion variants or mutant ALK fusions that are acquired and resistant to crizotinib treatment.

In vivo, PF-06463922 demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib resistant EML4 ALKL1196M or EML4 ALKG1269A mutations. PF-06463922 treatment significantly reduced the tumor size and prolonged animal survival in the orthotopic brain models (EML4 ALK and EML4 ALKL1196M) in mice. The anti tumor efficacy of PF-06463922 was dose dependent and demonstrated strong correlations to inhibition of ALK or ROS1 phosphorylation. The plasma levels associated with inhibitory activity of PF-06463922 against EML4 ALKL1196M phosphorylation and anti tumor efficacy in EML4 ALKL1196M dependent human NSCLC cell line models was utilized to project target human plasma concentrations for clinical studies.

There remains an unmet medical need to improve ALK+ NSCLC and ROS1+ NSCLC patients' outcomes as no ALK directed compounds so far evaluated have demonstrated curative results. Additional drugs are needed to overcome resistance mechanisms, to impact patient outcomes through improved response rates and progression free survival (PFS) and significant anti-tumor activity on central nervous system (CNS) metastases.

STUDY OBJECTIVES AND ENDPOINTS

Phase 1 Portion of the Study

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 pharmacokinetic (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 systemic therapies.

Exploratory Objectives:

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

Phase 2 Portion of the Study

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 systemic 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 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.

Endpoints

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 (Appendix 3). 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.[32]

Secondary Endpoints [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), 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 (Appendix 3) [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.[32]
- 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, eg, ALK kinase domain mutations, and Circulating Nucleic Acid (CNA), eg, ALK kinase domain mutations.

Secondary Endpoints [ALK+ NSCLC Phase 2 patients 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.

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 interval with PF-06463922 treatment.

STUDY DESIGN

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

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 50 patients (depending on toxicities observed). Additionally, a food effect substudy will be conducted in approximately 6 patients enrolled in Phase 1.

To understand the single-dose pharmacokinetics (PK) of PF-06463922, a lead-in period preceding the continuous daily dosing will be conducted. To evaluate the effect of PF-06463922 on CYP3A inhibition/induction, a midazolam (MDZ) drug-drug interaction (DDI) substudy will be conducted at 3 to 4 PF-06463922 dose levels in Phase 1 (fewer dose levels may be evaluated depending on emerging PK results). During the study, real-time pharmacokinetic monitoring will be conducted as much as possible.

The Phase 2 portion of the study 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.

To evaluate the safety and tolerability of PF-06463922 in Japanese patients, a Japanese patient-only lead-in cohort (LIC) will be enrolled to examine the safety and PK of PF-06463922 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 the 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 discontinuation 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, 3 additional patients to a total of 6 will be enrolled and treated. Additional patients may be enrolled depending on the overall safety and PK profile.

To evaluate the potential interaction of PF-06463922 on 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 (6 evaluable for each probe substrate) 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 comparing the subject's time-matched PR interval (approximately 10 points) with exposure of PF-06463922 following a single dose and again at steady state. In addition, arrhythmia analysis will be performed in these patients and these data will be analyzed separately from Phase 2 data. 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.

The Phase 2 portion 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 ALK+ NSCLC treatment-naïve patients to receive PF-06463922 in the first-line treatment setting, patients will not be enrolled in 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-3A-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 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 ROS1+ NSCLC treatment-naïve patients to receive PF-06463922 in the first-line treatment setting, patients will not be enrolled in 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.

Guidance on the management of patients on study is provided to investigators in Table 1. The revised schedule of activities will allow the investigators to perform most study tests and procedures per standard of care or clinical judgement.

STUDY TREATMENT

The starting dose for PF-06463922 in the Phase 1 will be 10 mg administered once daily (or twice daily [BID] dosing) 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 in the Phase 2 will receive PF-06463922 as a single agent at the RP2D of 100 mg once daily (QD) in 21-day cycles.

For patients participating in the MDZ DDI study in Phase 1, PF-06463922 will be administered with MDZ on Cycle 1 Day 15. In the MDZ interaction sub-study, patients will receive a single 2 mg oral dose of MDZ on Day -7 and will receive another single 2 mg oral dose of MDZ concurrently with PF-06463922 on Cycle 1 Day 15 (morning dose if on BID dosing schedule).

For patients participating in the food effect study in Phase 1, PF-06463922 will be administered following an overnight fast of at least 10 hours on Cycle 1 Day -7 and Cycle 1 Day 1.

For patients participating in the DDI and Holter monitoring part of the study, patients will be administered a dose of probe substrate alone in the fasted state when possible (no food 2 hours before through 2 hours after dosing of probe substrate) on Day -2, and then starting on Cycle 1 Day 1, patients will begin daily dosing of 100 mg QD PF-06463922. On Cycle 1 Day 15, another single dose of the probe substrate will be administered in the fasted state when possible (no food 2 hours before through 2 hours after dosing of probe substrate) concurrently with PF-06463922. Twenty-four 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.

In all study parts, patients will continue with the study treatment until progression of disease as determined by the investigator, unacceptable toxicity, death or consent withdrawal. Patients may continue PF-06463922 treatment after objective progression of disease is determined if the patient is continuing to experience clinical benefit, in the opinion of the investigator, and after discussion with the Sponsor.

SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each assessment required for compliance with the protocol.

Upon approval of Amendment 8, study activities will be reduced as described in Table 1.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities in order to conduct evaluations or assessments required to protect the well-being of the patient.

The SOA for each of the two study sections and the Japanese patient-only LIC are separately reported in the Tables and Appendix below.

Table 1 reduced schedule of assessments upon approval of Amendment 8.

Table 2 and Table 3 for the Phase 1 Portion of the Study.

Table 4 and Table 5 for the Phase 2 Portion of the Study.

Table 6 for the Drug-Drug Interaction and Holter Monitoring Study Requirements

Appendix 9 for Japanese patient-only LIC.

Appendix 11 for patients receiving Crizotinib post PF-06463922.

SCHEDULE OF ACTIVITIES

Table 1. Reduced Schedule of Assessments upon approval of Amendment 8

	Study Treatment[1]		
Protocol Activity	**Visits on Day 1 of Every Other Cycle**	**End of Treatment[12]**	**Follow- Up[13]**
Visit or Assessment Window (days) Unless Otherwise Noted	**±4 days**	**±2 days**	**±7 days**
Contraceptive check (as appropriate)[2]	X (every cycle ±2 days)	X	X
Laboratory			
Pregnancy test[3]	X (every cycle ±2 days)	X	X
For France and Germany only: Transthoracic echocardiogram to assess PAP and right heart function[4]	Every 24 weeks ±2 weeks	X	
Study Treatment			
PF-06463922 Treatment[5]	Once a day continuously		
Tumor Assessments			
CT and MRI Scan or Equivalent[6]	As per local clinical practice		
Other Clinical Assessments			
Adverse Events[7]	X	X	X
Survival Follow-up			X
Other Samples			
De Novo Tumor Specimens[8]		'X'	
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[9]		X	
Cerebrospinal fluid (CSF) PF-06463922 concentration (optional)[10]	Any time during steady state, ideally 4-6 hours and 8-9 hours post-dose		
Blood sample (whenever CSF for PF-06463922 is collected)[11]	Same time as CSF PF-06463922 concentration sample collected		

1. All assessments should be performed prior to dosing with study medications unless otherwise indicated. All cycles are 3 weeks in duration (±2 days). Sufficient study medication for 2 cycles of treatment will be dispensed at each clinic visit. The Investigator is responsible for informing the patient to contact the clinical site in case of any adverse events.
2. **Contraceptive check**: patient may be contacted by phone to confirm contraception is still appropriate per the protocol. Males and females of childbearing potential must be contacted post-study to ensure that they continue to use appropriate contraception for at least 97 and 21 days, respectively, after the last dose of study drug.
3. **Serum Pregnancy Test:** Pregnancy tests will be routinely repeated at every cycle (±2 days) during the active treatment period, at the end of study therapy (± 2 days), at first follow-up visit (± 7 days), and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations. The pregnancy test should be performed at the clinical site's local laboratory. Where that is not possible, patients will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.
4. **For sites in France and Germany**, a transthoracic echocardiogram (TTE) will be performed every 6 months (±2 weeks) during treatment, and only at the End of Treatment visit if the previous assessment was >1 month. Pulmonary arterial pressure (PAP) will be assessed.
5. **Study Treatment:** described in the Study Treatments section.
6. **Tumor Assessments:** Will be repeated at the frequency as per local clinical practice, tumor assessment information should be retained in the patient's file for documentation purposes
7. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
8. **De Novo Tumor Specimens:** Optional de novo tumor biopsy at the time of progression is strongly encouraged for all patients enrolled in the study. If present, pleural effusion (PE) cell pellet may substitute for tumor core biopsy, as appropriate. Fine needle aspiration (FNA) samples (2-3 pathes prepared as FFPE cell block) are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. If local country regulations do not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) are acceptable. Tissue specimens from all patients will be used for additional biomarker analyses. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual
9. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling:** 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
10. **CSF PF-06463922 Concentration Sample (Optional)**: If a patient undergoes a lumber puncture, a sample of CSF should be collected for exploratory analysis of PF-06463922 concentration, if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample. If scheduling permits, one CSF sample should be taken between 4 and 6 hours post dose. If it is possible to take a second sample, collection should be between 8 and 9 hours post-dose.
11. If a CSF PF-06463922 concentration sample is collected, a blood sample for PK analysis should be collected at approximately the same time as the CSF sample.
12. **End of Treatment Visit:** Obtain these assessments if not completed in the last week. For patients who receive crizotinib following treatment with PF-06463922, assessments at the End of Treatment visit are according to Appendix 11.

13. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo assessment for resolution of any treatment-related toxicity, and pregnancy test for female patients. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. After study discontinuation the survival follow-up will be performed every 2 months and will include also the collection of information on subsequent anticancer therapies (telephone contact is acceptable).

Table 2. Phase 1 Portion of the Study

Note: The current table is no longer applicable after the approval of Amendment 8

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3- 25 (Up to Month 18) (21 days)	CYCLES >25 (Months >18) (21 days)		
Protocol Activity	**Screening [1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit Window (days)	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Informed consent[2]	X									
Tumor history	X									
Medical history	X									
Physical examination including weight	X	(X)	(X)			X	X	X		
Baseline signs and symptoms[3]		X	X							
Height	X									
Weight	X		X			X	X	X		
Vital signs[4]		X	X	X	X	X	X	X	X	
Performance status[5]	X		X			X	X	X	X	
Laboratory										
Hematology[6]	X		(X)		X	X	X	X	X	
Blood Chemistry[7]	X		(X)		X	X	X	X	X	
Coagulation[8]	X		(X)						X	
Lipids[9]	X		(X)		X	X	X	X	X	
Urinalysis[10]	X		(X)						X	
Pregnancy test[11]	X	X	(X)			X	X	X	X	
(12-lead) ECG[12]	X	X	X	X	X	X	X		X	
LVEF Assessments (Echocardiogram or MUGA)[28]	X					X	X	Every 4 Cycles	X	

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3- 25 (Up to Month 18) (21 days)	CYCLES >25 (Months >18) (21 days)		
Protocol Activity	**Screening [1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit Window (days)	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
For France and Germany only: Transthoracic echocardiogram to assess PAP and right heart function[30]							Every 6 months ±2 weeks	Every 6 months (±2 weeks)	X	
Registration and Treatment										
Registration[13]		X								
PF-06463922 Treatment[14,15]		X	Once a day or twice a day, continuously							
Midazolam Treatment for patients participating in the midazolam sub-study[16]		X (MDZ only)			X					
Tumor Assessments										
CT and MRI Scan or Equivalent[17]	X						X and then every 6 weeks ±1 week	Every 12 weeks ±1 week	(X)	
Cerebrospinal Fluid[18]	X						X	X		
Other Clinical Assessments										
Adverse Events[19]		X	X	X	X	X	X	X	X	X
Concomitant Medications and non-drug supportive interventions[20]	X		X			X	X	X		X
EORTC QLQ-C30, QLQ-LC13[25]		X				X	X	X	X	
Neurological exam[29]	X	Only as clinically indicated								
Survival Follow-up										X
Other Samples										

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3- 25 (Up to Month 18) (21 days)	CYCLES >25 (Months >18) (21 days)		
Protocol Activity	**Screening[1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit Window (days)	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Archival Tumor Tissue Specimen[21]	X									
De Novo Tumor Specimens[22]	'X'								'X'	
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[23]	X								X	
Banked Biospecimen[24]	X									

Footnotes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.

1. **Screening:** To be obtained within 28 days prior to registration.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
3. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening of baseline signs and symptoms will be recorded on the Adverse Events CRF page.
4. **Vital Signs:** Blood pressure and pulse rate to be recorded in sitting position.
5. **Performance Status:** use ECOG – see Appendix 4.
6. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 1.
7. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 1.
8. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 1.
9. **Lipids:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 1.
10. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 1.
11. **Serum Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Adequate contraception (2 forms as described in the protocol) must be initiated after the first negative pregnancy test is obtained at screening. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period (every other Cycle beyond 18 months), at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.

12. **Triplicate 12-lead ECGs:** At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected as follows: a) at Screening, b) Day -7 (Lead-in) after single-dose administration at pre-dose, at projected C_{max} (1 hr), and at 4 hrs post-dose, c) Cycle 1 Day 1, Day 8, and Day 15 at pre-dose (0 hour) and 1 hours post-dose. For Cycles 2-5, 1 hr post-dose (time matched with PK), and d) End of Treatment. In addition to these time points, ECGs should be repeated as clinically indicated. Additional ECG time points may be included based on the emerging data.

    When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection such that the blood sample is collected at the nominal time. If the mean QTc is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. All ECG assessments should be matched with a PK sample.
13. **Registration:** patient number and dose level allocation operated by Pfizer Inc. Registration will be within 2 days prior to lead-in single dose as appropriate.
14. **Trial Treatment:** described in the Study Treatments section.
15. **Lead-in PF-06463922 Dose:** A single dose of PF-06463922 will be given on Day –7 (lead-in period) for all patients in the Phase 1 except the patients who are scheduled for the midazolam (MDZ) interaction substudy. The timing of the lead-in dose may be modified based on PK data obtained.
16. **Midazolam (MDZ) Treatment:** For patients who are scheduled for the MDZ interaction substudy only. A single 2-mg oral dose of MDZ will be given on Day –7 and Cycle 1 Day 15. On Cycle 1 Day 15, MDZ will be given concurrently with PF-06463922. Patients participating in the MDZ substudy will NOT receive any lead-in dose of PF-06463922 on Day -7.
17. **Tumor Assessment:** Tumor assessments will include all known or suspected disease sites. CT or MRI scans of Chest Abdomin Pelvis [CAP] and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5 mm for lesions greater than 10 mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases are observed at baseline. For all tumor assessments, the method of assessment that was used at baseline should be the same method used throughout the study. For patients who are without documented disease progression, CT and MRI scans to be done every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ±1 week beyond 18 months,and responses to be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment will be done every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ±1 week beyond 18 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients who have documented disease progression but are still receiving PF-06463922, CT and MRI scans are to be done according to local institutional standard of care. Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1 especially if there are dosing cycle interruptions due to toxicities. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks (more than 12 weeks beyond 18 months) have passed since the last evaluation. CSF sampling in patients with asymptomatic leptomenigeal disease/carcinomatous meningitis (LM/CM) will be performed at baseline, and if clinically safe and feasible, further CSF cytology will be performed on study every 2 cycles of treatment (every 12 weeks beyond 18 months) to assess disease.
18. **Cerebrospinal Fluid (CSF)**: CSF is mandatory for patients who have asymptomatic radiologically suspected leptomeningeal disease (LM) or carcinomatous meningitis (CM) but negative spinal fluid. CSF will be collected at baseline and on study to determine PF-06463922 concentrations. A blood sample for PK analysis should also be collected at approximately the same time as the post-dose CSF sample.
19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
20. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.

21. **Archival Tumor Tissue Specimen:** All patients will provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen, specifically a FFPE tissue block that contain sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that are 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block cannot be submitted. If an archival tumor tissue sample is not available, a de novo tumor specimen must be obtained. Specimens will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation.
22. **De Novo Tumor Specimens:** Optional de novo tumor biospy at screening and at the time of progression is encouraged. If present, pleural effusion (PE) cell pellet may substitute for tumor core biopsy, as appropriate. Fine needle aspiration (FNA) samples (2-3 pathes prepared as FFPE cell block) are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. If local country regulations do not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) are acceptable. In all cases, this specimen will be provided in addition to the archival tumor tissue specimen that is required for enrollment. Tissue specimens from all patients will be used for additional biomarker analyses. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
23. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling:** 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at screening and at end of treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
24. **Banked Biospecimen**: Unless prohibited by local regulations, a blood specimen (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, will be collected at screening.
25. **EORTC QLQ-C30 and QLQ-LC13:** Patients must complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points prior to dosing. At Day -7 (lead- in period) site staff (eg, site coordinators) should instruct patients that the assessment should be completed without help from friends or family members and also recommend that this assessment be completed in the morning. All scheduled assessments of the EORTC QLQ-C30 and QLQ LC13 cannot be taken home and must be completed in the clinic prior to any other study or medical procedures.
26. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuing treatment for reasons other than progression of disease will continue to perform tumor assessments until PD or a new anti-cancer therapy is commenced. Survival followup every 2 months after PD or new anti-cancer therapy has commenced will be performed (telephone contact is acceptable).
27. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments if during the first 18 months, then last 12 weeks if beyond month 18).
28. **LVEF Assessments:** Echocardiogram or MUGA to be performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.) up to approximately 18 months, and then every 4 cycles thereafter, and at the End of Treatment visit (±2 days time window applicable at the discretion of the investigator). The same method should be used at each time point.
29. **Neurological Examination:** A neurological examination by a licensed neurologist may be conducted in at least 12 patients in Phase 1 at baseline and, if clinically indicated, at any time point thereafter.
30. For sites in France and Germany, a transthoracic echocardiogram (TTE) will be performed every 6 months (±2 weeks) during treatment, and only at the End of Treatment visit if the previous assessment was >1 month. Pulmonary arterial pressure (PAP) will be assessed.

Table 3. Phase 1 Portion of the Study Pharmacokinetic Assessments

Note: After cycle 5, PK samples collection is not required anymore, except for CSF sample collection as detailed on Footnote 9

			CYCLE 1 (21 days)			CYCLE 2-5 (21 days)
Protocol Activity	**Screen (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**
Visit Window	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**
All patients						
Plasma sampling for full PF-06463922 PK in patients not participating in the MDZ or the food effect substudy[1]		X	X	X	X	X
MDZ Substudy						
Plasma sampling for full PF-06463922 PK in patients participating in the MDZ substudy[2]			X	X	X	X
Plasma sampling for full MDZ PK[3]		X			X	
Food Effect Substudy						
Blood sample for PF-06463922 in Food Effect Study[4]		X	X	X	X	X
Blood sample for PF-06463922 metabolite profiling[5]					X	
24-hour urine collection for PF-06463922 PK[6]					X	
All Patients						
Urine Sample for 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio[7]		X	X	X	X	X (Cycle 2 only)
4β-hydroxycholesterol/ Cholesterol Blood Sample[8]		X	X	X	X	X
Cerebrospinal fluid for PK concentration (optional)[9]					Anytime at steady state	

Footnotes

1. **PF-06463922 PK Sampling:** *Blood samples will be collected for PK sampling on the following days 1*) ***Day-7 (Lead-in)*** Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96 and 120 hours post dose (two samples between 48 to 120 hrs). 2) **Cycle 1 Day 1 and Day 8** at pre-dose, 1 hour and 4 hours post dose, 3) **Cycle 1 Day 15**: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hours**. For patients on BID dosing, the 24-hour time point sample need not be collected.** 4) **Day 1 of Cycles 2 to 5**: Pre-dose and 1 hour post dose (time matched with ECG).
2. **PF-06463922 PK Sampling f*or patients who participate in the MDZ interaction* substudy:** Blood samples will be collected on Cycle 1 Day 1 and Cycle 1 Day 15 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hours post dose. On Cycle1 Day 8, a blood sample will be collected at pre-dose, 1 and 4 hours post-dose. Cycles 2-5: Pre-dose and 1 hour (time matched with ECG).
3. **MDZ PK Samples:** In MDZ interaction substudy, a PK profile of MDZ will be collected after a single oral MDZ dose on Day –7 (lead-in period) and Cycle 1 Day 15 at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 9, and 24 hours post dose.

4. **Food-Effect Substudy:** PK samples will be collected on Day -7 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96, and 120 hrs post dose (2 samples between 48 to 120 hrs) and Cycle 1 Day 1 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hrs post-dose. For patients on BID dosing, the 24 hour time point sample need not be collected. Each patient will serve as their own control in which PF-06463922 will be administered in the morning under either "fed" or "fasted" conditions on Day (-7) and Day 1 of Cycle 1. PK samples after Cycle 1 Day 1 will follow same schedule as footnote (1). The testing order for fed versus fasted conditions will be as follows: The first half of the patients in this substudy will be tested under fed followed by fasted conditions and the second half of the patients will be tested under fasted followed by fed conditions.
5. **Blood Sample for PF-06463922 Metabolite Profiling:** Metabolite profiling will be conducted in the food effect cohort for all patients. Blood samples will be collected at steady-state on Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs post-dose.
6. **Urine for PF-06463922 PK:** Urine will be collected for 24 hrs after PF-06463922 dosing on Cycle 1 Day 15 from food effect cohorts over the following intervals: 0 to 4 hrs, 4 to 12 hrs and 12 to 24 hrs post-dose. For patients on BID dosing, 12-24-hour post-dose urine collection is not required.
7. **Urine Sample for 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio:** Morning urine sample (pre-dose) will be collected on Day-7, Day 1 of Cycle 1, Day 8 & 15 of Cycle 1 and Day 1 of Cycle 2.
8. **Blood Sample for 4β-hydroxycholesterol/Cholesterol**: Blood sample will be collected at pre-dose on Day-7, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycles 2 to 5 Day 1.
9. **CSF Sample (Optional):** If a patient undergoes a lumber puncture, a sample of CSF should be collected for exploratory analysis of PF-06463922 concentration, if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample.

Table 4. Phase 2 Portion of the Study

Note: The current table is no longer applicable after the approval of Amendment 8

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)		
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Informed consent[2]	X									
Tumor history	X									
Medical history	X									
Physical examination	X	(X)	(X)			X	X	X		
Baseline signs and symptoms[3]		X	X							
Height	X									
Weight	X		X			X	X	X		
Vital signs[4]			X	X	X	X	X	X	X	
Performance status[5]	X		X			X	X	X	X	
Contraceptive check (as appropriate)		(X)	X			X	X	X		
Laboratory										
Hematology[6]	X		(X)		X	X	X	X	X	
Blood Chemistry[7]	X		(X)		X	X	X	X	X	
Lipids[8]	X		(X)		X	X	X	X	X	
Hypogonadism (male patients)[9]	X				X	X	C5D1 and Q 4 cycles thereafter	Every 4 Cycles	X	
Coagulation[10]	X		(X)						X	
Urinalysis[11]	X		(X)						X	
Pregnancy test[12]	X	X	(X)			X	X	X	X	
(12 lead) ECG[13]	X	X	X	X	X	X	X (upto Cycle 5)		X	

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)		
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
LVEF Assessments (Echocardiogram or MUGA)[28]	X					X	X	Every 4 Cycles	X	
For France and Germany only: Transthoracic echocardiogram to assess PAP and right heart function[32]							Every 6 months ±2 weeks	Every 6 months ±2 weeks	X	
Registration and Treatment										
Registration[14]		X	(X)							
PF-06463922 Treatment[15,16]		X	Once a day continuously							
Tumor Assessments										
CT and MRI Scan or Equivalent[17]	X						X and then every 6 weeks ±1 week	Every 12 weeks ±1	(X)	(X)
Cerebrospinal fluid if leptomenigeal/carcinomatous meningitis [LM/CM]disease is present[18]	X									
Other Clinical Assessments										
Adverse Events[19]		X	X	X	X	X	X	X	X	X
Concomitant medications and non drug supportive interventions[20]	X		X			X	X	X		X
EORTC QLQ-C30, QLQ-LC13[25]		X	X			X	X	X	X	

			CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)		
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[27]**	**Follow- Up[26]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Cognitive Assessment[29]	X	X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Mood Assessment[30]		X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Suicidal Ideation and Behavior[31]		X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Survival Follow-up										X
Other Samples										
Archival Tumor Tissue Specimen[21]	X									
De Novo Tumor Specimens[22]	X								‘X’	
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[23]	X						X		X	
Banked Biospecimen[24]	X									

Footnotes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required. For example, if a patient will not have the Lead-In (Day -7) Visit, some assessments may be required on Cycle 1 Day 1 instead of Day -7 and vise versa.

1. **Screening:** To be obtained within 28 days prior to registration.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures that are not considered standard of care.
3. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening Baseline signs and symptoms will be recorded on the Adverse Events CRF page.
4. **Vital signs:** blood pressure and pulse rate to be recorded in sitting position.
5. **Performance Status:** use ECOG – see Appendix 4.

6. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, hematology labs may be done within 72 hours of dosing with results checked prior to dosing.
7. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, blood chemistry may be done within 72 hours of dosing with results checked prior to dosing.
8. **Lipids:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, lipids may be done within 72 hours of dosing with results checked prior to dosing.
9. **Hypogonadism Laboratory Test:** to be performed in male patients only. The required blood tests are reported in Appendix 2. Blood draws MUST be done between 08.00-11.00 AM. Should a decrease of ≥25% from baseline be observed in total testosterone or free testosterone a repeat laboroatory analysis of both these parameters must be performed at the next clinical visit to confirm hypogonadism.
10. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, coagulation may be done within 72 hours of dosing with results checked prior to dosing.
11. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, urinalysis may be done within 72 hours of dosing with results checked prior to dosing.
12. **Serum Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period (every other cycle beyond 30 months), at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
13. **Triplicate 12-lead ECGs:** At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected as follows: a) at Screening, b) Day -7 (Lead-in) at pre-dose, 1 hr, 2 hr and 4 hrs post-dose, c) Cycle 1 Day 1, Day 8, and Day 15 at pre-dose, 1 hr and 2 hrs post-dose, d) Cycles 2-5 Day 1 at pre-dose and 1 hr and 2 hrs post-dose and e) End of Treatment. If at any of these time-points the mean QTc is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

    When an ECG and PK sample are scheduled at the same time, ECG assessments should be performed prior to PK sample such that the PK sample is collected at the nominal time (but regardless, the exact time of ECG assessment and PK collection should always be recorded).
14. **Registration:** Registration will be within 2 days prior to lead-in or study treatment start.
15. **Trial Treatment:** described in the Study Treatments section.
16. **Lead-in PF-06463922 Dose:** A single dose of PF-06463922 will be given on Day –7 (lead-in period) for 10 Non-Japanese and 3 Japanese (non-LIC) patients, after which exemptions to this lead- in period requirement may be granted after discussion with Sponsor. Consideration will be given by the sponsor to shorten the duration of the lead in period for those patients who experience disease related symptom flare.

17. **Tumor Assessment:** Tumor assessments will include all known or suspected disease sites. CT or MRI scans of Chest Abdomin Pelvis [CAP] and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5mm for lesions greater than 10mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases is observed at baseline. For all tumor assessments, the method of assessment that was used at baseline should be the same method used throughout the study. CT and MRI scans to be done at every 6 weeks ±1 week up to approximately 30 months, and then every 12 weeks ±1 week beyond 30 monthsand responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment will be done every 6 weeks ±1 week up to approximately 30 months, and then every 12 weeks ±1 week beyond 30 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients who have documented disease progression but are still receiving PF-06463922, CT and MRI scans are to be done according to local institutional standard of care. Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1 especially if there are dosing cycle interruptions due to toxicities. Tumor assessment should be repeated at the end of treatment and study visits if more than 6 weeks (more than 12 weeks beyond 30 months) have passed since the last evaluation. Tumor assessments will continue until progression of disease or a new anti-cancer therapy has commenced. For all patients, copies of radiologic images must be available for independent central radiology review as determined by the sponsor. Detailed instructions will be provided in the Study Reference Manual.
18. **Diagnostic Cerebrospinal fluid (CSF)** CSF analysis will not be required unless patients have suspected or confirmed leptomeningeal carcinomatosis not visualised on MRI. When applicable, CSF sample will be collected at Screening (optional CSF collection post Screening). See PK assessments for PF-06463922 CSF concentration sampling (optional).
19. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
20. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
21. **Archival Tumor Tissue Specimens:** All patients will provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen, specifically a FFPE tissue block that contain sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that are 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block cannot be submitted. Specimens will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation.
22. **De Novo Tumor Specimens:** De novo tumor core biopsy collection will be mandatory at screening unless it is considered to pose a safety risk to the patient, in the opinion of the Investigator, and only after discussion with the Sponsor; please refer to Section 7.3 for further guidance. For patients who are treatment naïve at Screening (ie, no previous systemic therapy in the metastatic setting), a de novo tumor biopsy is not required if a previous tumor biopsy was performed within 4 months of first dose of PF-06463922. Pleural effusions (PE) cell pellets may substitute for tumor core biopsy as appropriate. Fine needle aspiration (FNA) samples (2-3 pathes prepared as FFPE cell block) are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. If local country regulations do not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) are acceptable. Specimens will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation. In addition, optional de novo tumor biospy collection at the time of progression is encouraged. Tumor tissue specimens from all patients will be used for additional biomarker analyses. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

23. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling:** 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at screening, at the end of Cycle 2 (matching the first tumor restaging, in practical terms this may be C3D1 pre-dose) and at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
24. **Banked Biospecimens**: Unless prohibited by local regulations, a blood sample (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, will be collected at screening.
25. **EORTC QLQ-C30 and QLQ-LC13:** Patients must complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points prior to dosing. At Day -7, or Cycle 1 Day 1 if this is the first dose, site staff (eg, site coordinators) should instruct patients that the assessment should be completed without help from friends or family members and also recommend that this assessment be completed in the morning. All scheduled assessments of the EORTC QLQ-C30 and QLQ LC13 cannot be taken home and must be completed in the clinic prior to any other study or medical procedures.
26. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuating treatment for reasons other than progression of disease will continue to perform tumor assessments until PD or a new anti-cancer therapy is commenced. Bimonthly survival followup after PD or new anti-cancer therapy has commenced will be performed (telephone contact is acceptable). For patients who receive crizotinib following treatment with PF-06463922, follow-up is according to Appendix 11.
27. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments up to 30 months and then last 12 weeks beyond 30 months). For patients who receive crizotinib following treatment with PF-06463922, assessments at the End of Treatment visit are according to Appendix 11.
28. **LVEF Assessments**: Echocardiogram or MUGA will be performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.) up to approximately 30 months, and then every 4 Cycles thereafter, and at the End of Treatment visit. A ±2 days time window applicable at the discretion of the investigator is allowed at all time points. The same method should be used at each time point.
29. **Cognitive Assessment:** A computerized cognitive test compromised of verbal learning, psychomotor function, attention and memory will be administered to patients prior to study drug dosing. This test will take approximately 10-20 minutes to complete and will be administered via qualified site personnel. A practice test will be performed at Screening and a baseline test will be done on the first day of PF-06463922 dosing (ie, day -7 or C1D1, whichever is their first dose), and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this test will be administed prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).
30. **Mood Assessment:** An assessment of mood via the Beck Depression Inventory-II (BDI-II) scale will be administered to patients prior to the first day of PF-06463922 dosing (ie, day -7 or C1D1, whichever is their first dose) and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this test will be administered prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).
31. **Suicidal Ideation and Behavior Assessment:** An assessment of suicidal ideation and behavior via the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to patients prior to study drug dosing (ie, day -7 or C1D1, whichever is their first dose) and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this will be administered prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).
32. For sites in France and Germany, a transthoracic echocardiogram (TTE) will be performed every 6 months (±2 weeks) during treatment, and only at the End of Treatment visit if the previous assessment was >1 month. Pulmonary arterial pressure (PAP) will be assessed.

Table 5. Phase 2 Portion of the Study - Pharmacokinetic Assessments (Not Applicable for Patients in the DDI and Holter Study)

Note: After cycle 10, PK samples collection is not required anymore, except for CSF sample collection as detailed on Footnotes 4 and 5

			CYCLE 1 (21 days)			CYCLE 2-5 (21 days)	CYCLE 6, 8 and 10 (21 days)
Protocol Activity	**Screen (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**
Visit Window	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**
Full PF-06463922 PK samples[1]		X	X	X	X	X	X
Sparse PF-06463922 PK samples[2]			X			X	X
PF-06463922 metabolite profiling blood samples[3]					X		
Cerebrospinal fluid (CSF) PF-06463922 concentration (optional)[4]					Any time during steady state, ideally 4-6 hrs and 8-9 hrs post-dose		
Blood sample (whenever CSF for PF-06463922 is collected)[5]					Same time as CSF PF-06463922 concentration sample collected		

Footnotes.

1. **PF-06463922 Full PK Sampling (10 Non-Japanese patients and 3 Japanese (non-LIC) patients enrolled in the trial): NO LONGER APPLICABLE upon Amendment 6.** *Blood samples will be collected for PK sampling on the following days 1*). ***Day-7 (Lead-in)*** Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96 and 120 hours post dose (2 samples between 48 to 120 hrs). 2) **Cycle 1 Day 1 and Day 8** at pre-dose, 1 hr, 2 hr, and 4 hr post dose, 3) **Cycle 1 Day 15**: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs**.** 4) **Day 1 of Cycles 2 to 5:** Pre-dose 1 hr and 2 hrs post-dose 5) **Day 1 of Cycle 6 and Day 1 of every other Cycle thereafter**: Pre-dose. Sites will be notified via letter when full PK sampling is no longer required (ie, after 10 Non-Japanese patients and 3 Japanese (non-LIC) patients). Where required by local regulations and after agreement by the study sponsor, patients may be hospitalized for PK sampling. For all other patients, sparse plasma samples will be collected as per table footnote 2 below. Additional PK plasma samples may also need to be collected at the time of optional CSF sample collection according to footnote 4.
2. **Sparse Plasma Sampling for PF-06463922 (in all patients after 10 Non-Japanese and 3 Japanese (non-LIC) patients with full PK sampling)** Blood samples will be collected pre-dose on Day 1 of Cycles 1-5 and pre-dose on Day 1 of Cycle 6,Day 1 of Cycle 8 and Day 1 of Cycle 10. Sites will be notifed via letter when sparse PK sampling is in effect.

3. **PF-06463922 Metabolite profiling (10 Non-Japanese and 3 Japanese (non-LIC) patients enrolled in the trial): NO LONGER APPLICABLE upon Amendment 6.** Blood samples will be collected at steady-state on Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hrs post-dose. Sites will be notified via letter when metabolite profiling is no longer required.
4. **CSF PF-06463922 Concentration Sample (Optional):** If a patient undergoes a lumber puncture, a sample of CSF should be collected for exploratory analysis of PF-06463922 concentration, if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample. If scheduling permits, one CSF sample should be taken between 4 and 6 hours post dose. If it is possible to take a second sample, collection should be between 8 and 9 hours post-dose.
5. If a CSF PF-06463922concentration sample is collected, a blood sample for PK analysis should be collected at approximately the same time as the CSF sample.

Table 6. Drug-Drug Interaction and Holter Monitoring Study

Note: The current table is no longer applicable after the approval of Amendment 8

	Screen	Pre Cycle 1		CYCLE 1 (21 days)				CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)	Post Treatment	
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -2)**	**Baseline ECG Day -1**	**Day 1**	**Day 8**	**Day 14**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[33]**	**Follow- Up[34]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**N/A**	**N/A**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Informed consent[2]	X											
Tumor history	X											
Medical history	X											
Physical examination	X	(X)		(X)				X	X	X		
Baseline signs and symptoms[3]				X								
Height	X											
Weight	X			X				X	X	X		
Vital signs[4]				X	X		X	X	X	X	X	
Performance status[5]	X			X				X	X	X	X	
Contraceptive check (as appropriate)				X				X	X	X		
Laboratory												
Hematology[6]	X			(X)			X	X	X	X	X	
Blood Chemistry[7]	X			(X)			X	X	X	X	X	
Lipids[8]	X			(X)			X	X	X	X	X	
Hypogonadism (male patients)[9]	X						X	X	C5D1 and Q 4 cycles thereafter	Q 4 Cycles	X	
Coagulation[10]	X			(X)							X	
Urinalysis[11]	X			(X)							X	
Pregnancy test[12]	X			X				X	X	X	X	

	Screen	Pre Cycle 1		CYCLE 1 (21 days)				CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)	Post Treatment	
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -2)**	**Baseline ECG Day -1**	**Day 1**	**Day 8**	**Day 14**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[33]**	**Follow- Up[34]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**N/A**	**N/A**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
(12 lead) ECG[13]	X							X	X (up to Cycle 5)		X	
LVEF Assessments (Echocardiogram or MUGA)[35]	X							X	X	Q 4 Cycles	X	
Registration and Treatment												
Registration[14]		X										
PF-06463922 Treatment[15]				Once a day continuously								
PK and Holter												
Serial blood samples for PF-06463922 PK[16]				X			X	X	X (Cycles 4, 6, 8 and 10)			
Blood samples for PF-06463922 metabolite(s)[17]				X			X					
Single-dose of probe[18]		X					X					
Serial blood plasma samples for probe substrate PK[18]		X					X					
Pharmacogenomics Sample[19]		X										
24-Hour Continuous ECG[20]			X	X		X						
Tumor Assessments												
CT and MRI Scan or Equivalent[21]	X								X and then every 6 weeks ±1 week	Every 12 weeks ±1	(X)	(X)

	Screen	Pre Cycle 1		CYCLE 1 (21 days)				CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)	Post Treatment	
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -2)**	**Baseline ECG Day -1**	**Day 1**	**Day 8**	**Day 14**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[33]**	**Follow- Up[34]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**N/A**	**N/A**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Cerebrospinal fluid if leptomenigeal/carcinomatous meningitis [LM/CM]disease is present[22]	X			Optional and as clinically indicated								
Other Clinical Assessments												
Adverse Events[23]		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and non drug supportive interventions[24]	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30, QLQ-LC13[25]				X				X	X	X	X	
Cognitive Assessment[26]	X			X				X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Mood Assessment[27]				X				X	X up to Cycle 6 and then D1 of every other cycle	X	X	

	Screen	Pre Cycle 1		CYCLE 1 (21 days)				CYCLE 2 (21 days)	CYCLES 3 – 38 (Up to Month 30) (21 days)	CYCLES >38 (Months >30) (21 days)	Post Treatment	
Protocol Activity	**Screen[1] (≤28 days)**	**Lead-in PK (Day -2)**	**Baseline ECG Day -1**	**Day 1**	**Day 8**	**Day 14**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[33]**	**Follow- Up[34]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**N/A**	**N/A**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Suicidal Ideation and Behavior[28]				X				X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Survival Follow-up												X
Other Samples												
Archival Tumor Tissue Specimen[29]	X											
De Novo Tumor Specimens[30]	X										'X'	
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[31]	X								X		X	
Banked Biospecimen[32]	X											
Cerebrospinal fluid (CSF) PF-06463922 concentration (optional)[36]							Any time during steady state, ideally 4-6 hrs and 8-9 hrs post-dose					
Blood sample (whenever CSF for PF-06463922 is collected)[37]							Same time as CSF PF-06463922 concentration sample collected					

Footnotes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.

1. **Screening:** To be obtained within 28 days prior to registration.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures that are not considered standard of care.
3. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening Baseline signs and symptoms will be recorded on the Adverse Events CRF page.

4. **Vital signs:** blood pressure and pulse rate to be recorded in sitting position.
5. **Performance Status:** use ECOG – see Appendix 4.
6. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, hematology labs may be done within 72 hours of dosing with results checked prior to dosing.
7. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, blood chemistry may be done within 72 hours of dosing with results checked prior to dosing.
8. **Lipids:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, lipids may be done within 72 hours of dosing with results checked prior to dosing.
9. **Hypogonadism Laboratory Test:** to be performed in male patients only. The required blood tests are reported in Appendix 2. Blood draws MUST be done between 08.00-11.00 AM. Should a decrease of ≥25% from baseline be observed in total testosterone or free testosterone a repeat laboroatory analysis of both these parameters must be performed at the next clinical visit to confirm hypogonadism.
10. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, coagulation may be done within 72 hours of dosing with results checked prior to dosing.
11. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, urinalysis may be done within 72 hours of dosing with results checked prior to dosing.
12. **Serum Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period (every other cycle beyond 30 months), at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
13. **Triplicate 12-lead ECGs:** At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected as follows: a) at Screening, b) Cycles 2-5 Day 1 at pre-dose and 1 hr and 2 hrs post-dose and e) End of Treatment. If at any of these time-points the mean QTc is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

    When an ECG and PK sample are scheduled at the same time, ECG assessments should be performed prior to PK sample such that the PK sample is collected at the nominal time (but regardless, the exact time of ECG assessment and PK collection should always be recorded).
14. **Registration:** Registration will be within 2 days prior to lead-in.
15. **Trial Treatment:** described in the Study Treatments section.
16. **PF 06463922 Full PK Sampling**: Blood samples (4 mL each) will be collected for PK sampling on the following days: 1). Cycle 1 Day 1 and Cycle 1 Day 15: Pre dose, 0.5, 1, 2, 3, 4, 6, 8, , and 24 hrs post PF-06463922 dose. 2) Day 1 of Cycle 2, Cycle 4, Cycle 6, Cycle 8 and Cycle 10: Pre-dose. Where required by local regulations and after agreement by the study sponsor, patients may be hospitalized for PK sampling.
17. **PF 06463922 Metabolite Sample**: Blood samples for evaluation of metabolite(s) will be collected in all patients in this cohort. Blood samples (4 mL each) will be collected on Cycle I Day 1 and at steady-state on Cycle 1 Day 15 at: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post-PF-06463922 dose (the following day).

18. **Probe Substrate and PK for Probe Substrate:** For evaluation of drug-drug interaction, eligible patients will be dosed with the probe substrate in the fasted state, when possible, (no food 2 hours before through 2 hours after probe substrate dosing) in the Lead-In portion on Day -2 and in combination with steady-state PF-06463922 on Cycle 1 Day 15. PK Sampling for probe substrates: Plasma blood samples (3ml) will be collected for PK sampling on the following days and times:

    a. Day-2 (Lead-in) Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose.

    b. Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post dose.

19. **Pharmacogenomic Sample**: A single 4-mL blood sample will be collected at any time on Day -2 for pharmacogenomics analysis.

20. **ECG Holter Monitoring:** The 24-hour continuous ECG monitoring by Holter telemetry will be in addition to the single/triplicate ECGs described in Footnote 13. Twenty four (24) hr continuous ECG monitoring will occur 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. Additional ECG time points may be included based on emerging data. Baseline values are defined as ECG collection prior to the very first dose of PF-06463922. When possible, on Day-1 and Day 1 and Day 14 of Cycle 1, breakfast should be consumed at least 2 hours after the PF-06463922 dosing. When possible, lunch and dinner should be consumed approximately 5 and 9 hours, respectively after PF-06463922 dosing. Similarly, every attempt should be made to have the starting clock time for continuous Holter telemetry on Day -1 of lead-in and Days 1 and 14 of Cycle 1 be as close as possible (ie, approximately at the same clock-time). Holter ECG monitoring: Subjects should be supine for at least 15 minutes prior to the corresponding clock time for each scheduled PK collection time point on Day 1 and Day 14: subjects will remain supine for 10 minutes after which ECGs will be extracted in the following 5 minutes, followed by PK collection. ECGs on Day 1 and Day 14 will be time-matched for PK collection on those days. In addition, baseline ECGs will be extracted on Day -1 that are approximately time-matched with ECGs on Day 1 and Day 14.

21. **Tumor Assessment:** Tumor assessments will include all known or suspected disease sites. CT or MRI scans of Chest Abdomin Pelvis [CAP] and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI for must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5mm for lesions greater than 10mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases is observed at baseline. For all tumor assessments, the method of assessment that was used at baseline should be the same method used throughout the study. CT and MRI scans to be done at every 6 weeks ±1 week up to approximately 30 months, and then every 12 weeks ±1 week beyond 30 months, and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment will be done every 6 weeks ±1 week up to approximately 30 months, and then every 12 weeks ±1 week beyond 30 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease), and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients who have documented disease progression but are still receiving PF-06463922, CT and MRI scans are to be done according to local institutional standard of care. Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1 especially if there are dosing cycle interruptions due to toxicities. Tumor assessment should be repeated at the end of treatment and study visits if more than 6 weeks (more than 12 weeks beyond 30 months) have passed since the last evaluation. Tumor assessments will continue until progression of disease or a new anti-cancer therapy has commenced. For all patients, copies of radiologic images must be available for independent central radiology review as determined by the sponsor. Detailed instructions will be provided in the Study Reference Manual.

22. **Diagnostic Cerebrospinal fluid (CSF)** CSF analysis will not be required unless patients have suspected or confirmed leptomeningeal carcinomatosis not visualised on MRI. When applicable, CSF sample will be collected at Screening (optional CSF collection post Screening). See PK assessments for PF-06463922 CSF concentration sampling (optional).

23. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

24. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.

25. **EORTC QLQ C30 and QLQ LC13:** Patients must complete all EORTC QLQ C30 and QLQ LC13 self assessment questionnaires in the clinic at the specified time points prior to dosing. On Cycle 1 Day 1, site staff (eg, site coordinators) should instruct patients that the assessment should be completed without help from friends or family members and also recommend that this assessment be completed in the morning. All scheduled assessments of the EORTC QLQ C30 and QLQ LC13 cannot be taken home and must be completed in the clinic prior to any other study or medical procedures.

26. **Cognitive Assessment:** A computerized cognitive test compromised of verbal learning, psychomotor function, attention and memory will be administered to patients prior to study drug dosing. This test will take approximately 10-20 minutes to complete and will be administered via qualified site personnel. A practice test will be performed at Screening and a baseline test will be done on the first day of PF-06463922 dosing (ie, C1D1), and then prior to dosing on Day 1 of Cycle 2 - Cycle 6 (±1 week). After C6D1, this test will be administed prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).

27. **Mood Assessment**: An assessment of mood via the Beck Depression Inventory-II (BDI-II) scale will be administered to patients prior to the first day of PF-06463922 dosing (ie, C1D1) and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this test will be administered prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).

28. **Suicidal Ideation and Behavior Assessment**: An assessment of suicidal ideation and behavior via the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to patients prior to study drug dosing (ie, C1D1), and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this will be administered prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).

29. **Archival Tumor Tissue Specimens:** All patients will provide a formalin fixed paraffin embedded (FFPE) archival tumor specimen, specifically a FFPE tissue block that contain sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that are 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block cannot be submitted. Specimens will be sent to the Sponsor designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF 06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor designated central laboratory for ROS1 status confirmation.

30. **De Novo Tumor Specimens:** De novo tumor core biopsy collection will be mandatory at screening unless it is considered to pose a safety risk to the patient, in the opinion of the Investigator, and only after discussion with the Sponsor; please refer to Section 7.3 for further guidance. For patients who are treatment naïve at Screening (ie, no previous systemic therapy in the metastatic setting), a de novo tumor biopsy is not required if a previous tumor biopsy was performed within 4 months of first dose of PF-06463922. Pleural effusions (PE) cell pellets may substitute for tumor core biopsy as appropriate. Fine needle aspiration (FNA) samples are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. If local country regulations do not allow for core biopsy block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) are acceptable. Specimens will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation. In addition, optional de novo tumor biospy collection at the time of progression is encouraged. Tumor tissue specimens from all patients will be used for additional biomarker analyses. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

31. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling:** 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at screening, at the end of Cycle 2 (matching the first tumor restaging, in practical terms this may be C3D1 pre-dose) and at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.

32. **Banked Biospecimens**: Unless prohibited by local regulations, a blood sample (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, will be collected at screening.

33. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments up to 30 months and then last 12 weeks beyond 30 months). For patients who receive crizotinib following treatment with PF-06463922, assessments at the End of Treatment visit are according to Appendix 11.

34. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuating treatment for reasons other than progression of disease will continue to perform tumor assessments until PD or a new anti-cancer therapy is commenced. Bimonthly survival followup after PD or new anti-cancer therapy has commenced will be performed (telephone contact is acceptable). For patients who receive crizotinib following treatment with PF-06463922, follow-up is according to Appendix 11.

35. **LVEF Assessments**: Echocardiogram or MUGA will be performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.) up to approximately 30 months, and then every 4 Cycles thereafter, and at the End of Treatment visit. A ±2 days time window applicable at the discretion of the investigator is allowed at all time points. The same method should be used at each time point.

36. **CSF PF-06463922 Concentration Sample (Optional)**: If a patient undergoes a lumber puncture, a sample of CSF should be collected for exploratory analysis of PF 06463922 concentration, if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample. If scheduling permits, one CSF sample should be taken between 4 and 6 hours post dose. If it is possible to take a second sample, collection should be between 8 and 9 hours post-dose.

37. **Blood PK for Optional CSF sample:** If a CSF PF-06463922 concentration sample is collected, a blood sample for PK analysis should be collected at approximately the same time as the CSF sample.

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APPENDICES

1. INTRODUCTION

1.1. Indication

Anaplastic Lymphoma Kinase (ALK)-positive (ALK+) or ROS oncogene 1 (ROS1)-positive (ROS1+) advanced non-small cell lung cancer (NSCLC).

1.2. Background

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). Non small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer.[1]

In 2007, two research groups independently reported the discovery of an NSCLC oncogenic fusion gene (EML4-ALK) that combines portions of the echinoderm microtubule-associated protein- like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene.[2,3] This fusion gene encodes for the cytoplasmic fusion protein EML4-ALK which upon dimerisation, results in constitutive activation of the kinase domain of ALK. ROS 1 fusions were identified as potential driver mutations in a NSCLC cell line (HCC78: SLCA2-ROS1) and a NSCLC patient sample (CD74-ROS1).[3] Approximately 3-5% of NSCLC is histologically defined as ALK+[4] and 1-2% ROS1+[5] The vast majority of ALK and ROS1 fusion positive cases were observed in young, non-smoking patients with lung adenocarcinoma, and are rarely coincident with each other, and with EGFR, HER2, or KRAS mutations.[6]

1.2.1. Efficacy of Targeted Inhibitors in Patients with ALK+ [rearrangement (WT) and resistance mutations (mu)] and ROS1+ NSCLC

Crizotinib, a potent and selective Adenosine triphosphate (ATP) competitive inhibitor of c-MET, ALK and ROS 1 receptor tyrosine kinases and relevant oncogenic variants, was first studied clinically in ALK+ NSCLC in an ongoing Phase 1 trial soon after the discovery of the EML4-ALK fusion protein oncogenic driver potential in NSCLC.[7] The clinical benefit of crizotinib led to the US approval in August 2011 of XALKORI® (crizotinib) in advanced ALK+ NCSLC patients. Crizotinib as single agent in previously treated ALK+ NSCLC patients demonstrated a median progression-free survival 7.7 months versus in the crizotinib group and 3.0 months in the chemotherapy (docetaxel or pemetrexed). The Objective Response Rates (ORR) were 65% (95% confidence interval (CI), 58 to 72) with crizotinib, as compared with 20% (95% CI,14 to 26) with chemotherapy (P<0.001)[16] Crizotinib has also demonstrated activity in ROS1-positive NSCLC patients.[15] In a series of 35 patients with ROS1+ NSCLC, of 25 evaluable patients an ORR of 60% was reported, 6-month PFS probability was 71% (95% CI: 45.6–86.0).

Although most patients with ALK+ NSCLC derive substantial clinical benefit from crizotinib, some ALK+ NSCLC patients will not derive any benefit (intrinsic resistance) while other patients who initially derived benefit may later develop resistance (acquired resistance). The pattern of ROS1 acquired resistance is still emerging but mutations in the kinase domain are similarly considered likely to contribute to the observed resistance to ROS1 inhibitor treatment.[17]

Unlike acquired resistance to EGFR inhibitor where T790M gatekeeper mutation accounts for approximately all secondary mutation-driven resistance cases, and 50% of all resistance,[8] the resistance to ALK inhibitors appears much more complex as a greater variety of mutations are found in patients along with the activation of bypass resistance mechanisms.[11,9] To date, multiple types of ALK kinase domain mutations have been identified in crizotinib refractory patients including *ALK*^{g1269a}, *ALK*^{l1196m}, *ALK*^{c1156y}, *ALK*^{l1152r}, *ALK*^{f1174l}, *ALK* ^{g1202r}, *ALK*^{s1206y}, *ALK*^{1151tins} and *ALK* gene amplification,[9,12,21] and account for about one third of resistant samples tested. Among these ALK mutations, *ALK*^{g1202r} conferred high-level resistance to almost all of the ALK inhibitors tested.[9,12,21] In the case of crizotinib resistant ALK+ NSCLC patients, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[8] While other mechanisms of resistance (independent of ALK mutation) are active, the tumor cell may still remain dependent upon ALK signaling. It was also reported that the brain was the most common single site of disease progression (>30%) following initial crizotinib treatment.[13,14] It is unknown if this is due to the formation of resistance mutations or the intact blood brain barrier (BBB) creates a sanctuary site preventing the passage of crizotinib. Finally another roughly 5% of patients acquire resistance through amplification of the EML4-ALK fusion gene.[9]

Several investigational agents targeting ALK and ROS1 are now in clinical trials. These agents, mostly small molecule tyrosine kinase inhibitors, have reported anti-tumor activity in both ALK+ wild type and mutated NSCLC. Preliminary data of those most advanced in clinical trials to date report ORRs of 70-85% in patients with ALKinhibitor treatment naïve ALK+ NSCLC and in patients with ALK+ NSCLC relapsed after ALK inhibitor treatment.[18,19,20] While there are other compounds being evaluated no ALK nor ROS1 targeted TKI has demonstrated curative results and additional drugs are needed to overcome resistance mechanisms, to impact patient outcomes through improved response rates and PFS and significiant anti-tumor activity on CNS metastases.

1.3. PF-06463922

1.3.1. PF-06463922 Background

PF-06463922 is a selective, ATP-competitive small molecule tyrosine kinase inhibitor of the ALK and ROS1 (c-ROS oncogene 1) receptor tyrosine kinases (RTK) that also potently inhibits ALK kinase domain mutations responsible for resistance to crizotinib. Oncogenic fusions of *ALK* and *ROS1* define two distinct subsets of human lung adenocarcinoma patients and play essential roles in regulation of tumor cell survival, growth and metastasis.[2,5]

In cell assays, PF-06463922 inhibited ALK kinase activity (measured by inhibition of its autophosphorylation) with cell IC50's of 1.5 nM and 21 nM for EML4-ALK and EML4-ALK (L1196M), the most common mutation that occurs within the gatekeeper residue of the ALK kinase, which compares favourably to crizoitinib IC50's of 80 nM and 841 nM, respectively). Data from in vivo efficacy models bearing the EML4-ALK (L1169M] mutation predicted the efficacious concentration (C_{eff}) to be 51 nM (unbound), which corresponds to achieving tumor stasis (100% tumor growth inhibition) in this preclinical

model. In the 3T3-EML4-ALKG1202R model for the G1202R EML4-ALK mutation, 80% tumor growth inhibition was seen at C_{eff} of 125 nM (unbound), which corresponds to 150 ng/mL total concentration.

PF-06463922 has been studied in a variety of in vitro and in vivo model systems to determine potency for inhibition of ALK or ROS1 tyrosine kinase activity, kinase selectivity, anti-tumor efficacy, pharmacokinetic (PK)/pharmacodynamic (PD) relationships, and mechanism of action. In vitro, PF-06463922 demonstrated potent, concentration-dependent inhibition in catalytic activities of ALK, ALK mutants and ROS1 kinases in recombinant enzyme and cell based assays. PF-06463922 also inhibited ALK and ROS1 dependent oncogenic functions in human NSCLC cell lines, and demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting either non-mutant ALK and ROS1 fusion variants or mutant ALK fusions that are acquired and resistant to crizotinib treatment.

In vivo, PF-06463922 demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib resistant EML4-ALK^{L1196M} or EML4-ALK^{G1269A} mutations.

PF-06463922 treatment significantly reduced the tumor size and prolonged animal survival in the orthotopic brain models (EML4-ALK and EML4-ALK^{L1196M}) in mice. The anti-tumor efficacy of PF-06463922 was dose dependent and demonstrated strong correlations to inhibition of ALK or ROS1 phosphorylation. The plasma levels associated with inhibitory activity of PF-06463922 against EML4-ALK^{L1196M} phosphorylation and anti-tumor efficacy in EML4-ALK^{L1196M} dependent human NSCLC cell line models was utilized to project target human plasma concentrations for clinical studies. The C_{eff} (unbound) for EML4-ALK, EML4-ALK^{L1196M}, and EML4-ALK^{G1202R} of 6.5nM, 51 nM, and 125 nM, respectively, when corrected for human plasma protein binding results in C_{eff} (total) of 7.6 ng/mL, 62 ng/mL, and 150 ng/mL, respectively.

More details of the complete in vitro and in vivo efficacy package may be found in the PF-06463922 Investigator's Brochure.[22]

The single safety reference document for midazolam is the United States package insert USPI for Midazolam Hydrocholoride supplied by Paddock Laboratories, Inc., Minneapolis, MN.[41]

1.3.2. PF-06463922 Pre-Clinical Safety Data

1.3.2.1. Pancreas

Pancreatic toxicity was observed in the rat and dog repeat dose studies. Severity was dose-related and ranged from minimal to marked. With increased severity, the changes were more diffuse and pancreatic exocrine tissues became affected such that intralobular fibrous tissue appeared more prominent. The pancreatic changes observed with PF-06463922 did not elicit an acute inflammatory response, though scattered minimal mononuclear or mixed cell infiltrates were occasionally present. While minor elevations (<1-fold) in mean amylase and lipase levels were identified in the rat, there was no clear correlation to the pancreatic

lesions. Minor elevations (minimal or mild) in amylase and lipase (<1-fold) in the dog were not associated with minimal or mild pancreatic lesions; however, moderate to high amylase and lipase elevations (4- and 8-fold, respectively) were found to coincide with pancreatic acinar atrophy in the dog and included more prominent single cell necrosis in the absence of inflammation. Elevations in glucose and cholesterol (up to 2.2-fold) were observed in rat and dog studies; however, these were small in magnitude, without historical reference range, or lacked histological correlates and were therefore considered non-adverse and without toxicological significance. At the end of a 1-month non-dosing period, all clinical chemistry parameters were comparable to control values (except cholesterol), and full to partial recovery of the pancreatic lesions was observed in both the rat and dog. Pancreatic changes were considered minimal or mild at 8 mg/kg/day in male rats. One month dosing (up to 25 mg/kg/day) is associated with low severity pancreatic findings in dogs. Furthermore due to the known occurrence of spontaneous lesions of comparable severity in Beagle dogs, a safety margin ≥12-fold over the predicted minimal efficacious dose in humans (10 mg BID, based on an unbound AUC comparison) is estimated for PF-06463922 (499 ng49/mL) A no effect level was identified at 2 mg/kg/day in male rats and was not identified in dogs (<2 mg/kg/day) following 1 month of dosing (<2-fold margin based on a comparison of unbound AUC to that projected at the minimal efficacious dose in humans at 10 mg BID).

1.3.2.2. Liver

Liver effects were identified following 14 days and 1 month of dosing in the rat. Liver enzyme (ALT, AST, ALP, GLDH, and/or GGT; up to 5-fold control) and total bilirubin elevations correlated with hepatocellular hypertrophy, single cell necrosis, and/or bile duct hyperplasia in the rat at ≥15 mg/kg/day. Increased sinusoidal cells were also observed in male rats at 60 mg/kg/day following 14 days of dosing. A no effect level for liver effects was identified at 8 and 4 mg/kg/day in male and female rats, respectively, providing a 12- to 14-fold margin over the predicted minimal efficacious exposure in humans at 10 mg BID based on an unbound AUC comparison.

1.3.2.3. Hematopoietic

Hematopoietic effects were observed in the rat and dog, primarily reflected by an effect on the erythron that elicited a regenerative erythropoietic response. Decreases in red blood cell parameters (RBC count, hematocrit, hemoglobin) up to 30% compared to control were observed at ≥2 mg/kg/day in the rat and dog following 14 days and 1 month of dosing, respectively. The observed erythroid effects provide safety margins from the 1-month studies of up to 60-fold based on a comparison of unbound AUC to that projected at the minimal efficacious dose in humans at 10 mg BID. Increases in white blood cell (up to 8-fold; white blood cell counts, lymphocytes, neutrophils, monocytes, large unstained cells) were noted. Slight increase in platelets was observed suggesting a a collateral effect from RBC regeneration.

1.3.2.4. Cardiovascular

Cardiovascular changes (blood pressure, heart rate) and secondary effects on cardiac parameters were identified in telemetered rats and dogs following single- and/or repeat-doses (up to 19 days). Increases or decreases in blood pressure (up to 37 mmHg systolic, diastolic, and mean) were observed in the rat and dog at ≥10 mg/kg/day. Heart rate was also altered at ≥10 mg/kg/day, characterized by a biphasic response in the rat with an initial decrease of up to 36 bpm and subsequent increase of up to 32 bpm (12 to 15 hours post dose), whereas an increase in heart rate was identified in the dog (up to 17 bpm). The differences in cardiovascular profiles between rats and dogs for both blood pressure and heart rate parameters may reflect a species-specific response to PF-06463922, but are considered indicative of the potential for a cardiovascular effect. Observed changes are believed to reflect compensatory mechanisms versus a direct effect on heart tissue. Reversal of effects on electrocardiogram (ECG) intervals and blood pressure was demonstrated following a 5- day non-dosing interval in the dog.

1.3.2.5. Cognition and Neurological Function

PF-06463922 was shown to be a brain penetrable compound, with measurable levels in the brain and cerebral spinal fluid (CSF) in the rat. The potential for central nervous system (CNS) effects and cognitive deficit were suggested from safety pharmacology and general toxicity studies. Functional observational battery (FOB) assessments included in a 14-day repeat-dose toxicity study in the rat identified CNS effects, including abnormal behavior (ie, teeth chattering), involuntary movements (ie, retropulsion and trembling), reduced handling reactivity, decreased arousal, abnormal gait, and reduced reflex responses (ie, uncoordinated air righting-reflex, and reduced extensor thrust response) at 60 mg/kg/day. It is unclear whether the observations were due to a direct effect on the CNS or secondary to a general lack of tolerance to PF-06463922 administration; however, the FOB findings were primarily observed in moribund animals. In addition, CSF and brain concentrations (up to 319 ng/mL and 40.5 ng/mL, respectively) achieved at this dose suggest that concentrations well exceeding primary pharmacology were reached (wild-type cell-based ALK IC_{50} 0.6 ng/mL). A pharmacology-driven effect, however, cannot be completely ruled out given that ALK expression has been demonstrated in the brain of mice, where it is thought to play an important role in brain development and function.[23,24,25] As such, it is possible that the CNS effects are a result of ALK inhibition in the brain. No FOB effects were identified in the definitive assessment following 26 days of dosing at doses up to 30 mg/kg/day, despite achieving comparable plasma concentrations, providing a 59-fold margin over the predicted minimal efficacious exposure in humans at 10 mg BID based on an unbound C_{max} comparison.

The potential for an effect on cognitive function was suggested from an ex vivo hippocampal brain slice assay and an exploratory in vivo model, the rat contextual renewal model. PF-06463922 caused a significant reduction in amplitude of long term potentiation, a measure that is widely considered as one of the cellular mechanisms that underlie learning and memory formation.[26] This effect was observed at 1 μM (406 ng/mL) but not at 100 nM (41 ng/mL). In the contextual renewal model, a decrease in memory recall and cue-induced renewal responding was observed at ≥3 mg/kg, though variability in the pharmacologic

sensitivity was identified with both the tool compound used for validation, as well as with PF-06463922. The variable response with PF-06463922 was observed at 3 mg/kg, a dose where relevant brain concentrations (≥262 ng/mL) were achieved for inhibition of wild-type ALK (cell-based IC_{50} 0.52-0.98 ng/mL) and TrkB (cell-based IC_{50} 93 ng/mL).

As TrkB receptors have been implicated in synaptic plasticity, long term potentiation, as well as memory processes in rats,[27] the results with PF-06463922 may reflect a potential to affect cognitive function that is driven by secondary pharmacology at the TrkB receptor; however, these results cannot be used to assess safety margins relevant to human exposure due to the exploratory nature and variability in sensitivity of the model.

1.3.2.6. Gastrointestinal

Clinical signs of gastrointestinal effect, and stomach and intestinal findings were observed in the rat and dog in 14-day toxicity studies. Clinical signs of emesis in dogs and abnormal feces (soft, watery, and/or mucoid) in rats and dogs observed acutely and following multiple doses were considered mild in the absence of a significant effect on body weight or clinical toleration. There were no PF-06463922-related stomach changes in the dog. Minimal or mild single cell necrosis in the gastric glands of the pyloric stomach was observed at the highest doses tested in rats (30 mg/kg/day in males and 15 mg/kg/day in females) following 1 month of dosing. Full recovery was shown following a 1-month non-dosing period. There were no PF-06463922-related microscopic effects in the stomach or intestines of rats or dogs following 1 month of dosing at doses up to 30 and 25 mg/kg/day, respectively, providing up to a 60-fold margin over the predicted minimal efficacious exposure in humans at 10 mg BID based on an unbound AUC comparison.

1.3.2.7. Effects on the Skin

Skin effects were identified in the rat following repeat-dosing at ≥15 mg/kg/day. Following 1 month of dosing, gross findings of wound, scar, or crust on skin of the head, neck or limbs were characterized microscopically by erosion, ulcer or dermal fibrosis at 30 mg/kg/day in male rats and 15 mg/kg/day in female rats. Dermal fibrosis was considered consistent with resolution of the erosion or ulcer. Skin findings were not present following a 1-month non-dosing period.

1.3.2.8. Effects on the Thymus

Effects on the thymus were observed in the dog following 14 days and 1 month of dosing. An increased incidence of decreased lymphoid cellularity (minimal to moderate) was observed in the thymus at 25 mg/kg/day in male dogs following 1 month of dosing. Decreased thymic weights corresponded with this histological change in some animals given that 25 mg/kg/day was a non-severely toxic dose, a direct effect of PF-06463922 cannot be out ruled. Partial recovery was observed after a 1-month non-dosing period.

1.3.2.9. Inflammatory Response

Increases in white blood cell (up to 8-fold; white blood cell counts, lymphocytes, neutrophils, monocytes, large unstained cells), increased fibrinogen (up to 6-fold), and clinical chemistry parameters (up to 54%; increased globulin, decreased albumin) suggestiveof an inflammatory response were observed in the rat and dog following acute exposure (dog) and 14 days and/or 1 month of repeat-dosing at ≥2 mg/kg/day. An increase in myeloid cellularity (minimal to mild) in the bone marrow correlated with this inflammatory response following 1 month of dosing at ≥2 mg/kg/day in dogs. While there was generally no clear source of the inflammatory response, inflammation was sporadically noted on the skin of rats with erosion/ulcer or dermal fibrosis at 30 mg/kg/day (males) and 15 mg/kg/day (females) in 1-month toxicity study. With the exception of residual clinical chemistry changes at 25 mg/kg/day in male dogs, full recovery was observed following a 1-month non-dosing period in the rat and dog.

1.3.2.10. Effects on Peripheral Nerves

Minimal axon degeneration in the peripheral nerve was identified in rats following 1 month of dosing at 30 mg/kg/day in males and 15 mg/kg/day in females. This change was characterized by swollen and hypereosinophilic axons in clear vacuoles and occasional formation of digestion chambers. No active axon degeneration was identified following a 1- month non-dosing period, suggesting the reversible nature of this finding when the neuronal soma is viable.

1.3.2.11. Teratogenicity

Preliminary developmental toxicity studies using PF-06463922 have been completed in rats and rabbits. Embryonic and fetal toxicity (including embryo lethality, fewer and smaller viable fetuses with some external and visceral malformations) was observed in both species at all doses, where the low dose was projected to yield similar exposure as the recommended Phase 2 dose of 100 mg once daily.

For more details about the preclinical safety profile of PF-06463922, refer to the Investigator's Brochure (IB).[22]

1.3.3. PF-06463922 Clinical Trial Experience

PF-06463922 has been administered to 54 patients in the Phase 1 part of this study across 7 once daily (QD) doses of 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg and 3 twice daily (BID) doses of 35 mg BID, 75 mg BID, and 100 mg BID. As described in Section 3.4.3, a continual reassessment method (CRM) model was used in Phase 1 to determine which dose(s) to test based on the DLTs observed during Cycle 1. The CRM was initiated at 25 mg QD and recommended escalation to 75 mg QD, 150 mg QD, and 200 mg QD based on no DLTs observed at the previous dose levels tested. At 200 mg QD, one (1) DLT occurred in a patient who failed to receive 16 of the planned 21 doses of PF-06463922 due to Grade 1 and Grade 2 CNS effects. Although the CRM model recommended continuation to the next higher dose above 200 mg QD, a decision was made among the treating investigators and the sponsor to re-test lower doses (ie, outside of the

CRM model) to better understand and evaluate the CNS effects observed at the higher dose levels. The protocol was amended at that time (Amendment 3) to formalize testing doses outside of the CRM model and to evaluate BID dosing and effects of food on PF-06463922. Lower doses of 50 mg QD, 75 mg QD, and 100 mg QD were also evaluated. BID doses tested included 35 mg BID, 75 mg BID, and 100 mg BID. A food effect cohort was tested at 100 mg QD (3 patients in fed/fasted state and 3 patients in fasted/fedstate). Finally, a CSF sampling cohort was tested at 100 mg QD to obtain preliminary information about PF-06463922 penetration in the brain.

Overall, PF-06463922 was well tolerated in Phase 1. As of the data cutoff date for Amendment 4 (15 June 2015), the most commonly occurring treatment-related adverse events across all of the doses tested in Phase 1 were hypercholesterolemia (64%), CNS effects (36%), peripheral oedema (32%), peripheral neuropathy (28%), and hypertriglyceridemia (26%). The most frequently occurring treatment-related Grade ≥3 adverse events were hypercholesterolemia (10%) and hypertriglyceridemia (4%). Because the adverse events were varied in their presentation and description, higher level ("cluster") terms (ie, CNS effects and peripheral neuropathy, etc.) were used to further describe the safety profile of PF-06463922. A breakdown of the specific preferred terms that comprise these higher level terms can be found in the Investigator's Brochure.

Dosing interruptions and dose reductions were reported in 9 (18%) and 18 (36%) of patients, respectively. Most of these delays and reductions occurred at doses higher than 100 mg QD and the most common reasons for dosing interruption and/or dose reduction at these higher doses were hypercholesterolemia and CNS effects.

A total of 5 patients had treatment-related serious adverse events; 3 of them had CNS events that included Grade 2 hallucinations and Grade 2 seizure in 1 patient (150 mg QD); Grade 2 seizure in a second patient (75 mg BID), and mental status changes in a third patient (150 mg QD). In addition, 1 patient (150 mg QD) had Grade 3 dermatomyositis, and 1 patient (100 mg QD) had Grade 3 lipase increased. No Grade 4 or Grade 5 treatment-related SAEs were reported. There were neither any adverse events that led to treatment discontinuation, nor any treatment-related deaths.

Treatment-related CNS effects were observed in 18 (36%) Phase 1 patients. These events were considered mild (Grade 1 and Grade 2), transient, and were most commonly reported after Cycle 3; however, at the higher dose levels (≥150 mg QD), these events occurred earlier on. These events were reversible upon dosing interruption and/or dose reduction, and no patients were permanently discontinued due to these events. A summary of Grade 2 and higher individual CNS effect preferred terms, including the dose at which they occurred and whether or not they required a dose modification, are described below in Table 7. Grade 1 individual CNS preferred terms can be found in the Investigator's Brochure.

Table 7. Grade ≥2 Treatment-Related CNS Effects in Phase 1

Preferred Term	Toxicity Grade	Dose at Which AE Occurred	Dose Modification Required
Cognitive Disorder	2	200 mg QD	Dose Delay and Dose Reduction
Aphasia	2	200 mg QD	Dose Delay and Dose Reduction
Hallucination	2	150 mg QD	Dose Delay
Hallucination	2	150 mg QD	Dose Delay
Irritability	2	200 mg QD	Dose Delay and Dose Reduction
Mental status changes	3	150 mg QD	Dose Delay
Seizure	2	100 mg QD	Dose Delay
Seizure	2	75 mg BID	Dose Delay
Visual Impairment	2	100 mg QD	Dose Reduction

Treatment-related increases in lipids, including cholesterol and triglycerides, were observed in 32 (64%) and 13 (26%) of Phase 1 patients, respectively. The majority of these elevations were Grade 1 and Grade 2 in severity and well managed with the use of a statin or other lipid-lowering agent. Lipid testing was added later in the study (ie, introduced in Amendment 3), and thus, there are limited data on patients treated at earlier cycles on the initial doses; however, these laboratory abnormalities have been observed at all of the Phase 1 dose levels tested. There have been no associated cardiovascular changes.

Peripheral neuropathy was observed in 14 (28%) Phase 1 patients. These events were completely reversible upon dosing interruption and/or dose reduction. A summary of treatment-related Grade ≥2 individual peripheral neuropathy preferred terms, including the dose at which they occurred and whether or not they required a dose modification, are presented below in Table 8. Grade 1 individual peripheral neuropathy preferred terms can be found in the Investigator's Brochure.

Table 8. Grade ≥2 Treatment- Related Peripheral Neuropathy Events in Phase 1

Preferred Term	Toxicity Grade	Dose at Which AE Occurred	Dose Modification Required
Neuropathy peripheral	2	75 mg QD	None
Neuropathy peripheral	2	100 mg QD	None
Paraesthesia	2	150 mg QD	None
Neurotoxicity	2	100 mg QD	None

Treatment-related peripheral edema was observed in 16 (32%) Phase 1 patients. These events were manageable and reversible upon dosing interruption and/or dose reduction.

In terms of preliminary efficacy in Phase 1, PF-06463922 demonstrated robust clinical activity, although these patients represent a heterogeneous mix of driver mutations, prior treatments, and dose levels at which they were treated. Among 43 patients evaluable for efficacy as of the data cutoff date (15 June 2015) for Amendment 4, the ORR was 37% comprising 1 confirmed CR (2.3%) and 15 (35%) confirmed PRs. Further, 10 (23%) patients had SD as their best overall response. The response rate appeared similar whether patients had 1 or 2 prior TKIs.

Thirty-four (69%) patients had CNS metastases at study entry. Of the 30 patients evaluable for intracranial response at the time of the data cut-off, 4 (13%) patients had a confirmed intracranial CR and 5 (17%) patients had a confirmed intracranial PR. Further, 10 (33%) patients had intracranial SD as their best CNS response.

Taken together, these preliminary efficacy results from Phase 1 suggest robust anti-tumor activity and brain penetration which should be further characterized in Phase 2.

1.3.4. Benefit/Risk Assessment

Non-Clinical

The nonclinical safety profile of PF-06463922 has been extensively evaluated in vitro, ex vivo, and in vivo in the rat and dog to support progression into clinical trials in advanced cancer indications. The primary target organ effects were observed on the pancreas, liver, hematopoietic and cardiovascular systems, and peripheral nerve. Additional effects were observed on male reproductive organs, cognitive performance and neurological function, the gastrointestinal system, and skin. The potential for reversibility of the target organ toxicities was established following a 1-month non-dosing period. PF-06463922 is also a potential phototoxicant based on Ultra Voilet –B (UVB)-absorbing properties, and an aneugen but not a mutagen. The nonclinical safety findings related to PF-06463922 administration represent toxicities that can be monitored and are considered clinically manageable or acceptable risks in the intended patient population.

The nonclinical efficacy profile of PF-06463922 has been extensively investigated in a series of relevant preclinical disease models in vitro and in vivo. PF-06463922 potently inhibited its kinase targets (ALK, ALK mutants and ROS1) in recombinant enzyme and cell assays, and demonstrated inhibitory effects against ALK-, mutant ALK- and ROS1-dependent cancer phenotypes including tumor cell proliferation and survival.

In vivo, PF-06463922 demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib resistant EML4-ALKL1196M or EML4 ALKG1269A mutations. PF-06463922 treatment significantly reduced the tumor size and prolonged animal survival in the orthotopic brain models harboring either EML4-ALK or EML4 ALK^{L1196M} in mice. The anti-tumor efficacy of PF-06463922 was dose dependent and demonstrated strong correlations to inhibition of

ALK or ROS1 phosphorylation, and there was no body weight loss observed in any of the in vivo efficacy studies. Collectively the data indicate that PF-06463922 is a potent inhibitor of ALK and ROS1 kinase. It is capable of inhibiting all clinically reported crizotinib resistant ALK fusion mutants at pharmacologically relevant concentrations, including the ALKG1202R mutation that is resistant to almost all of the ALK inhibitors tested to date. Additionally, it regressed both non-mutant and mutant ALK fusion positive tumors in the orthotopic brain models. Therefore the benefit to risk assessment is in favor of studying PF-06463922 in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC and within those patient groups, to also assess the anti tumor activity of PF-06463922 on CNS metastases.

Clinical

The clinical safety and efficacy profile of PF-06463922 as observed in Phase 1 patients indicated that PF-06463922 is overall well tolerated and demonstrated robust clinical activity (ORR of 37%) and brain penetration (CNS response rate of 30%). As described in Section 1.3.3, the most commonly occurring treatment-related adverse events in Phase 1 were effects on lipids, effects on CNS, peripheral edema, and effects on peripheral nerves. These events were considered manageable and reversible upon dosing interruption and/or dose reduction. Patients in Phase 2 will be closely monitored for these effects; lipids will be routinely collected, and patients will be advised to initiate the use of a statin or other lipid-lowering agent early in order to prevent further increases (see Table 14 and Table 15 in Section 5.3.2.6). Additionally, patients will be assessed for changes in cognitive function or mood and any potential suicidal ideation or behavior.

The benefit/risk assessment remains favorable for continuing the development of PF-06463922 in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC with or without CNS metastases.

1.3.5. Safety Considerations in the Clinical Trial

Pancreatic acinar atrophy was identified in 14-day ETS and 1-month regulatory toxicology studies in both rodent and non-rodent species Minimal to mild findings at clinically relevant concentrations are non-adverse (mid dose in rats and all doses in dogs from 1-month study). The pathogenesis is considered distinct from acute pancreatitis, no inflammation nor necrotic cell death were observed. Published literatures report amylase and lipase as having high variability as biomarkers, but supplemented with clinical signs and symptoms monitored with abdominal radiology, their monitoring can still support clinical dose modification decision making during the study.[28,29,30] Patients with hyperglycemia, current gallstone disease, alcoholism, or other conditions in the investigator's judgment would predispose the patient to pancreatitis will be excluded to this study. There have been no reports of pancreatitis in patients treated to date with PF-06463922. Elevations in lipase and amylase have been observed in some patients but not associated with either radiographic or symptomatic findings of pancreatitis. These parameters will continue to be regularly monitored in Phase 2.

Increased blood pressure (BP) and biphasic heart rate (HR) changes were observed in rats at a therapeutic index (TI) >2.6X and decreased BP and increase in HR in dogs at TI=6.2X, with no ECG change. Therefore, in this study, blood pressure and heart rate changes as vital signs will be monitored along with close monitoring for clinical cardiovascular parameters, such as changes in left ventricular ejection fraction (LVEF), ECG changes and potential cardiovascular symptoms. Changes in LVEF and QTc were observed in some Phase 1 patients, although few were considered to be adverse events; 2 patients had Grade 1 QTc prolongation that was considered treatment-related, and no patients had treatment-related changes in LVEF. Heart rate changes were also observed in Phase 1, but none were considered adverse events. PR interval prolongation has been observed in both healthy volunteer studies (Study B7461008) and clinical trials (Study B7461001). In the healthy volunteer Study B7461008, the PR interval prolongation was associated with 1 episode of transient second-degree atrioventricular (AV) block (Mobitz type 1; Wenckebach). In the clinical Study B7461001, the PR interval prolongation may have been associated with the progression of pre-existing AV block to complete heart block. When the complete heart block was identified, the patient was immediately evaluated and subsequently treated by placement of an implanted pacemaker. In response to the observation of PR interval prolongation, data from all available human studies (approximately 100 patients in clinical studies and 45 in single dose healthy volunteer studies) was reviewed. Additional instances were identified of asymptomatic increases in the PR interval, usually most notable during Cmax (1-2 hours post-dose). Of note, the patients with a PR interval >200 msec were generally those with a baseline value at the upper end of the normal range. The ECG changes appear limited to the PR interval, with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies, as described in the current IB. To further characterize the observed PR prolongation, a separate drug-drug interaction (DDI) and Holter monitoring study will be performed in a cohort of patients.

Prompt medical intervention is recommended at the first sign of appearance of cutaneous toxicity including topical or oral corticosteroids if required according to investigator's judgment.

Regenerative anemia was observed in dogs at TI =24X and lymphoid hypocellularity in the spleen in rats TI=13X. In this study hematological parameters will be regularly monitored. Anemia was reported in some Phase 1 patients, although few cases were considered to be adverse events; 2 patients had Grade 2 treatment-related anemia and 1 patient had treatment-related Grade 3 anemia. Hematologic parameters will continue to be regularly monitored in Phase 2.

As the potential for CNS effects and cognitive deficit were suggested from safety pharmacology and general toxicity studies, close clinical monitoring including a site staff directed questioning tool and a patient reported outcome measure with cognitive domains, will be performed for signs or symptoms of cognitive disturbance or neurotoxicity. Because various CNS effects were reported among the first 15 patients enrolled and treated with PF-06463922 in the Phase 1 portion of this clinical study, at least 12 patients in Phase 1 will be evaluated by a licensed neurologist at baseline, and during the study if clinically indicated,

to better characterize these CNS effects. Additionally, the Phase 1 portion will be modified to additionally assess the impact of twice daily (BID) dosing and of food on PF-06463922 safety and PK. Treatment-related CNS effects were observed in 18 (36%) Phase 1 patients. In Phase 2, close monitoring for these effects will be performed by routine cognitive assessment, mood characterization, and suicidal ideation and behavior monitoring.

Weickhardt et al[31] recently reported decreases in total testosterone levels in 32 ALK+ NSCLC patients on crizotinib treatment. There were several limitations of this analysis, including but not limited to diurnal timing of the blood samples and insufficient baseline versus on-treatment total and free testosterone levels over time, and thus a further systematic assessment of testosterone levels to understand the validity of these data is warranted. However, and even if no preclinical safety signal was observed with PF-06463922, the study of hypogonadism laboratory assessments will be performed in this study to understand if these observed laboratory findings can be attributed to a ALK inhibitor class effect.

Elevations in cholesterol (up to 2.2-fold) were observed in rat and dog studies. Therefore, in this study, cholesterol (a complete cholesterol panel) and triglycerides will be regularly monitored. Hypercholesterolemia was the most frequently occurring adverse event in Phase 1. Patients who have elevated cholesterol or triglyceride levels should receive concomitant treatment with a statin or other lipid-lowering agent at the first instance of elevation and then be closely monitored for any changes. Agents that should be considered are provided in Section 5.3.2.6. The choice and dosing of statins may be guided by information on the differential metabolism by the cytochrome P450 pathway.

PF-06463922 has been shown to induce embryonic and fetal toxicity in animals. Patients who are pregnant and who are breastfeeding are excluded from the study. Additionally, male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of the first negative pregnancy test at screening, throughout the study, and for 97 days after the last dose of assigned treatment if male patients, 21 days if female patient. Male patients must agree to refrain from donating sperm throughout the study and for 97 days after the last dose of assigned treatment.

1.3.6. PF-06463922 Pharmacokinetics in Animals and Projection of Human Pharmacokinetics

The single-dose pharmacokinetics of PF-06463922 was evaluated in nonclinical species following intravenous (IV) and oral administration. Plasma clearance (CL) in rats and dogs were 16 mL/min/kg and 9 mL/min/kg, respectively. PF-06463922 was moderately to rapidly absorbed after a single oral dose to rats and dogs, with high oral bioavailability observed in both species (~100% rats; 97% dogs). Renal excretion of the parent drug was limited in rats and dogs. Systemic exposures (peak concentration [C_{max}] and area under the concentration-time curve [AUC]) to PF-06463922 increased with increasing dose in an approximately proportional manner in the pivotal toxicology studies in rats (up to 30 mg/kg/day) and dogs (up to 25 mg/kg/day). The binding of PF-06463922 to plasma proteins ranged from 64%, 71% and 66% for rat, dog, and human, respectively. PF-06463922 was detected in the brain and cerebrospinal fluid (CSF) after oral dosing to rats, indicating that PF-06463922 can cross the blood brain barrier.

In vitro and in vivo metabolite profiling suggested that the primary clearance mechanisms for PF-06463922 were by cytochrome P450 (CYP)- and uridine 5'-diphosphoglucuronosyltransferase (UGT)-mediated oxidation and glucuronidation reactions, respectively. In vitro studies using human recombinant CYP and UGT enzymes suggested that CYP1A2, 2B6, 2C9, and 3A4 primarily mediated oxidative metabolism of PF-06463922, and UGT1A4 was the primary enzyme responsible for the glucuronidation. Comparison of hepatocyte metabolic profiles across nonclinical species and human suggested that human metabolism is substantially different from mouse, rat, and dog, with 3 unique metabolites to human in vitro preparations. PF-06463922 did not inhibit CYP1A2, 2B6, 2C8, 2C19, or 2D6 enzymes (50% inhibitory concentration [IC50] >100 μM) by either competitive or time-dependent inhibition. While CYP2C9 was inhibited by PF-06463922 with an IC50 value of 44 μM, PF-06463922 was not a time-dependent inhibitor of CYP2C9. CYP3A4/5 activities were inhibited by PF-06463922, with IC50 values of 23, 10, and 22 μM, measured as testosterone 6β-hydroxylase, midazolam 1′-hydroxylase, and nifedipine oxidase activities, respectively. Time-dependent inhibition was demonstrated for CYP3A4/5 by PF-06463922, with a shift in IC50 values (0.81, 0.74, and 0.87 μM) after a 30 minute pre-incubation period. In in vitro studies using 3 lots of human hepatocytes, CYP2B6 and 3A4 activities and messenger Ribonucleic acid (mRNA) concentrations were induced by PF-06463922. Therefore, PF-06463922 can potentially alter the pharmacokinetics of other coadministered drugs that are eliminated by the CYP2B6 and 3A4 pathways.

The human pharmacokinetics of PF-06463922 were predicted using in vitro to in vivo scaling of human hepatocyte data and GastroPlus® human physiological based pharmacokinetic modeling. Human CL, steady-state volume of distribution (Vss), half-life (t½), and oral bioavailability are predicted to be 3 mL/min/kg, 3 L/kg, 12 hours, and 86%, respectively. Using the pharmacodynamic parameters estimated from mouse xenograft studies and predicted human pharmacokinetic parameters, it is projected that twice daily (BID) doses of 10 mg of PF-06463922, corresponding to a steady-state average concentration ($C_{av,ss}$) of 51 nM (21 ng/mL) free or 150 nM (61 ng/mL) total, would be required to significantly inhibit ALK phosphorylation in patient tumors and achieve the expected significant antitumor efficacy. Safety margins were calculated using animal exposures relative to the projected human steady-state total exposure (C_{max} 87 nM [35 ng/mL] free or 256 nM [104 ng/mL] total; AUC 1228 nM•h [499 ng/mL] free or 3612 nM•h [1468 ng•h/mL] total) at the predicted human efficacious dose of 10 mg BID.

For more details about the ADME of PF-06463922, refer to the Investigator's Brochure (IB).[22]

1.3.6.1. PF-06463922 Pharmacokinetics in Phase 1

1.3.6.2. Study B7461001

The B7461001 dose-escalation study evaluated pharmacokinetics (PK) in 34 and 37 patients for single- and multiple-dose PK, respectively. Doses ranged from 10-200 mg QD. Also evaluated was the effect on midazolam (as a probe for CYP3A4), fed/fast conditions, and BID regimens, using the acetate solvate solid oral tablet formulation.

Preliminary single-dose PK of PF-06463922 under fasted conditions indicated peak plasma concentrations (C_{max}) of PF-06463922 were achieved at median time (T_{max}) ranging from 1.0-2.0 hours. Mean C_{max} and AUC_{inf} values for PF-06463922 ranged from 50.8 to 1201 ng/mL and from 900 to 21429 ng•hr/mL, respectively, and increased in a relatively dose-proportionate manner. Mean estimates of terminal half-life ranged from 16.3 to 27.4 hours.

After multiple once daily doses of PF-06463922 in the fasted state of PF-06463922 were achieved at median time (T_{max}) ranging from 1.0-2.0 hours. Mean C_{max} and AUC_{τ} values for PF-06463922 ranged from 67.3 to 1043 ng/mL and from 713 to 8057 ng•hr/mL, respectively. At doses greater than 50 mg QD, steady state AUC values increased in a less than dose-proportional manner. Mean estimates of effective half-life ranged from 11.8 to 23.4 hours. At 75 mg and 100 mg QD for 15 days, the accumulation indices were 0.52 and 0.61 of those predicted, respectively.

In vitro data indicated that PF-06463922 had time-dependent inhibition of CYP3A4/5. The CYP3A4/5 substrate drug midazolam was given with and without 25 mg and 150 mg PF-06463922 to a total of 6 patients (see Section 1.3.9). Preliminarily, the AUC_{inf} and C_{max} geometric mean (CV%) were reduced about 48 and 63% and 24 and 18% in the presence of daily PF-06463922 at either 25 mg or 150 mg, respectively, due to PF-06463922 inducing CYP3A4/5. Concomitant use of PF-06463922 with medications which are CYP3A4/5 substrates has potential to reduce the concentration of sensitive CYP 3A4/5 substrates and caution is advised when co-administering with PF-06463922.

PF-06463922 100 mg single-dose acetate solvate solid oral tablet formulation was given after an overnight fast or after a high-fat, high-calorie breakfast. Preliminary data from 5 patients indicated that the geometric mean C_{max} and $AUC\tau$ were centered around 1 with a wide 90% confidence interval (CI), which did not allow establishment of any significant differences between fed and fast conditions based on the available data. T_{max} values were shifted to the right in presence of food, with similar C_{max} values. The range of data for the fed condition was entirely contained within the range of the fasted condition suggesting no significant difference between fed and fasted conditions.

Three dose levels were given BID: 35 mg, 75 mg, and 100 mg. All 3 dose levels had steady-state $AUC\tau$ less than the steady-state $AUC\tau$ from the corresponding dose given QD. Administering PF-06463922 BID was not pursued due to the limited information available from these patients and the lack of tolerability, especially at 100 mg BID.

1.3.6.3. Relative Bioavailability Study B7461005

This study (B7461005) was a Phase 1, randomized (3 Period, 6 Sequence, Crossover), open-label study in 19 healthy volunteers to estimate the bioavailability of 2 new PF-06463922 formulations (using free base and maleate forms of API) relative to acetate solvate reference formulation (given in Phase 1 part of Study B7461001) given under fasted conditions. These new formulations were evaluated to identify options for improved drug product stability over the acetate formulation.

The results of the B7461005 bioavailability study indicated that the free base AUC_{inf} ratio to acetate solvate reference was contained within the 90% CI and met the bioequivalence criterion of 80 to 125%. The C_{max} for the free base formulation was decreased by 15% and the 90% CI did not include 100%, and the lower bound was less than 80%. However, no starting dose adjustment would be needed between free base and acetate formulations based on similar AUC results.

While the results for the maleate versus acetate reference were similar for AUCinf and Cmax, the free base formulation provides optimum drug product stability and was therefore selected for use in the Phase 2 part of Study B7461001.

1.3.7. Rationale for Selection of the Starting Dose in Phase 1

The starting dose for PF-06463922 in the first-in-patient trial in cancer patients has been determined to be 10 mg daily, based on information derived from the 1-month repeat dose toxicology studies in rats and dogs.

According to DeGeorge et al,[10] the currently accepted algorithm for calculating a starting dose in clinical trials for cytotoxic agents is to use one-tenth of the dose that causes severe toxicity (or death) in 10% of the rodents (STD10, severely toxic dose) on a mg/m^2 basis, provided this starting dose does not cause serious, irreversible toxicity in a non-rodent species. If irreversible toxicities are produced at the proposed starting dose in non-rodents or if the non-rodent is known to be the more appropriate animal model, then the starting dose would generally be one-sixth of the highest dose tested in the non-rodent that does not cause severe, irreversible toxicity (HNSTD, highest non severely toxic dose). The doses tested in the 1-month toxicology study in the male/female rats were 2/1, 8/4, and 30/15 mg/kg/day orally, and in the 1-month dog study were 2, 7, and 25 mg/kg/day orally. The STD10 in male/female rats was determined to be 8/15 mg/kg/day respectively (free AUC_{24} 5760/24660 ng.h/mL) and HNSTD following 1 month of dosing was 25 mg/kg/day in dogs (free AUC_{24} 40000 ng•h/mL).

The human equivalent starting dose was calculated to be 8.6 mg based on the rat STD10 of 8 mg/kg/day, and 150 mg based on the HNSTD of 25 mg/kg/day in the dog (assuming a body surface area of 1.8 m^2 for humans). Because the rat was determined to be the more sensitive species and provides a lower starting dose, the dose of PF-06463922 will be rounded to 10 mg and used as the starting dose for the FIP study. At the starting dose of 10 mg dose once daily, the projected unbound exposure (AUC_{24}, 249 ng/ml) is ~23-fold lower than the unbound exposure observed ($AUC_{24,}$ 5760 ng/ml) at rat STD10 dose and provides a good safety margin.

1.3.8. Rationale for Recommended Phase 2 Starting Dose

Although the adverse event profile of PF-06463922 in Phase 1 consists mostly of laboratory abnormalities, none of which were dose limiting, there was concern over the appearance of CNS effects particularly at those doses higher than 100 mg QD. Although the CRM model recommended dose escalation above 200 mg QD, the CNS effects observed at this dose and at the 150 mg QD dose were considered intolerable to some patients and were a cause for dose modification (ie, dosing interruption and/or dose reduction). As a result, it was agreed

upon by the sponsor and the Phase 1 investigators to test and re-test doses lower than 200 mg QD and consider an alternative dosing regimen.

BID dosing was employed to potentially modulate these adverse events, but the patients in BID cohorts had limited time on therapy (75 mg BID and 100 mg BID) and did not tolerate 100 mg BID well.

Overall, 100 mg QD was a well-tolerated dose. None of the patients at this dose required dose reduction. Dose delays did occur in 29% of patients, but these dose delays were not attributed to CNS effects, but rather to hypercholesterolemia or hypertriglyceridemia, or to disease-related events.

Additionally, based on the PK data observed, simulated patient exposure suggested that the 100 mg QD dose was the lowest dose that would exceed the PF-06463922 C_{eff} of 150 ng/mL during the majority of the dosing cycle once steady-state was reached. The C_{eff} of 150 ng/mL was a concentration predicted to result in >80% tumor growth inhibition of the ALK G1202R resistance mutation. Further, PF-06463922 demonstrated response rates of 37% (including a 30% intracranial response rate), which indicated that this compound is active both inside and outside the brain.

Taken together, the 100 mg QD dose was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

1.3.9. Rationale for Evaluation of Midazolam (MDZ) Interaction

PF-06463922 showed time-dependent inhibition of CYP3A isozymes in human liver microsomes with a kinact and KI of 0.218 min-1 and 2.81 μM, respectively, and inactivation efficiency (kinact/KI) of 77.6 min-1 *μM-1. CYP3A induction was also observed in human hepatocytes. Preliminary SimCYP™ simulations were performed to assess the net effect of steady-state PK of PF-06463922 on the metabolic activity of midazolam (2 mg). At projected human efficacious dose of 20 mg once daily (or 10 mg BID), the ratios of AUC and C_{max} of midazolam with and without PF-06463922 were 12 and 3, respectively, suggesting a net effect of inhibition. There is a potential for more potent inhibition in patients receiving higher doses, leading to substantial drug interactions with commonly coadministered drugs that are CYP3A substrates. In addition, PF-06463922 may display nonlinear pharmacokinetics in patients that may require dose adjustments. To mitigate these risks, a MDZ interaction sub-study has been built into this First in Patient (FIP) study to assess the potential PF-026463922 related CYP3A inhibition/induction.

MDZ is a benzodiazepine used clinically for conscious sedation. It undergoes extensive metabolism via CYP3A4/5 and is a widely accepted in-vivo probe for assessing CYP3A activity. In the current trial, midazolam PK following a single oral 2-mg dose will be evaluated before and after repeated daily administration of PF-06463922 at 3-4 dose levels (fewer dose levels may be evaluated depending on emerging PK results), in order to assess the effects of PF-066463922 on CYP3A activity in the gastro-intestinal tract and the liver. The results of MDZ interaction study will be used to assist selection of the RP2D and to

determine if there is any need for concomitant medication restrictions or dose modifications in future studies.

1.3.10. Rationale for Crizotinib Treatment after PF-06463922 Resistance

Crizotinib was the first approved ALK inhibitor for advanced ALK+ NSCLC patients, and since that time, much has been learned about its anti-tumor activity as well as the subsequent development of acquired resistance. In contrast, less is known about the development of resistance to the second-generation ALK inhibitors, alectinib and ceritinib; even less is known about the development of resistance to PF-06463922. However, certain key principles have emerged which shape the current understanding and support the use of crizotinib after failure of PF-06463922 in ALK+ NSCLC patients who were treatment naive prior to receiving PF-06463922.

Resistance has been characterized as either ALK-independent (eg, bypass track activation) or ALK-dependent (eg, gene amplification or ALK mutation).

The bypass tracks for crizotinib have been noted to be EGFR, KIT, SRC, and IGF-1R.[45] In considering activation of other oncogenic drivers in response to treatment with second-generation ALK inhibitors, it is important to note that crizotinib inhibits tyrosine kinase c-MET (MET) whereas alectinib and ceritinib do not. Notably, MET has been described as a mechanism of resistance to alectinib in preclinical work selecting for alectinib resistance in cell lines and has been described in clinical experience with alectinib.[46,47,48] As a MET inhibitor, crizotinib was effective at inhibition of cell growth in vitro of alectinib-resistant cells lines and was effective in treating the alectinib-resistant patient reported by Gouji and colleagues. Because PF-06463922 is not an inhibitor of MET, it is plausible that MET induction is also a potential mechanism of resistance to PF-06463922.

An additional line of evidence supports the use of crizotinib after PF-06463922. In the Phase 1 portion of this trial, a patient whose disease progressed on PF-06463922 was subsequently treated with crizotinib off study and had a second response; the mechanism of this activity may be the result of a new mutation which conferred sensitivity to crizotinib but resistance to study drug.

Thus, treatment with crizotinib after the emergence of resistance to PF-06463922 is reasonable and worth exploring in a population of patients who were treatment naïve prior to receiving PF-06463922.

1.3.11. Rationale for Drug-drug Interaction and Holter Monitoring

In vitro studies in human hepatocytes indicate that PF-06463922 may induce the metabolic enzyme CYP2B6 that could in turn lead to decreased exposure of drugs that are metabolized by CYP2B6. In addition, the in vitro observation that PF-06463922 also induces the metabolic enzyme CYP3A was confirmed clinically in a DDI evaluation with midazolam in the Phase I portion of this study.

The nuclear receptor PXR (pregnane X receptor) is widely accepted as the principal transcriptional regulator of CYP3A induction by xenobiotics. Activation of PXR is hypothesized to induce various other drug metabolizing enzymes, such as CYP2C8, CYP2C9, and CYP2C19, selected isoforms of UGTs, and efflux proteins such as P-gp. Further, In vitro data also indicates that PF-06463922 is a time-dependent inhibitor of CYP3A, and also inhibits CYP2C9, UGT1A1, UGT2B7 and P-gp.

Complex interactions, such as induction or net effect of induction along with inhibition of a specific enzyme or efflux transporter, can only be adequately evaluated following continuous multiple dosing of the perpetrator drug and using selective probes for the enzyme/transporter being investigated. The potential of PF-06463922 to induce key CYP enzymes and P-gp following multiple dosing of PF-06463922 will be evaluated in subjects enrolled in this cohort using selective probes substrates.

Additionally, as detailed in Section 1.3.5, PR interval prolongation has been observed in both healthy volunteer studies (Study B7461008) and the ongoing B7461001 study. To characterize the effects of PF-06463922 on ECG endpoints, continuous Holter telemetry of patients enrolled in this substudy 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.

In order to ensure patients have had exposure to prior treatments, this study will only be conducted in patients who meet the prior treatment requirements of EXP groups 2-6, as defined in Section 3.1.

Complete information for PF-06463922 may be found in the Single Reference Study Document (SRSD), which for this study is the Investigator's Brochure.[22]

Complete information for crizotinib (as applicable) may be found in the Investigator's Brochure.[42]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This study has separate primary and secondary objectives for the Phase 1 and Phase 2 study portions.

Phase 1 Portion of the Study

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 systemic therapies.

Exploratory Objectives:

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

Phase 2 Portion of the Study

Primary Objective:

- To evaluate overall (intra- and extra-cranial) and intracranial anti-tumor activity of single-agent PF-06463922 at RP2D in patients with advanced ALK+ NSCLC and 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 systemic 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 UGT isoforms.
- To characterize the effects of PF-06463922 on ECG endpoints.
- To characterize the safety and efficacy of PF-06463922 of patients entering the DDI/Holter monitoring study.

2.2. Endpoints [Please ensure endpoints changes remain aligned with Section 9.]

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 (Appendix 3). 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.[32]

Secondary Endpoints [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.
- Phase 1 only: pharmacokinetic parameters of midazolam: C_{max}, T_{max}, AUC_{last}, CL/F, and Vz/F and $t_{1/2}$, AUC_{inf} as data permit.
- 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), 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 (Appendix 3) [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.[32]
- 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 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, eg, ALK kinase domain mutations and circulating nucleic acid (CNA), eg, ALK kinase domain mutations.

Secondary Endpoints [ALK+ NSCLC Phase 2 patients 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.

Phase 1 Exploratory Endpoints:

- Time to Progression (TTP).

Phase 1 and 2 Exploratory Endpoints:

- CSF concentration of PF-06463922.

Japanese Patient Only Lead-In Cohort (LIC)

- Cycle 1 Dose Limiting Toxicities (DLTs).

Endpoint 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 interval with PF-06463922 treatment.

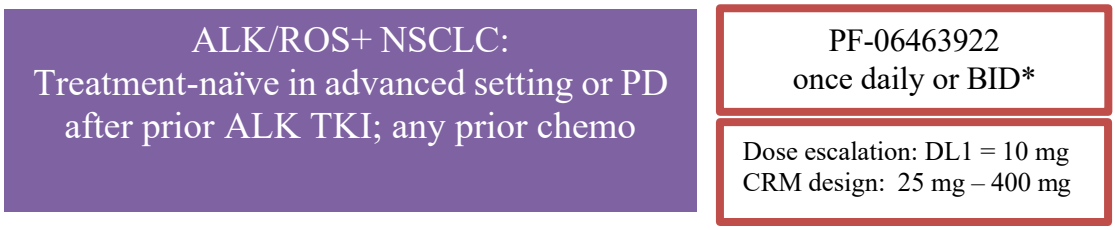
3. STUDY DESIGN

3.1. Study Overview

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.

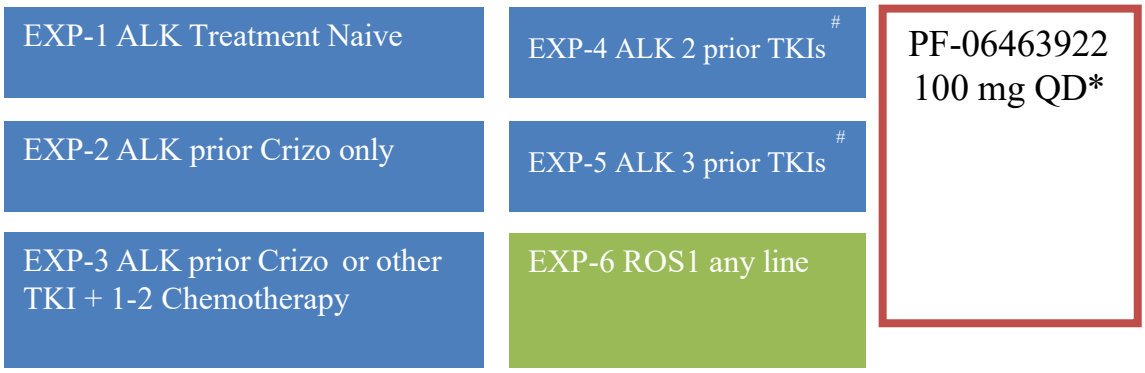
Figure 1. Study Schema

Phase 1:



* Treatment until PD or unacceptable toxicity.

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.

\# 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 are 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 lead-in period and

subsequent doses timing, dosing regimen, and PK time points may be modified based on the emerging PK data.

To evaluate the effect of PF-06463922 on CYP3A inhibition/induction, a midazolam (MDZ) drug-drug interaction (DDI) substudy will be conducted at 3 to 4 PF-06463922 dose levels (fewer dose levels may be evaluated depending on emerging PK results) in Phase 1. Patients enrolled in the MDZ interaction sub-study will receive a single 2 mg oral dose of MDZ on Day –7. These patients will receive another single 2-mg oral dose of MDZ concurrently with PF-06463922 on Cycle 1 Day 15 (morning dose if BID schedule). During the study, real-time pharmacokinetic monitoring will be conducted as much as possible. Additionally, a food effect substudy will be conducted in approximately 6 Phase 1 patients to gain preliminary information about the effects of food on PF-06463922 PK.

On Cycle 1 Day 15, MDZ will be given concurrently with PF-06463922. Patients participating in the MDZ substudy will NOT receive any lead-in dose of PF-06463922 on Day -7.

The Phase 2 portion of the study will be with single-agent PF-06463922 at the identified MTD/RP2D and will enroll patients with advanced ALK+ NSCLC and patients with advanced ROS1+ NSCLC, with or without asymptomatic CNS metastases. 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 (see Appendix 11).

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. The required assessments and safety review process for the Japanese patient only LIC are outlined in Appendix 9 and Appendix 10, respectively.

To evaluate the potential interaction of PF-06463922 on 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 (6 evaluable for each probe substrate) 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 comparing the subject's time-matched PR interval (approximately 10 points) with exposure of PF-06463922 following a single dose and again at steady state. In addition, arrhythmia analysis will be performed in these patients and these data will be analyzed separately from Phase 2 data. 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.

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-3A -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.

Guidance on the management of patients on study is provided to investigators in Table 1. The revised schedule of activities will allow the investigators to perform most study tests and procedures per standard of care or clinical judgement.

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.

Safety assessments (laboratory, instrumental and clinical) will be regularly performed to assess the safety profile of PF-06463922 as a single agent.

Tumor assessments by computerized tomography/magnetic resonance imaging (CT/MRI) scans of Chest Abdomen Pelvis [CAP] and MRI of the brain will be performed at baseline, and the brain MRI and CAP will be repeated every 6 weeks ±1 week on study for the first 18 months in Phase 1 and first 30 months in Phase 2, and then every 12 weeks ±1 week beyond regardless of tumor involvement. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients (regardless of bone involvement) and repeated every 12 weeks on study, only if evidence of bone metastases are observed at baseline. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment will be done every 6 weeks ±1 week up to 18 months in Phase 1 and up to 30 months in Phase 2, and every 12 weeks ±1 week thereafter (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For all tumor assessments, the method of assessment used at baseline should be the same method

used throughout the study. For patients who have documented disease progression, but are still receiving PF-06463922, tumor assessments are to be done according to local institutional standard of care. Tumor response will be assessed by the RECIST v1.1 (Appendix 3) with modification to account for intracranial tumor response as described below.

For those patients entering the study with asymptomatic CNS metastases, the response of measurable intracranial disease (ie, lesions ≥5 mm) will be assessed by a modified version of RECIST v1.1.[32] The RECIST v1.1 will be extended to include up to 5 intracranial target lesions and up to 5 extracranial target lesions. Intracranial target lesions must be between 5 mm and 40 mm in diameter. Intracranial disease assessment may only be by gadolinium-enhanced MRI with MRI contingent slices of 1 mm for assessment of CNS metastases ≥5 mm but less than 10 mm. CNS lesions ≥10 mm will be assessed with gadolidium- enhanced MRI with MRI contingent slices of 5 mm. All other CNS lesions considered non measurable under these conditions will still be assessed by gadolidium MRI with contingent slices of 1 mm but will be reported as Non Target.

Patients who have asymptomatic radiologically suspected leptomeningeal disease (LM) or carcinomatous meningitis (CM) and have negative cerebrospinal fluid (CSF) cytology may be eligible for Phase 1. In addition, in the Phase 2, patients who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) will be eligible if the LM/CM is visualized on MRI or if documented baseline cerebral spinal fluid (CSF) positive cytology is available. These will be considered Non Target lesions.

All radiologic images must be available for independent central radiology review as determined by the sponsor. Instructions for submission of these images will be provided in the Study Reference Manual. The independent central radiology review will be stopped when the data collection required for the primary and secondary endpoints is deemed sufficient.

Upon approval of Amendment 8, the radiologic assessments will be performed according to local practice.

Biomarker studies on tumor tissue and blood will be carried out to help understand the mechanism of action of PF-06463922, as well as potential mechanisms of resistance. Such results may help in the future development of PF-06463922. These analyses may also result in the identification of potential biomarkers of response to PF-06463922, ultimately leading to development of a patient selection strategy for further clinical investigation.

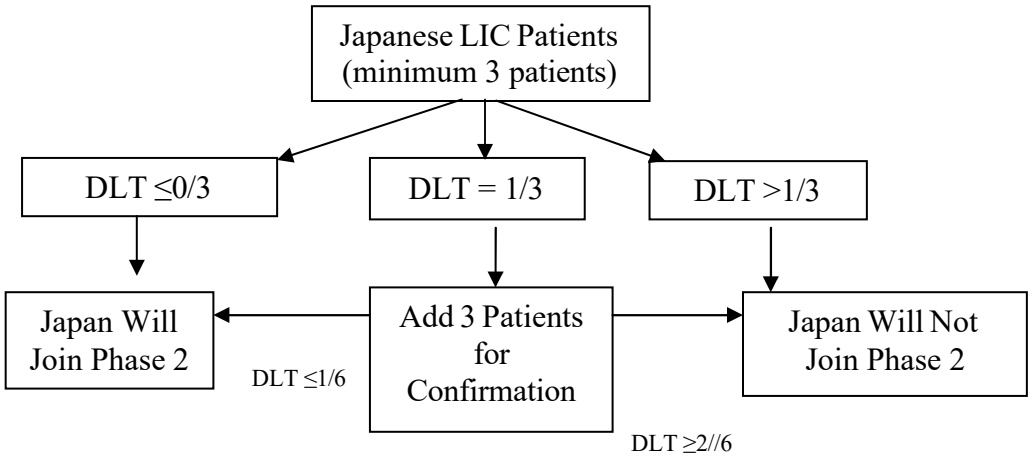
In all study parts, patients will continue with the study treatment until progression of disease as determined by the investigator, unacceptable toxicity, death or consent withdrawal. Patients may continue PF-06463922 (or crizotinib, if administered after PF-06463922) treatment after objective progression of disease is determined if the patient is continuing to experience clinical benefit, in the opinion of the investigator, and after discussion with the Sponsor.

3.2. 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. The required Schedule of Activities and safety review process for the Japanese patient only LIC is outlined in Appendix 9 and Appendix 10, respectively.

A reduced schedule of activities will be followed upon approval of Amendment 8 as indicated in Table 1.

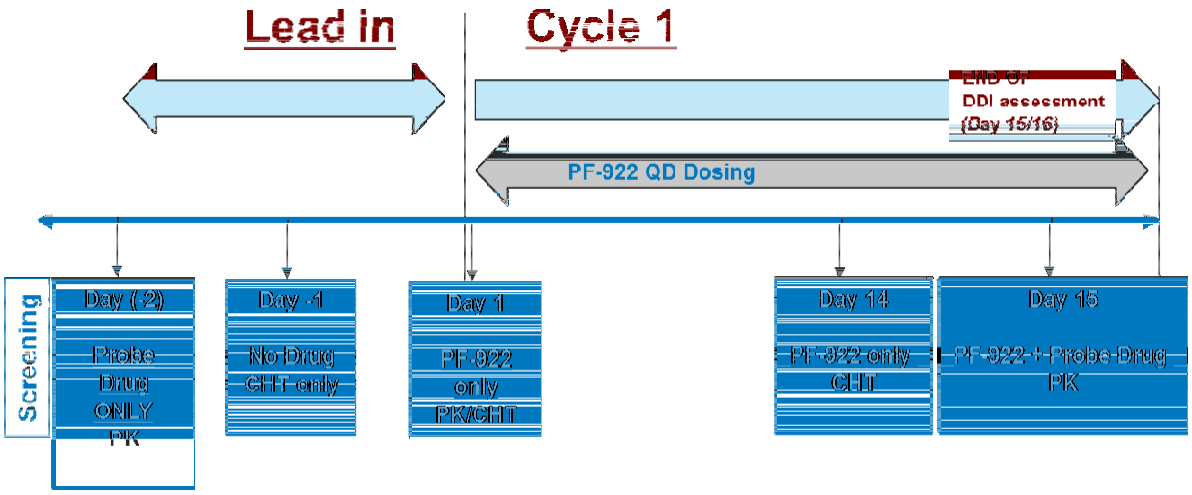
Figure 2. Japanese Patient-Only Lead-In Cohort Schema



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

For evaluation of the drug interaction potential of PF-06463922, approximately 30 patients (6 evaluable patients with each drug probe) will be administered a single dose of a 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 patients 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 Section 4.2. Additionally, patients will only be eligible to participate if they meet the prior treatment requirements of EXP groups 2-6.

A reduced schedule of activities will be followed upon approval of Amendment 8 as indicated in Table 1.

3.4. Starting Dose

3.4.1. Phase 1

The starting dose of PF-06463922 will be 10 mg given once daily (or twice daily), continuously in 21-day cycles.

3.4.2. Phase 2

Patients will receive PF-06463922 as a single agent at the RP2D determined in Phase 1 once daily in 21-day cycles.

3.4.3. Criteria for Dose Escalation

In the Phase 1 portion, PF-06463922 will be evaluated at escalating doses of 10, 25, 50, 75, 100, 150, 200, 250, 300, and 400 mg/once daily (QD) as per Table 9. The doses that will be evaluated for BID dosing are provided in Table 13. After the 25 mg dose has been evaluated and has cleared the dose-limiting toxicity (DLT) observation period for confirming that higher doses may be tested, doses of PF-06463922 will be assigned to each cohort of patients using a Continuous Reassessment Method (CRM) model. The goal of the Phase 1 portion is to determine the dose of PF-06463922 that is the closest to but no higher than a 33% probability of a DLT (ie, a target DLT rate of 0.33). Each dose cohort will initially include at least 3 patients evaluable for toxicity within the first cycle. The first 3 patients (ie, the first cohort) will be treated at 10 mg QD, and the following dose level explored will be 25 mg QD. To assign the dose level for each subsequent patient, the probability of DLT is estimated to a target rate ≤33%. This estimate is achieved for each level taking into account all the collected toxicity data from all treated patients up to that time and the prior expectations of toxicity. Based on the observed toxicity profile, CRM permits dose-level skipping during dose escalation. However, in order to prevent overly aggressive dose escalation, for every escalation the maximum allowed dose level skipped will be limited to one dose level. No restriction is applied for dose de-escalation.

The probabilities of DLT are estimated based on a Bayesian statistical model with prior distribution to learn about the overall dose-toxicity relationship. Patients' DLT data will be reported to the study statistician who will update the dose-toxicity model before the next dose level is explored. Details on the CRM method are provided in Section 9.2 and the Statistical Analysis Plan.

Patients who discontinue treatment before completing Cycle 1 (ie, the DLT evaluation time window) 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.

To avoid overly rapid escalation and to retain the efficiency of dose administration when enrollment is fast, the following restrictions will be applied:

- For each dose level, 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). The first 2 patients may enroll together, but the next patient(s) will enroll at least 1 week later. The timing of patient enrollment may be further evaluated as safety and PK data become available.

- Enrollment for the next cohort of patients will open when patients on the current dose cohort have completed the pre-specified DLT observation period or experienced a DLT.

- Enrollment in dose level cohorts lower than the highest tested dose level cohort may occur before the completion of the pre-specified DLT observation period.

- Dose level skipping in escalation to untested doses will be limited to only one level ($k \rightarrow k+2$). In particular, at least 3 patients should have been treated for at least one cycle at dose level k before escalation to dose level k+2.

- Dose escalation recommendation by the CRM algorithm may be overruled (but frequency should be minimized) by the Sponsor if the nature of the existing data causes safety concern.

- Further exploration of doses lower than those recommended by the CRM model may be evaluated based on the totality of the safety data.

In case the DLT rate at the initial dose level of 10 mg QD exceeds 33%, the dose level of 5 mg QD will be tested.

Table 9. Phase 1 PF-06463922 Dose Levels

DOSE LEVEL (DL)mg mg/day	Phase 1*	MDZ DDI# Evaluation
5	DL -1	-1
10	Starting Dose	n/a
25	DL 2**	1
50	DL 3	n/a
75	DL 4	2
100	DL 5	
150	DL 6	3
200	DL 7	
250	DL 8	4
300	DL 9	
400	DL 10	

* Dose levels may be skipped in the CRM algorithm depending on the observed toxicities.

**CRM design design commences after the evaluation of toxicities observed in DL2.

Potential dose levels (one dose at each level) for MDZ DDI substudy.

n/a: not applicable

Intra-patient dose escalation may be permitted if all of the following conditions are satisfied:

- Cycle 1 was completed without any DLT;
- His/her maximum drug-related toxicity during prior cycles of therapy was Grade ≤2 and did not require a dose modification;
- Observation of Grade ≥3 laboratory abnormalities not requiring dose modifications (as identified in Table 10) would be permitted;
- Three patients at the next higher dose level have completed Cycle 1 with study drug without having a DLT.

The decision to increase the dose has been approved by discussion with both the Investigator and the Sponsor. A patient whose dose has been escalated will not contribute to the assessment of the number of DLTs at the escalated dose level.

Dose administration (dose escalation and de-escalation) within the context of the CRM model of the Phase 1 portion of the trial stops if: (1) the maximum sample size has been reached (36 in total, see Section 9.3 for details), (2) at least 12 patients have been treated at a dose that is predicted to be the MTD or (3) all doses appear to be overly toxic and the MTD cannot be determined in the current trial.

The final posterior probability and 90% posterior probability interval estimates of DLT at each dose level will be calculated, with data from all patients that are enrolled and treated. Once one of the aforementioned conditions for stopping the CRM is met, the dose identified as MTD will be evaluated together with information gathered from PK analyses and the overall safety profile. The dose(s) likely to be considered the RP2D will be expanded to 12 patients if not already tested within the CRM context in order to confirm the RP2D.

3.5. 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 as indicated in Table 10) 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.

3.6. MTD Definition

The MTD estimate is the highest dose level associated with ≤33% of patients experiencing a DLT. Due to the discreteness of the dose levels and in the interest of safety of patients, the estimated MTD is the highest dose level with a DLT rate less than 0.33.

3.7. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Phase 1 results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D lower than the MTD. The final RP2D will be communicated by a letter to site investigator participating to the Phase 2.

3.8. Midazolam DDI Study (Phase 1)

The potential of PF-06463922 to inhibit/induce CYP3A will be evaluated using MDZ as a CYP3A probe substrate. In Phase 1, the MDZ interaction study will be evaluated at 3-4 dose levels (fewer dose levels may be evaluated depending on emerging PK results) starting in the second PF-06463922 dose level (ie, 25 mg, see Table 9 Section 3.4.3). For this substudy, at least 3 evaluable patients per cohort will be assessed for the effect of repeat PF-06463922 administration on the pharmacokinetics of midazolam.

Patients enrolled in the MDZ interaction substudy will receive a single 2 mg oral dose of MDZ on Day –7 and another single 2-mg oral dose of MDZ concurrently with PF-06463922 on Cycle 1 Day 15 (morning dose if on BID schedule).

3.9. Food Effect Study (Phase 1)

The effect of food on the pharmacokinetics of PF-06463922 will be evaluated in a food effect substudy in approximately 6 patients in Phase 1. The testing order for fed versus fasted conditions will be as follows: the first half of the patients to participate in this substudy will be tested under fed followed by fasted conditions, the next half of the patients will be tested under fasted followed by fed conditions. Patients who have had a gastrectomy or have dietary or other restrictions that preclude a 10-hour overnight fast (water permitted) or consumption of the required high-fat, high-calorie meal will not participate in this sub-study.

The effect of a high-fat, high-calorie breakfast on PF-06463922 pharmacokinetics will be studied. Each patient will serve as his/her own control in which PF-06463922 will be administered in the morning under either “fed” or “fasted” conditions on Day (-7) and Day 1 of Cycle 1, respectively. After Cycle 1 Day 1 in the food effect cohort only, PF-06463922 should be administered with food (ie, normal diet) regardless of which condition the patient was last dosed (ie, fed or fasted).

No trial drug will be administered during the interval between the Day-7 and Day 1 of the first cycle.

3.10. Drug-Drug Interaction and Holter Monitoring Study

To evaluate the potential interaction of PF-06463922 on drugs that are metabolized via pathways that include CYP2B6, CYP2C9, P-gp, and select UGT isoforms, a drug-drug interaction study will be conducted in approximately 30 ALK-positive NSCLC patients (6 evaluable patients for each drug probe). Additionally, an evaluation of the effects of PF-06463922 on the PR interval will be conducted via continuous Holter telemetry comparing the subject’s pre-drug baseline values with observations of PR interval changes associated with exposure of PF-06463922 following a single dose and again at steady state.

For patients participating in the DDI and Holter monitoring study, when possible, breakfast, lunch and dinner should be consumed at approximately at the same times on days of Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14). On Day -2 and Cycle 1 Day 15, the probe substrate should be administered in the fasted state, when possible, (no food at least 2 hours before through 2 hours after probe substrate dosing). On days of continuous Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14), patients should be advised to not undergo any exercise. Additionally on Holter monitoring days substances that may alter ECG readings (such as caffeine-containing products, alcohol and tobacco containing products) should be avoided.

4. PATIENT SELECTION

Section 4 includes Patient Selection criteria for PF-06463922. When applicable, patients who receive crizotinib following PF-06463922 should also follow the Patient Selection criteria as outlined in Appendix 11.

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Baseline assessments (eg, tumor assessments) performed as standard of care and prior to signing of the informed consent may be used provided these do not exceed the timelimit windows provided in the Schedule of Activities.

4.1. Inclusion Criteria

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

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

1. Evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, AJCC v7.0) that carries an ALK 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 rearrangement as determined by FISH or RT-PCR or Next Generation Sequencing (NGS) via a local diagnostic test (LDT). A central laboratory confirmation by a Sponsor-selected, validated test will retrospectively determine final ROS1 status. All patients (ALK positive and ROS1 positive) must have archival tissue sample available and collected prior to enrollment.

2. Disease Status Requirements:

   Phase 1: ALK-positive NSCLC patients must either be treatment naïve in the advanced setting or have had disease progression after at least 1 previous ALK inhibitor therapy(ies). ROS1-positive NSCLC patients must either be treatment naïve in the advanced setting or have had disease progression after at least 1 previous ROS1 inhibitor therapy(ies).

   Phase 2:

   ALK-positive NSCLC patients must either be or have had:

   - Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ALK inhibitor therapy allowed). [EXP-1];

   - Disease progression after crizotinib only. No prior chemotherapy is allowed in the metastatic disease setting. [EXP-2];

- Disease progression after crizotinib and 1 or 2 prior regimens of chemotherapy in the metastatic disease setting. [EXP-3A];

- Disease progression after 1 prior ALK inhibitor therapy other than crizotinib. Patients may have had any number of prior chemotherapy regimens in any disease setting. [EXP-3B];

- Disease progression after 2 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. [EXP-4];

- Disease progression after 3 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. [EXP-5].

ROS1-positive NSCLC patients may be:

- Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ROS inhibitor therapy). [EXP-6];

- Any number of prior therapies (ie, chemotherapy and/or ROS inhibitor therapies). [EXP-6].

DDI and Holter Monitoring Study patients may be:

- ALK-positive or ROS1-positive NSCLC patients who meet the above disease status requirements for EXP groups 2-6.

3. Tumor Requirements:

Phase 1: All Patients must have at least one measurable target extracranial lesion according to RECIST v1.1. In addition patients with asymptomatic CNS metastases (including patients asymptomatic by means of stable or decreasing doses of steroids within the last 2 weeks prior to study entry) will be eligible. The brain metastases may be newly diagnosed or be present as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery (see Exclusion Criterion #3 for the lapsed time period required between the end of radiotherapy and study entry). Patients who have asymptomatic radiologically suspected leptomeningeal disease (LM) or carcinomatous meningitis (CM) and negative spinal fluid (CSF) are eligible to enter **Phase 1**.

Phase 2: All Patients must have at least one measurable target extracranial lesion according to RECIST v1.1. In addition patients with asymptomatic CNS metastases (including patients controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry) will be eligible. The brain metastases may be newly diagnosed or be present as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery (see Exclusion Criterion #3 for the lapsed time period

required between the end of radiotherapy and study entry). Patients who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) will be eligible if the LM/CM is visualized on MRI or if documented baseline cerebral spinal fluid (CSF) positive cytology is available.

DDI and Holter Monitoring Study: All Patients must have at least one measurable intracranial or extracranial lesion according to RECIST v1.1 (ie, patients may be eligible with only 1 CNS lesion provided it is measurable per RECIST 101). Patients with CNS metastases are eligible if they are asymptomatic (including patients controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry). The brain metastases may be newly diagnosed or be present as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery (see Exclusion Criterion #3 for the lapsed time period required between the end of radiotherapy and study entry). Patients who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) will be eligible if the LM/CM is visualized on MRI or if documented baseline cerebral spinal fluid (CSF) positive cytology is available.

4. Age ≥18 years (or ≥20 years of age if required by local regulation).

5. ECOG Performance Status (PS):

   - **Phase 1**: 0 or 1;
   - **Phase 2:** 0, 1, or 2.

6. Adequate Bone Marrow Function, including:

   - Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L;
   - Platelets ≥100 x 10^9/L;
   - Hemoglobin ≥9 g/dL.

7. Adequate Pancreatic Function, including:

   - Serum total amylase ≤1.5 ULN;
   - Serum lipase ≤1.5 ULN.

8. Adequate Renal Function, including:

   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

9. Adequate Liver Function, including:

   - Total serum bilirubin ≤1.5 x ULN;

- Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver metastases involvement.

10. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator' judgment do not constitute a safety risk for the patient.

11. Serum pregnancy test (for females of childbearing potential) negative at screening (before the patient may receive the investigational product). A patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active.

12. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

13. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

14. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception from the time of the first negative pregnancy test at screening, throughout the study and for 97 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

    Japan Sites Only: A female patient who is not of childbearing potential is one that (ie, meets at least one of the following criteria):

    - Has undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Has medically confirmed ovarian failure; or
    - Has achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause (which may be confirmed with a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women).

4.2. Exclusion Criteria

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

1. Spinal cord compression is excluded unless the patient demonstrates good pain control attained through therapy and there is stabilization or recovery of neurological function for the 4 weeks prior to study entry.

2. Major surgery within 4 weeks of study entry. Minor surgical procedures (eg, port insertion) are not excluded, but sufficient time (eg, up to 2 weeks) should have passed for wound healing.

3. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have completed at least 2 weeks prior to study entry. Whole brain radiation must have completed at least 4 weeks prior to study entry.

4. Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study entry (unless clinically meaningful tumor flare per discretion of the investigator, in which discussion with the sponsor is warranted).

5. Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including, but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody.

6. Previous high-dose chemotherapy requiring stem cell rescue.

7. Prior irradiation to >25% of the bone marrow (see Appendix 5 Bone Marrow Reserve in Adults).

8. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

9. Clinically significant cardiovascular disease (that is, active or <3 months prior to enrollment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), second-degree or third-degree AV block (unless paced) or any AV block with PR >220 msec.

   Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read ECG with QTc >470 msec, or congenital long QT syndrome.

10. Patients with predisposing characteristics for acute pancreatitis according to investigator judgment (eg, uncontrolled hyperglycemia, current gallstone disease, alcoholism [more than 4 drinks on any day or 14 drinks per week where 1 drink is defined as the alcoholic beverage containing approximately 14 grams of pure alcohol, eg, 12 fl oz/360 mL regular beer or 5 fl oz/150 mL of wine] in the last month.

11. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersentivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis and pulmonary fibrosis. Patients with history of prior radiation pneumonitis are not excluded.

12. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

13. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.

14. Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, DCIS of the breast or localized and presumed cured prostate cancer) within the last 3 years.

15. Active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease or previous gastric resection or lap band.

16. Current use or anticipated need for food or drugs that are known strong or moderate CYP3A4 inhibitors, including their administration within 10 days prior to the first PF-06463922 dose (ie, strong CYP3A4 inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan; Moderate CYP3A4 inhibitors: erythromycin, verapamil, atazanavir, delavirdine, fluconazole, darunavir, diltiazem, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine). Concomitant medication with a suspected CYP3A4 inhibitory effect must be approved by the Sponsor.

17. Current use or anticipated need for drugs that are known strong CYP3A4 inducers, including their administration within 12 days prior to the first PF-06463922 dose (ie, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St. John's Wort). Concomitant medication with a suspected CYP3A4 inductive effect must be approved by the Sponsor.

18. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, such as astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, (alfentanil and fentanyl, including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) is not permitted or caution is warranted. Concomitant medication suspected of being a CYP3A4 substrate with narrow therapeutic index must be approved by the Sponsor.

19. Concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or a sensitive substrate such as celecoxib is not permitted or caution is warranted. Concomitant medication suspected of being a CYP2C9 substrate with narrow therapeutic index must be approved by the Sponsor.

20. Concurrent use of drugs that are sensitive CYP2B6 substrates, such as bupropion, efavirenz is not permitted or caution is warranted. Concomitant medication suspected of being a CYP2B6 substrate with narrow therapeutic index must be approved by the Sponsor.

21. Current use or anticipated need for drugs that are known strong CYP2C19 inhibitors, including their administration within 12 days prior to study entry (ie, fluconazole, fluvoxamine, ticlopidine). Concomitant medication with a suspected CYP2C19 inhibitory effect must be approved by the Sponsor.

22. Current use or anticipated need for drugs that are known strong CYP2C8 inhibitors, including their administration within 12 days prior to study entry (ie, gemfibrozil). Concomitant medication with a suspected CYP2C8 inhibitory effect must be approved by the Sponsor.

23. Current use or anticipated need for drugs that are known P-gp substrates with a narrow therapeutic index, including their administration within 12 days prior to study entry (ie, digoxin). Concomitant medication with a suspected P-gp substrates with a narrow therapeutic index must be approved by the Sponsor.

24. Patients presenting with abnormal Left Ventricular Ejection Fraction (LVEF) by echocardiogram or Multi-Gated Acquisition Scan (MUGA) according to institutional lower limits.

25. Breastfeeding female patients (including patients who intend to interrupt breastfeeding).

Additional Exclusion Criteria for Patients participating in the Drug-drug Interaction Holter Monitoring Study:

1. CYP2B6: for the DDI evaluation with buproprion, aCYP2B6 probe substrate, patients should not be taking any moderate/strong inhibitors or inducers of CYP2B6 within 2 weeks of the lead-in probe substrate dosing and until the DDI assessment portion is completed on Day 15 of Cycle 1. Refer to the buproprion product insert for complete information on contraindications.

2. CYP2C9: for the DDI evaluation with tolbutamide, a CYP2C9 probe substrate, patients should not be taking any moderate/strong inhibitors or inducers of CYP2C9 within 2 weeks of the lead-in probe substrate dosing and until the DDI assessment portion is completed on Day 15 of Cycle 1. Please refer to the tolbutamide product insert for complete information on use and contraindications.

3. UGTs: for the DDI evaluation with acetaminophen, a UGT probe substrate, patients subjects should not be taking any moderate/strong inhibitors or inducers of UGTs within 2 weeks of the lead-in probe substrate dosing and until DDI assessment portion is completed on Day 15 of Cycle 1. Refer to acetaminophen product insert for complete information.

4. P-gp: for the DDI evaluation with fexofenadine, a probe substrate for P-gp, patients should not be taking any moderate/strong inhibitors or inducers of P-gp within 2 weeks of the lead-in probe substrate dosing and until DDI assessment portion is completed on Day 15 of Cycle 1. Refer to fexofenadine product insert for complete information.

5. All subjects with a history of risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesemia, congenital long QT syndrome, myocardial ischemia or infarction) will be excluded from this cohort.

4.3. Life Style Guidelines

4.3.1. Contraception

PF-06463922 is teratogenic and an aneugen, and can therefore cause harm when administered to a pregnant woman. Therefore, use of a highly effective method of contraception during treatment with this study drug is mandatory.

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected a highly effective method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see below, Section 4.3.1.2) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of assessments, the investigator or designee will inform the participant of the need to use a highly effective method of contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least one of the appropriate methods of contraception).

The investigator, at each study visit, will discuss with the patient the need to use a highly effective contraception consistently and correctly and document such conversation in the patient chart. In addition, the investigator will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

Women of childbearing potential enrolled in the study (WOCBP, definition provided below, Section 4.3.1.1) must agree to use a nonhormonal method of contraception. PF-06463922 can render hormonal contraceptives ineffective because they are metablized by CYP3A, which may be induced by PF-06463922. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Contraception must be continued for at least 21 days after completing therapy.

During treatment with PF-06463922, all sexually active male patients must agree to prevent potential transfer to and exposure of partner(s) to PF-06463922 through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 97 days after the last dose of PF-06463922. Male patients with pregnant partners must be agreed to use condoms. Male patients must agree to refrain from donating sperm throughout the study and for 97 days after the last dose of assigned treatment.

4.3.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   Documented hysterectomy;

   Documented bilateral salpingectomy;

   Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.3.1.2. Contraception Methods

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided a condom is used in combination with the hormonal method. The patient must have been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom must be used in association with a highly effective female method of contraception.

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

4.3.2. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity UVb sources such as tanning beds, tanning booths and sunlamps. Patients should be advised to apply sunscreen and wear appropriate clothing to minimize exposure to the sun during treatment with PF-06463922.

4.3.3. Additional Lifestyle Guidances

Patients will be advised to avoid eating or drinking grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos] that strongly inhibit/induce CYP3A (refer to Section 5.3). Because there are no available data on concurrent alcohol use with PF-06463922, patients should be advised to limit alcohol consumption during the study treatment period.

4.4. Sponsor Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the team Sharepoint site/study portal.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk

number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

4.5. Mini Mental State Examination (MMSE) Rater Qualifications (Phase 1 only; No longer required per Amendment 6)

The Mini Mental State Examination (MMSE) rater administration instructions will be provided in the Study Manual and these along with the tool can be found in the publication of Folstein et al, 1975.[37] The rater must hold a degree, certificate, or license to practice in a health care profession or occupation, including (but not limited to) the following: clinical psychology, medicine, neurology, neuropsychology, nursing, occupational therapy and other allied health care professions, physicians' assistants, psychiatry, school psychology, social work, speech-language pathology; plus appropriate training and experience in the ethical administration, scoring, and interpretation of clinical behavioral assessment instruments.

The rater may be any one of the site staff who have contact with the patient on a regular basis eg, study co-ordinator, sub investigator, research nurse, principal investigator.

4.6. Rater Requirements for Assessment of Mood and Assessment of Suicidal Ideation and Behavior (Phase 2 only)

A rater is defined an individual(s) who administers the Columbia Suicide Severity Rating Scale[43] (C-SSRS) and/or the Beck Depression Inventory-II (BDI-II) scale to patients in the study. At least 2 raters will be identified at each site and trained to administer the C-SSRS and the BDI-II to patients enrolled in Phase 2.

5. STUDY TREATMENTS

Section 5 includes Study Treatment details for PF-06463922. When applicable, patients who receive crizotinib following PF-06463922 should follow Study Treatment details as outlined in Appendix 11.

5.1. Allocation to Treatment

In Phase 1 dose level allocation will be performed by the Sponsor after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax or email a complete Registration Form to the designated Sponsor study team member. Registration will be within 2 days prior to lead -in single dose as appropriate. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient and fax or email to the site.

No patient shall receive study drug until the Investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the patient’s enrollment;
- Specification of the dose level for that patient; and

- Permission to proceed with dosing the patient.

The Sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

Patient registration to Phase 2 will utilize an automated registration system where a randomization number will be assigned. Study treatment should begin approximately 2 days after the patient is registered.

For patients participating in the DDI and Holter monitoring study, registration should occur within 2 days of administration of the probe drug . Sites will inform Pfizer of the concomitant medications that a patient is receiving and suggested probe drug.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

PF-06463922: In Phase 1, PF-06463922 will be supplied for oral administration as, 25 mg and 100 mg acetate solvate tablets in HDPE (High Density Polyethylene) bottles with desiccant. Tablets have different sizes and shapes according to different strengths. Study medication will be supplied by Pfizer. In Phase 2, PF-06463922 will be supplied for oral administration as 25 mg free base tablets in HDPE (High Density Polyethylene) bottles with desiccant. Study medication will be supplied by Pfizer.

Midazolam (MDZ) [Phase 1 only]: Midazolam (2 mg/mL, oral syrup) will be used in the study and supplied by the Sponsor.

Drug –drug Interaction and Holter Monitoring study Probe Drugs (DDI/Holter study only): The suggested probe drugs bupropion, tolbutamide, acetaminophen or fexofenadine will be used and supplied by the participating study sites.

5.2.2. Preparation and Dispensing

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

5.2.2.1. PF-06463922

In Phase 1, PF-06463922 will be provided in bottles containing 25 mg, or 100 mg acetate solvate tablets. The bottles will be labeled with different color labels to differentiate between dosage strengths.

In Phase 2, PF-06463922 will be provided in bottles containing 25 mg free base tablets.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Adminstration Cards and Patient Diaries. In addition, administration instructions will be detailed in the Investigational Product (IP) Manual.

PF-06463922 will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

5.2.2.2. Midazolam (Phase 1 Only)

Midazolam will be dispensed using the manufacturer specified dispensing instructions. Qualified personnel will prepare and dispense the MDZ dose in accordance with the current package insert.

5.2.2.3. Drug-drug Interaction and Holter Monitoring Study Probe Drugs

The probe drugs will be dispensed using the manufacturer specified dispensing instructions. Qualified personnel will prepare and dispense the probe drug dose in accordance with the current package insert. The recommended individual probe drugs and their doses for administration are outlined in Section 3.3.

5.2.2.4. PF-06463922

All patients will receive single-agent PF-06463922.

The starting dose for PF-06463922 in the Phase 1 will be 10 mg. PF-06463922 will be administered once daily (or twice daily) in 21-day cycles. Patients in the Phase 2 will receive PF-06463922 as a single agent at the RP2D of 100 mg once daily in 21-day cycles.

Administration will be performed on an outpatient basis. PF-06463922 should be taken with at least 8 oz (240 mL) of water and may be taken with or without food. See Section 5.2.3.1 for dosing instructions in food effect cohort (Phase 1 only). Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time. However, a variance of up to 12 hours is allowed for any given dose, rather than miss a day's dose. For patients receiving BID dosing (Phase 1 only), study medication should be taken approximately 12 hours apart; however, a 3-hour variance is allowed.

If a patient misses a daily dose, they must be instructed not to "make it up" the next day. If a patient vomits anytime after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-06463922. Patients should also be instructed to swallow the trial medication whole and not chew the tablet prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact. Doses may be modified according to Table 10. Patients requiring dose reduction in Phase 1 should undergo reduction to the next lower dose level as outlined in Table 11 (Table 13 for BID dose levels). Patients requiring dose reduction in Phase 2 should undergo reduction to the next lower dose level as outlined in Table 12. Patients must be instructed to record all doses (and missed or vomited doses) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

For patients participating in the MDZ DDI study (Phase 1), PF-06463922 will be administered with MDZ on Cycle 1 Day 15 (morning dose if on BID dosing schedule).

For patients participating in the food effect study (Phase 1), PF-06463922 will be administered following an overnight fast of at least 10 hours on Cycle 1 Day -7 and Cycle 1 Day 1.

For patients participating in the DDI and Holter monitoring study, when possible, breakfast, lunch and dinner should be consumed at approximately at the same times on days of Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14). On Day -2 and Cycle 1 Day 15, the probe substrate should be administered in the fasted state, when possible (no food at least 2 hours before through 2 hours after probe substrate dosing). On days of continuous Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14), patients should be advised to not undergo any exercise. Additionally on Holter monitoring days substances that may alter ECG readings (such as caffeine-containing products, alcohol and tobacco containing products) should be avoided.

In all study parts, patients will continue with the study treatment until progression of disease as determined by the investigator, unacceptable toxicity, death or consent withdrawal. Patients may continue PF-06463922 treatment after objective progression of disease is determined if the patient is continuing to experience clinical benefit, in the opinion of the investigator, and after discussion with the Sponsor.

The study investigator may implement PF-06463922 dose suspension and/or reduction in order to ensure patient safety at any time in the course of the study (see Recommended Dose Modifications).

5.2.2.5. Midazolam (Phase 1)

In the MDZ interaction sub-study, patients will receive a single 2 mg oral dose of MDZ on Day -7 and will receive another single 2 mg oral dose of MDZ concurrently with PF-06463922 on Cycle 1 Day 15 (morning dose if on BID dosing schedule).

Patients should refrain from food and beverages (except water) 8 hours prior to MDZ dosing and 2 hours after dosing. Qualified personnel will administer MDZ syrup (1 mL to provide 2 mg of MDZ) using an oral disposable syringe followed by 8 oz (240 ml) of ambient temperature water. Additionally, to standardize conditions for PK sampling, patients should refrain from lying down (except as needed for vital sign and ECG assessments) in the 2-hour period following MDZ administration.

5.2.3. Food Requirements (Phase 1)

5.2.3.1. Patients Not Included in the Food Effect Cohort

Oral PF-06463922 will be administered QD/BID with at least 8-oz (240 mL) of water on an empty stomach (morning dose if the patient is on the BID dosing schedule). No food or liquids other than water will be consumed for 2 hours before and 2 hours following each dose throughout the study. These fasting requirements may be removed (via a letter to the investigators) if the data from the food effect substudy indicate that there is no effect of food on the bioavailability of PF-06463922.

5.2.3.2. Requirements for the Food Effect Cohort

A food effect substudy will be conducted in Phase 1 at selected dose levels to evaluate the effect of a high-fat, high-calorie breakfast on PF-06463922 pharmacokinetics will be studied (morning dose if the patient is on the BID dosing schedule). For all patients participating in the food effect substudy, PF-06463922 will be administered following an overnight fast of at least 10 hours. For those patients scheduled to receive the "fed" treatment, a test breakfast meal (described below) will be provided and must be consumed over 30 minutes. Study drug will be administered with approximately 8-oz (240 ml) of water 30 minutes after the start of the meal. No additional food will be allowed until at least 4 hours post-dose. For patients scheduled to receive the "fasted" treatment, study drug will be administered with 8 ounces (240 mL) of water. No food will be allowed for an additional 4 hours post-dose. For either treatment day, water will be allowed ad libitum except for 1 hr before and 1 hr after drug administration.

After Cycle 1 Day 1 in the food effect cohort only, PF-06463922 should be administered with food (ie, normal diet) regardless of which condition the patient was last dosed (ie, fed or fasted).

The test meal to be consumed will be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be 2 eggs fried in butter, 2 strips of bacon (may be replaced with ham and cheese of similar caloric content), 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole-fat milk. Substitutions to this test meal can be made after discussion with the Sponsor, as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity (if substitutions are made, the contents of the meal will be documented by a dietitian or designate to confirm it matches the FDA requirements for protein, carbohydrate and fat described above). However, it is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed.

5.2.4. Recommended Dose Modifications

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

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

Dose modifications of an oral medication given continuously may occur in two ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle; this may persist delaying the start of a new cycle.

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

5.2.5. Dosing Interruptions

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in the dose modification tables.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Modification Tables unless expressly agreed otherwise following discussion between the Investigator and the Sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >1 week, treatment resumption will be decided in consultation with the Sponsor.

Patients not recovering from PF-06463922 related toxicity within 42 day since last dose should discontinue PF-06463922 treatment.

If a treatment interruption continues beyond Day 21 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. Every effort should be made to maintain the tumor assessments scheduling as described in Schedule of Activities ie, every 6 weeks (±1 week) versus the date of Cycle 1 Day 1.

5.2.6. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the PF-06463922 dose may need to be reduced when treatment is resumed.

In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

Patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Dose reduction of PF-06463922 (Table 11 for QD dose levels in Phase 1, Table 12 for QD dose levels in Phase 2 and Table 13 for BID dose levels in Phase 1) will be allowed depending on the type and severity of toxicity encountered (Table 10). Patients requiring more than 3 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the Investigator and the Sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and CRF.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is allowed per investigator discretion for appropriate patient management.

Patients experiencing a DLT (Phase 1 only) may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved.

5.2.7. Dose Modifications

PF-06463922

Patients will be monitored closely for toxicity, and the dose of PF-06463922 may be adjusted. Patients requiring dose reduction per Table 10 should undergo reduction to the next lower dose level as outlined in Table 11 for Phase 1 and Table 12 for Phase 2 (Table 13 for BID dosing).

Table 10. PF-06463922 Dose Modifications for PF-06463922-Related Toxicities

Non-Hematologic Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Pancreatitis	If both amylase and lipase are Grade ≤2 in the absence of radiological findings of pancreatitis: continue at the same dose level without dosing interruption. Repeat lipase and amylase. If radiologically confirmed pancreatitis: withhold dose. Repeat radiology and lipase and amylase weekly. If appropriate, resume treatment at one dose level lower if radiology has returned to baseline and lipase and amylase are Grade ≤2.		Discontinue	Discontinue
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment		Discontinue	Discontinue
Prolonged QTc interval	Assess electrolytes and concomitant	Assess electrolytes and concomitant medications.	Withhold dose. Assess	Discontinue

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
	medications. Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Upon recovery to Grade ≤1 resume treatment at one dose level lower.	
LVEF Dysfunction	Not Applicable	Not Applicable	Discontinue	Discontinue
Other (see separate tables below for Lipid and CNS toxicities and subsection on PR Interval Prolongation below).	Consider no dose modification or reduce by one dose level, as clinically indicated.		Withhold dose until toxicity is Grade ≤1(or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose.	Withhold dose until toxicity is Grade ≤1(or has returned to baseline), then reduce the dose by 1 level. Or discontinue at the discretion of the investigator.

Hematologic Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Lymphopenia	Continue at the same dose level.	Continue at the same dose level.	If no evidence of infection or other clinically significant toxicity, continue at the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then rechallenge at the same dose or reduce the dose by 1 dose level.	If no evidence of infection or other clinically significant toxicity, continue at same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.
Other	Consider no dose modification or reduce by one dose level, as clinically indicated.		Withhold dose until toxicity is Grade ≤2 (or has returned to baseline), then reduce the dose by 1 dose level.	

Lipid Elevation Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Total Cholesterol	Continue at the same dose. Introduce or modify lipid-lowering therapy.		Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent, or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or, increase the dose of ongoing statin/ lipid lowering agent, or change to a new agent. Withhold dose until toxicity is Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.
Triglycerides	Continue at the same dose. Introduce or modify lipid-lowering therapy.		Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.	Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Withhold dose until toxicity is Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.

CNS Effect Toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
CNS effects*	Continue at the same dose or withhold dose until recovery to baseline and then continue at the same dose.	Withhold dose until toxicity is Grade ≤1. Reduce dose to the next lower dose.		Discontinue

* Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision.

PR Interval Prolongation

PR-interval prolongation has been observed in patients receiving PF-06463922. Below are guidelines for patients who develop first-degree, second-degree, or complete heart block. Guidelines distinguish between asymptomatic vs. symptomatic heart block. Symptoms that could be attributed to heart block include, but are not limited to include, dizziness, lightheadedness, and fatigue, shortness of breath, fainting and palpitations.

If a patient develops second-degree or third-degree heart block, discussion with the sponsor is warranted to discuss appropriate management.

Event	Asymptomatic	Symptomatic
First-degree heart block (PR-interval >200 msec)	**No dose hold or reduction needed**. Assess concomitant medications and assess and correct electrolyte imbalance that may prolong PR interval. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if symptoms develop that may be related to heart block.	**Withhold dose**. Assess concomitant medications, and assess and correct electrolyte imbalance that may prolong PR interval. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at reduced dose when symptoms resolve.
Second-degree heart block	**Withhold dose**. Assess concomitant medications, and assess and correct electrolyte imbalance that may prolong PR interval. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at reduced dose if subsequent ECG does not show 2nd degree block.	**Withhold dose**. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree block resolves. If patients revert to 1st degree block with no symptoms, resume at reduced dose.
Complete Heart Block	**Withhold dose**. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose. If no pacemaker placed, restart at reduced dose only when symptoms resolve AND PR <200 msec.	

Additionally, for patients with PR interval prolongation, the concomitant use of medicinal products known to prolong PR interval is not advised and these should be used with caution (see Appendix 12).

Table 11. Phase 1 PF 06463922 QD Dose Level Reductions

Current Dose Level	Dose Level -1	Dose Level -2
200 mg QD	150 mg QD	100 mg QD
150 mg QD	100 mg QD	50 mg QD
100 mg QD	50 mg QD	25 mg QD
75 mg QD	50 mg QD	25 mg QD
50 mg QD	25 mg QD	N/A

Table 12. Phase 2 PF 06463922 QD Dose Level Reductions

Current Dose Level	Dose Level -1	Dose Level -2	Dose Level -3
100 mg QD	75 mg QD	50 mg QD	25 mg QD

BID dosing schedules in Phase 1 may include 75 mg BID, 50 mg BID, 35 mg BID, and 25 mg BID. Additional dose levels may be considered for BID dosing depending on emerging safety and PK data. Dose reductions for patients receiving BID dosing should be based on Table 10 above and Table 13 below. Additional doses to select for BID dosing and additional reduction modification guidelines may be communicated to sites in the form of letters to investigators.

Table 13. PF-06463922 BID Dose Levels (Phase 1)

Current Dose Level	Dose Level -1	Dose Level -2
75 mg BID	50 mg BID	25 mg BID*
50 mg BID	35 mg BID	25 mg BID*
35 mg BID	25 mg BID	10 mg BID*
25 mg BID	10 mg BID	5 mg BID

*Further dose reduction to the next lower dose schedule in this table in patients who are otherwise benefiting from PF-06463922 treatment may be permitted after discussion with the Sponsor's medical monitor.

5.2.8. Compliance

Patients will be required to return all unused PF-06463922 study medication at the beginning of each cycle. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded. Patients will be provided with Patient Diaries. These will be detailed in the Investigational Product (IP) manual.

5.2.9. Drug Storage and Drug Accountability

PF-06463922 tablets should be stored in accordance with the drug label. Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Patients should be instructed to keep their medication in its original container and stored according to the label. Returned medication should be stored separately from

medication that is yet to be dispensed. Storage conditions stated in the SRSD (ie, Investigator Brochure [IB] will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that the equipment/device(s) are working correctly as required for proper storage of investigational products. These may include thermometers for both the room storage and refrigerator storage (if applicable). Any temperature excursions should be reported to the Sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product.

The temperature of all locations where investigational product (IP) are stored should be monitored continuously and verified as appropriate per the site processes, preferably using a thermometer that measures minimum and maximum temperatures. Storage temperature should be recorded and monitored consistently by the site personnel. If a continuous measuring instrument/device is not available, daily temperature (and as applicable, humidity) recordings must be taken to ensure compliance with Pfizer requirements and/or site standard operating procedures (SOPs), where applicable. If the site has its own SOPs, the most conservative standard will be applied, so that Pfizer requirements are always met.

Midazolam (Phase 1 only) should be stored according to the label.

The probe drugs used in the DDI and Holter monitoring study should be stored according to the label.

5.2.10. Temperature Excursions

For any study drugs supplied by Pfizer (ie, PF-06463922 and crizotinib, when applicable), if a temperature excursion occurs, the site should immediately contact their study monitor to alert them and escalate to Pfizer for evaluation and disposition. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. When reporting an excursion, the following information, at a minimum, should be included:

- Protocol Number;
- Site Number;
- Length of Excursion;
- Minimum/Maximum Temperatures for the Excursion;
- Impacted Container Numbers (if applicable);

- Confirmation of whether impacted containers were dispensed/administered to patients;

- Copy of temperature monitoring log.

The site should not use the supplies until a disposition is received from Pfizer via study management. The IP should continue to be stored in its appropriate location pending the disposition from Pfizer. If the materials are rejected, Pfizer will initiate a replacement shipment to the site.

At D1 of each cycle visit, and at the end of the treatment study, all unused or partially used bottles must be returned by patients to the Investigator and Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer (if applicable). Destruction must be adequately documented.

5.3. Concomitant Treatments

Concomitant treatment considered necessary for the patient's well being may be given at discretion of the treating physician.

All concomitant medications, blood products, as well as non drug interventions (eg, paracentesis) received by patients from screening until the end of study visit will be recorded on the CRF. All concomitant medications must be approved by the Sponsor at study entry.

5.3.1. Concomitant Medications (Additionally, refer to Section 5.3.1.1 for Concomitant Medications specific to patients participating in the DDI and Holter Monitoring study)

-In vitro studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of PF-06463922, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of PF-06463922 systemic exposure.

Initial in vitro assessment for inhibition and induction drug-drug interaction potential indicated that PF-06463922 is a time-dependent inhibitor of CYP3A and also an inducer of CYP3A and CYP2B6. At substantially higher concentrations than those observed clinically, PF-06463922 also inhibited CYP2C9 in vitro studies.

To protect patient safety, the following cautions are provided:

- PF-06463922 metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in PF-06463922 toxicities.

- Coadministration of strong CYP3A inhibitors (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]) is not recommended and alternate medications should be considered. If the concomitant use of the strong CYP3A inhibitor cannot be avoided, reduce the starting dose of PF-06463922 from 100 mg orally once daily to 75 mg orally once daily. In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the PF-06463922 dose to 50 mg orally once daily. The patient should be closely monitored for safety and reduction of the lorlatinib dose if necessary.

- Use of strong CYP3A inducers with PF-06463922 is contraindicated. PF-06463922 metabolism may be induced when taking strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) resulting in reduced plasma concentrations. Furthermore, when PF-06463922 was coadministered with rifampin (Study B7461011), increases in AST and ALT were noted. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating PF-06463922 and until study treatment discontinuation. In addition, use with moderate CYP3A inducers should be avoided due to the potential reduction in PF-06463922 exposure.

- PF-06463922 inhibits CYP2C9 (in vitro), so concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or celecoxib, may have increased effect. Concomitant CYP2C9 substrates should be used with caution, as the net clinical effect of PF-06463922 on CYP2C9 is currently being investigated.

- PF-06463922 induces CYP2B6 (in vitro) so concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Concomitant CYP2B6 substrates should be used with caution, as the net clinical effect of PF-06463922 on CYP2B6 is currently being investigated. PF-06463922 induces CYP3A (in vivo) which may lead to a decreased effect of concurrently used CYP3A substrates. Coadministration of PF-06463922 with CYP3A substrates with a narrow therapeutic index (NTI) such as alfentanil, fentanyl (including transdermal patch), astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* (*withdrawn from US market) is not permitted at study entry. However if it is absolutely necessary to use, sponsor approval is required and the dose of the CYP3A substrate may need to be increased. The NTI CYP3A substrate should be started only after at least 14 days of continuous PF-06463922 dosing. If there is a change in the PF-06463922 dosing regimen such as a dosing interruption or dose reduction, the administration of the NTI CYP3A substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed PF-06463922 dosing.

- PF-06463922 inhibits P-gp (in vitro) so concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have increased effect. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study, it should be initiated following sponsor approval, and be used then with caution. The net clinical effect of PF-06463922 on P-gp is currently being investigated.

5.3.1.1. Concomitant Medications for Patients participating in the DDI/Holter Monitoring Study

In vitro studies in human hepatocytes indicate PF-06463922 may induce the metabolic enzyme CYP2B6 that could in turn lead to decreased exposure of drugs that are metabolized by CYP2B6. In addition, the in vitro observation that PF-06463922 also induces the metabolic enzyme CYP3A was confirmed clinically in a DDI evaluation with midazolam in the Phase I portion of this study. For evaluation of the interaction potential of PF-06463922, the following concomitant medications should not be used based on assignment of drug probe.

1. CYP2B6: for the DDI evaluation with buproprion, aCYP2B6 probe substrate, patients should not be taking any moderate/strong inhibitors or inducers of CYP2B6 within 2 weeks of the lead-In probe substrate dosing and until the DDI assessment portion is completed on Day 15 of Cycle 1. Refer to the buproprion product insert for complete information on contraindications.

2. CYP2C9: for the DDI evaluation with tolbutamide, a CYP2C9 probe substrate, patients should not be taking any moderate/strong inhibitors or inducers of CYP2C9 within 2 weeks of the leadIn probe substrate dosing and until the DDI assessment portion is completed on Day 15 of Cycle 1. Please refer to the tolbutamide product insert for complete information on use and contraindications.

3. UGTs: for the DDI evaluation with acetaminophen, a UGT probe substrate, patients should not be taking any moderate/strong inhibitors or inducers of UGTs within 2 weeks of the lead-In probe substrate dosing and until DDI assessment portion is completed on Day 15 of Cycle 1. Refer to acetaminophen product insert for complete information.

4. P-gp: for the DDI evaluation with fexofenadine, a probe substrate for P-gp, patients should not be taking any moderate/strong inhibitors or inducers of P-gp within 2 weeks of the lead-In probe substrate dosing and until DDI assessment portion is completed on Day 15 of Cycle 1. Refer to fexofenadine product insert for complete information.

5. All subjects with a history of risk factors for QT prolongation or torsades de pointes (eg, organic heart disease, congestive heart failure, hypokalemia, hypomagnesemia, congenital long QT syndrome, myocardial ischemia or infarction) will be excluded from this cohort.

5.3.2. Other Anti-Tumor or Experimental Drugs

No additional systemic anti-tumor therapy will be permitted while patients are receiving a study therapy. Additionally, the concurrent use of select herbal supplements is not permitted.

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

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06463922 with radiotherapy, PF-06463922 treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

5.3.2.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first cycle but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

If approved and available for use per country regulations, erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

5.3.2.2. Anti-Diarrheal, Anti-Emetic, and Acid-Reducing Therapy

In Phase 1 primary prophylaxis of diarrhea, nausea and vomiting is not permitted in the first cycle while assessing DLTs. Primary prophylaxis in subsequent cycles is at the investigator's discretion.

The choice of the prophylactic drug is up to the investigator with Sponsor approval and assuming the drug is not included in the Concomitant section, as well as the duration of treatment assuming there is no known or expected drug-drug interaction. If so it must be approved by the Sponsor.

A study to assess the impact of PF-06463922 coadministration with proton-pump inhibitiors (PPIs) (eg, lansoprazole [Prevacid®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]) was conducted during the ongoing Phase 2 portion of the study. After review of the study results, the observed effect of PPIs on PF-06463922 exposure was minor, and not clinically significant. As a result, there is no restriction on the use of PPIs (or H_2-antagonists, or locally-acting antacids) used concomitantly with PF-0646922. Further details of this study can be found in the Investigator Drug Brochure.

5.3.2.3. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant section.

5.3.2.4. Cutaneous Toxicity Therapy

Prompt medical intervention is recommended at the first sign of appearance of cutaneous toxicity including topical or oral corticosteroids if required according to investigator's judgment, assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant section.

5.3.2.5. Testosterone Replacement

Testosterone replacement therapy is only allowed in the presence of signs and symptoms clearly attributable to hypogonadism in consultation with an endocrinologist, who should also exclude any potential confounding effects of elevated prolactin and/or estradiol, or a significant recent change in corticosteroid dose, before doing so.

5.3.2.6. Lipid-Lowering Therapy

Treatment with a statin is recommended at the first signs of elevated (Grade 1) cholesterol and/or triglycerides. Clinically, PF-06463922 has limited data, but it is a moderate inducer of CYP3A. Combined with the in vitro data that PF-06463922 can itself be metabolized by CYP3A, 2C19, 2C8 and UGT1A as well as inhibit 2C9 and induce 2B6, the choice and dose of statin should be considered carefully.

Statins can be metabolized by CYP enzymes affected by PF-06463922, or affect the CYP enzymes that metabolize PF-06463922 (Table 14). Therefore, the statins with the least involvement of the CYP450 enzyme systems to use concomitantly with PF-06463922 would be pitavastatin or pravastatin followed by rosuvastatin. However, clinical drug-drug interactions have not been formally studied with PF-06463922, so careful monitoring is advised.

Similarly, if hypertriglyceridemia requires treatment, the drugs with the least involvement of the CYP450 enzyme systems to use concomitantly with PF-06463922 would be fenofibrate or fish oils followed by nicotinic acid (Table 15). Again, clinical drug-drug interactions have not been formally studied with PF-06463922, so careful monitoring is advised.

Table 14. Pharmacokinetic Properties of Statins

Generic name (or equivalent)	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Atorvastatin*	*Simvastatin*	*Lovastatin*	*Fluvastatin*
Metabolism†	++	+	+	+++	+++	+++	+++
Metabolizing CYP enzymes (of lactone or acid form)	(2C9)	(3A4)	2C9 (2C19)	3A4 (2C8)	3A4 2C8	3A4 2C8?	2C9
Inhibitor of CYP3A4‡			+	+	+	+	+
Inhibitor of CYP2C9‡			(+)				+
Triglyceride lowering effect	22-30%**	11-14%*	17%*	14-19%*	10-14%*	13%*	0-5%***

Parentheses indicate minor significance.
†Three plus signs indicate extensively metabolized, and 1 plus sign indicates limited metabolism, eliminated mainly unchanged.
‡A plus sign indicates yes, and a minus sign indicates no.
* Baseline TG 100-200 mg/dL; Effect of Statins vs Placebo on Triglyceride Levels in 10 Primary and Secondary Placebo-Controlled Outcome Trials. http://www.medscape.org/viewarticle/589010.
** Baseline TG ≥150 mg/dL; Cardiovascular Drug Reviews. 2003; 21(3): 199–215.
*** Am J Cardiol 2004;93:31–39.
adapted from Clin Pharmacol Ther 2006;80:565-81.

Table 15. Pharmacokinetic Properties of Lipid Lowering Agents

		Fibric Acids		***Fish Oils***
Generic Name (or equivalent)	***Nicotinic Acid***	***Gemfibrozil***	***Fenofibrate***	***Ethyl esters of omega-3 fatty acids***
Metabolism‡	-	-	-	-
Metabolizing CYP enzymes (of lactone or acid form)‡	-	-	-	-
Inhibitor of CYP3A4‡	-	-	-	-
Inhibitor of CYP2C9‡	-	+++	++	-
Inhibitor of CYP2C19‡	-	++	+	-
Inhibitor of CYP1A2‡	-	+	-	-
Triglyceride lowering effect (TG ≥150 mg/dL)	20-50%*	20-50%*	36% - 55%[a]	45%[a]
Drug Interactions	Caution should be used when prescribing niacin with statins	Concomitant administration with statins is contraindicated	May increase exposure to pravastatin and its metabolite (13-29%) when used concomitantly	

‡A plus sign indicates yes, and a minus sign indicates no.
[a] primary hypertriglyceridemia – severe hypertriglyceridemia (Baseline TG levels >500 mg/dL).
[b] PI, 4/2015.
[c] PI, 11/2014.
[d] PI, 12/2014.
[e] PI, 05/2014.
* NCEP-ATP III, 2001.

5.3.3. Supportive Care

Palliative and supportive care for disease-related symptoms may be administered at the Investigator's discretion and according to available American Society of Clinical Oncology (ASCO) guidelines.

5.3.4. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06463922 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06463922 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate PF-06463922 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

Section 5 includes Study Procedures for PF-06463922 only. When applicable, patients who receive crizotinib following PF-06463922 should follow the required Study Procedures as outlined in Appendix 11.

6.1. Screening

For screening procedures, see Schedule of Activities (Table 3, Table 4, Table 5) and Assessments section. For the Japanese patient-only LIC, refer to Appendix 9 for the schedule of required assessments. For patients in the DDI and Holter monitoring study, refer to Table 6.

6.1.1. Archival Tumor Tissue

These samples are mandatory for all patients enrolled in the study. Formalin fixed, paraffin embedded (FFPE) tissue block(s) from initial diagnosis that contain sufficient tissue to generate at least 6 (preferably 12), 5-micron thick unstained slides will be collected. If no FFPE block is available, then at least 6 (preferably 12) unbaked, 5-micron thick unstained slides containing FFPE tumor tissue must be provided. The archived tumor tissue may be obtained and analyzed outside the 28 day screening window. In cases where archived tumor tissue is not available, a de novo biopsy should be obtained for this purpose.

Samples will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of various genes, expression and/or phosphorylation of various proteins, etc); for ROS1+ NSCLC patients samples will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation. Tissue samples from all patients will be used for additional biomarker analyses. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

6.1.2. De Novo Tumor Biopsy

These samples will be mandatory for all patients enrolled in the Phase 2 (and in Phase 1 if archival tumor tissue is not available), unless it is considered to pose a safety risk to the patient, in the opinion of the Investigator, and only after discussion with the Sponsor; please refer to Section 7.3 for further guidance. For patients who are treatment naïve at Screening (ie, no previous systemic therapy in the metastatic disease setting), a de novo tumor biopsy is not required if a previous tumor biopsy was performed within 4 months of first PF-06463922 dose. When applicable, this de novo biopsy must be taken no more than 28 days prior to starting study treatment. The de novo biopsy will consist of an incisional or excisional biopsy, or a core needle biopsy, of a primary or metastatic lesion. Pleural effusions (PE) cell pellets may substitute for a tumor core biopsy, as appropriate. Fine needle aspiration (FNA) samples (2-3 pathes prepared as FFPE cell block as per institutional practice) are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. If local/country regulations do not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) are acceptable. The tumor tissue will be processed as specified in the Laboratory Manual.

Additional, optional de novo tumor specimen collection at screening (Phase 1) and at the time of progression (Phase 1 and Phase 2) is strongly encouraged from all patients. If present, pleural effusion (PE) cell pellet may substitute for tumor core biopsy. As noted above, a de novo biopsy should be obtained in cases where archived tumor tissue is not available.

6.2. Study Period

For treatment period procedures, see Schedule of Activities (Table 2, Table 3, Table 4, Table 5) and Assessments section. For the Japanese patient-only LIC, refer to Appendix 9 for the schedule of required assessments. For patients participating in the DDI and Holter monitoring study refer to Table 6.

A reduced schedule of assessments (Table 1) will be followed for all patients after Amendment 8 is approved locally. Sufficient study medication for 2 cycles of treatment will be dispensed at each clinic visit. The Investigator is responsible for informing the patient to contact the clinical site in case of any adverse events. Laboratory tests will be performed as per local practice; the results will not be collected, however the copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.

The pregnancy test should be performed at the clinical site's local laboratory. Where that is not possible, patients will provide the laboratory test results carried out at a non-clinical site laboratory, eg, to the site staff by telephone, and bring a copy of the laboratory test results at the next cycle visit. The copy of the pregnacy test results must be retained in the patient's file at the clinical site for documentation purposes. The patient may be contacted by phone to confirm contraception is still appropriate per the protocol.

6.3. Follow-up Visit

For follow-up procedures, see Schedule of Activities (Table 2, Table 3, Table 4, and Table 5) and Assessments section. For the Japanese patient-only LIC, refer to Appendix 9 for the schedule of required assessments. For patients participating in the DDI and Holter monitoring study refer to Table 6.

At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to the site to undergo assessment for resolution of any treatment-related toxicity, and pregnancy test for females. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuing treatment for progression of disease or for reasons other than progression of disease will enter the follow-up phase. -The survival follow-up will be performed every 2 months and will include also the collection of information on subsequent anticancer therapies (telephone contact is acceptable). For patients who receive crizotinib following treatment with PF-06463922, a follow-up visit will not be required until discontinuation of crizotinib as outlined in Appendix 11.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression according to modified RECIST v1.1 unless in the investigator's opinion the patient is still deriving clinical benefit;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient by telephone etc and attempted contacts should be recorded in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient refuses further visits, the patient should continue to be followed for survival (if survival is a secondary endpoint) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Required assessments for all patients except those in the Japanese patient-only LIC or those patients receiving crizotinib following PF-06463922 are described in the Schedule of Activities tables (Table 2, Table 3, Table 4, Table 5, and Table 6). Refer to Appendix 9 for the schedule of required assessments for patients in the Japanese patient-only LIC. Refer to Appendix 11 for the required assessments for patients receiving crizotinib following PF-06463922. For patients participating in the DDI and Holter monitoring study refer to Table 6.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol required test can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

Upon approval of Amendment 8, Schedule of Activities will be reduced as indicated in Table 1.

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, Mini Mental State Exam (MMSE) [Phase 1 only; no longer required per Amendment 6] ECG (12-lead), echocardiogram or Multi Gated Acquisition Scan (MUGA), laboratory assessments, including pregnancy tests and verification of concurrent medications. Additionally, neurological examinations will be included in at least 12 Phase 1 patients. In Phase 2, assessments of cognitive, mood, and suicidal ideation and behavior will be collected.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and another negative pregnancy test will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at each cycle during the active treatment period, at the end of study therapy, at least 28 days and no more than 35 days after discontinuation of treatment, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards/Ethics Committees (IRBs/IECs) or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities (and in Appendix 1 and Appendix 2) and analyzed at local laboratories.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam to include weight, vital signs, assessment of ECOG status and height; height will be measured at screening only blood pressure and pulse rate to be recorded in sitting position after approximately 5 minutes of rest.

7.1.5. (12-Lead) Electrocardiograms

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of Investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the study drug will be held until the QTc interval decreases to ≤500 msec. Patients will then re-start the study drug at the next lowest dose level. If the QTc interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If a patient experiences asymptomatic or symptomatic first-degree or second-degree PR prolongation, or third-degree AV block,refer to Section 5.2.7.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event. When an ECG and PK sample are scheduled at the same time, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.1.6. Transthoracic echocardiogram (TTE) (France and Germany only)

As requested by Health Authorities in Germany and France, a TTE will be performed for patients in France and Germany at least every 6 months (±2 weeks) during treatment, and only at the End of Treatment visit if the previous assessment was >1 month. Pulmonary arterial pressure (PAP) will be assessed. Additional monitoring should be done as follows:

- A prompt TTE in the event of symptoms or signs suggesting pulmonary arterial hypertension (PAH) and all other explorations pursuant to PAH diagnosis guidelines.

- Should PAH occur during treatment, following multidisciplinary discussions involving a PAH specialist (cardiologist or pulmonologist), consider dose reductions or even permanently discontinuing lorlatinib in the absence of haemodynamic and clinical recovery.

7.1.7. Holter Monitoring (DDI and Holter Monitoring study only)

In order to characterize the effects of PF-06463922 on ECG endpoints, continuous Holter telemetry of patients will be used to evaluate the effect of PF-06463922 on the PR interval by comparing the patients pre-drug baseline with PR interval observations associated with exposure of PF-06463922 following a single dose and at steady state. Twenty-four 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. Refer to Table 6 of the Schedule of Activities.

7.1.8. Echocardiogram and Multi Gated Acquisition Scan (MUGA)

In order to monitor potential left ventricular ejection fraction dysfunction, an echocardiogram or MUGA will be performed at the time points described in the Schedule of Activities. The same method should be used at each time point.

7.1.9. Mini Mental State Exam (MMSE) (Phase 1 Only; no longer required per Amendment 6)

The Mini Mental State Exam (MMSE) is a tool that can be used to systematically and thoroughly assess mental status.[37] The standard version of the MMSE is a 30 item questionnaire that tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall and language. The maximium score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE takes 5-10 minutes to adminster. The MMSE is effective as a screening instrument to separate patients with cognitive impairment fromthose without it. In addition, when used repeatedly the instrument is able to measure changes in cognitive status over the study treatment period. It has been used in the advanced cancer setting.[38]

This screening assessment will not substitute the clinical assessment done for Adverse Event reporting. Should the sum of the rating score after all questions are completed be less than 24, the investigator should assess if there are clinical signs that fulfill the adverse event (AE) reporting criteria (Section 8.8 Severity Assessment).

7.1.10. Neurological Examination (Phase 1 Only)

A neurological examination by a licensed neurologist will be performed in at least 12 Phase 1 patients at baseline and, if clinically indicated, at any time point thereafter.

7.1.11. Assessment of Cognitive Function (Phase 2 Only)

In order to assess cognitive function and any changes associated with PF-06463922 adminsitration, a computerized test (using laptops provided to sites by Cogstate) will be administered to patients at the time-points described in the Schedule of Activities. The test will be administered by a qualified site personnel and will take approximately 15-20 minutes to complete. This test is developed and validated by Cogstate.[44] This test is a 5-part battery test consisting of the following:

The International Shopping List Task (Verbal Learning)

The International Shopping List task is a measure of verbal learning and uses a well-validated list-learning paradigm. The task is administered using a computer. High frequencies, high imagery, concrete nouns (items from a shopping list) are read to the patient by the qualified site personnel at the rate of one word every 2 seconds. Once all 12 words have been read, the patient is asked to recall as many of the words as he/she can as quickly as possible. The site qualified personnel uses a mouse or stylus to mark the words recalled by the patient on the computer screen. When the patient can recall no more words, the same list is read a second time. The qualified site personnel records the words recalled by the patient on this trial. This is then repeated a third time. The delayed recall condition requires the patient to recall the words from the list 10-30 minutes later without having the list read again. The software measures the number of correct responses as recorded by the qualified site personnel. **Duration of Task: approx. 5 minutes.**

Detection (Psychomotor Function)

The Detection task is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this task, the playing cards all depict the same joker. The patient is asked to press the **Yes** key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response. **Duration of Task: approx. 2 minutes.**

Identification (Attention)

The Identification task is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this task, the playing cards are all either red or black jokers. The patient is asked whether the card displayed in the center of the screen is red. The patient responds by pressing the **Yes** key when the joker card is red and **No** when it is black. The software measures the speed and accuracy of each response. **Duration of Task: approx. 2 minutes.**

One Back (Working Memory)

The One Back task is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this task, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The patient is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The patient responds by pressing the **Yes** or **No** key. Because no card has been presented yet on the first trial, a correct first response is always **No**. The software measures the speed and accuracy of each response. **Duration of Task: approx. 3 minutes.**

International Shopping List Test (Delayed Recall)

The delayed recall condition requires the patient to recall the words from the list 15-30 minutes later without having the list read again. During the recognition condition, the qualified site personnel reads a shopping list item that may or may not have been on the original list and the patient has to respond either affirmatively (if the item was on the original list) or negatively (if it was not). The software measures the number of correct responses. **Duration of Task: approx. 5 minutes.**

7.1.12. Assessment of Mood (Phase 2 Only)

An assessment of mood will be administered to patients via the Beck Depression Inventory-II (BDI-II) scale at the timepoints described in the Schedule of Activities. This is a 21 item self-report scale, with each item rated by patients on a 4 point scale (ranging from 0-3.). The scale includes items capturing mood, (loss of pleasure, sadness, irritability), suicidal ideation, and cognitive signs (punitive thoughts, self- criticism, self-dislike, pessimism poor concentration) as well as somatic signs (appetite, sleep, fatigue, libido).

7.1.13. Assessment of Suicidal Ideation and Behavior (Phase 2 Only)

To assess suicidal ideation behaviors, the Columbia Suicide Severity Rating Scale[43] (C-SSRS) will be administered to patients at the timepoints described in the Schedule of Activities. The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide. This paper based assessment will be provided by Cogstate.

7.2. Pharmacokinetics Assessments

For patients participating in the DDI and Holter monitoring study, refer to Section 7.2.8.

7.2.1. Blood for PK Analysis of PF-06463922

Blood samples (4 mL whole blood to provide at least 2 ml of plasma) will be collected for PK analysis of PF-06463922 as outlined in the Schedule of Activities (***Table 3 and Table 5***).

All patients in Phase 1 and 10 Non-Japanese and 3 Japanese (non-LIC) patients in Phase 2 will have full plasma PK sampling. Blood samples will be collected on Day (-7), in Cycle 1 on Day 1, Day 8, and Day 15 and Day 1 of Cycles 2-5. Additionally, in Phase 2 only, for Day 1 of Cycle 6 and Day 1 of every other cycle (ie, Cycle 6, Cycle 8, etc.).

For patients in Phase 2 who undergo sparse plasma PK sampling, blood samples will be collected at pre-dose on Day 1 of Cycles 1-5 (***Table 5)*** and predose on Day 1 of every other cycle beginning with Cycle 6 (ie, Cycle 6, Cycle 8, etc).

For patients who participate in the MDZ interaction sub-study (Table 3), blood samples for PF-06463922 PK will be collected on Day 1, Day 8, and Day 15 in Cycle 1. For Cycles 2-5, PK samples will also be collected on Day 1.

For patients who participate in the food effect sub-study (Table 3), blood samples for PF-06463922 PK will be collected on Day -7, Day 1, Day 8, and Day 15 in Cycle 1. For Cycles 2-5, PK samples will also be collected on Day 1.

PK sampling schedule may be modified based on emerging PK data. In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs and the date and time documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

PK samples will be assayed for PF-06463922 using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

7.2.2. Urine for PK Analysis of PF-06463922

In the Phase 1 food effect and midazolam interaction cohort, urine samples will be collected for 24 hours after PF-06463922 dosing on Cycle 1 Day 15 to measure PF-06463922 concentrations, and thereby determine the renal elimination of PF-06463922 from the body. Metabolites of PF-06463922 may also be measured in the urine samples. Urine will be collected on Cycle 1 Day 15 over the following intervals: 0 to 4 hours, 4 to 12 hours and 12 to 24 hours post-dose (Table 3). For patients on BID dosing, 12-24-hour post-dose urine collection is not required. Patients will empty their bladder just prior to dosing on Cycle 1 Day 15.

At the end of each urine collection period, the total volume will be measured and recorded. Voided urine should be collected in an amber container and protected form direct light. The urine will then be mixed thoroughly and a 20 mL aliquot will be withdrawn for the potential measurement of drug concentrations. The sample will be protected from light and frozen at approximately -20°C.

7.2.3. Blood for Metabolite Profiling of PF-06463922

Metabolite profiling will be conducted in the food effect cohort (Phase 1) and in 10 Non-Japanese patients and 3 Japanese non-LIC patients enrolled in Phase 2. Blood samples for metabolite profiling will be collected on Cycle 1 Day 15 (Table 3, Table 5). Two (2) mL of blood will be collected at each time point to obtain 1 mL of plasma.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

Once the metabolite profiling samples have been analyzed and the report completed, the samples will be disposed.

7.2.4. CSF for Analysis of PF-06463922 Concentration

If a patient is required to undergo a lumber puncture while on trial,, an additional ~5 mL sample of CSF should be collected for determining PF-06463922 concentrations any time at steady state. If a CSF sample is collected, a plasma PK sample should also be collected at approximately the same time. Detailed collection procedures will be provided in the laboratory manual.

7.2.5. Blood for PK Analysis of Midazolam

In the Phase 1 MDZ interaction sub-study, blood samples (2 ml each for 1 ml of plasma) for PK analysis of MDZ will be collected after a single oral MDZ dose on Day –7 and Cycle 1 Day 15 at the time points specified in the schedule of activities (Table 3).

7.2.6. Urine Sample for 6 beta-Hydroxycortisol/Cortisol (6β-OHC/C) Ratio

A midstream morning spot urine sample (10 mL) will be colleted into an appropriately labeled plastic screw topped collection container prior to dosing in Phase 1 of any drug on Day-7, Day 1 of Cycle 1, Day 8 of Cycle 1, Day 15 of Cycle 1 and Day 1 of Cycle 2 **(**Table 3). The urinary 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio will be determined to evaluate CYP3A induction.

7.2.7. Blood for 4 beta-Hydroxycholesterol/Cholesterol

Blood samples (3 ml to provide 1.5 ml of plasma) for the analysis of 4β-hydroxycholesterol and cholesterol will be collected in Phase 1 at pre-dose on Day-7, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15 and Cycle 2-5 Day 1 **(**Table 3). The 4 beta-hydroxycholesterol/Cholesterol is a new marker thatis being explored for assessing CYP3A induction.

7.2.8. PK for patients participating in the Drug-Drug Interaction and Holter Monitoring study

Refer to Table 6 in the Schedule of Activities. Refer to the study manaual for detailed requirements on PK collection, processing and shipping.

Blood samples (4 mL each) for PF-06463922 full PK sampling will be collected on the following days 1) Cycle 1 Day 1 and Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post PF-06463922 dose and 2) Day 1 of Cycle 2, Cycle 4, Cycle 6, Cycle 8 and Cycle 10: Pre-dose.

Where required by local regulations and after agreement by the study sponsor, patients may be hospitalized for PK sampling.

Blood samples (4 mL each) for PF-06463922 metabolite(s) will be collected in all patients on Cycle 1 Day 1, and at steady-state on Cycle 1 Day 15 at: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs post-PF-06463922 dose (the following day).

For evaluation of drug-drug interaction, plasma blood samples (3 mL each) for PK Sampling for probe substrates will occur *on the following days and times:*

a. Day-2 (Lead-in): Pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 and 24 hrs post dose.

b. Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 and 24 hrs post dose.

A single blood sample for genotyping will be collected at baseline to determine the genetic status of the major drug metabolizing enzymes and transporters. The K_2EDTA (ethylenediaminetetraacetic acid) samples will be analyzed in compliance with Pfizer standard operating procedures in a CLIA (Clinical Laboratory Improvement Amendments) regulated laboratory.

A 4-mL blood sample will be collected from each subject into a plastic edetic acid (K_2EDTA) tube on Day -2 and stored for prospective ADME genotyping (drug-metabolizing enzymes and transporters only). Immediately after the sample is collected, the tube should be gently inverted 10 to 15 times to ensure adequate mixing of the tube contents. Samples are to be stored frozen at -20ºC or colder in a secure freezer at the investigative site until shipment in batches on dry ice. Unless otherwise specified, samples will be retained for 3 years after the end of the study.

7.3. Pharmacodynamic Assessments

Biomarker studies on tumor tissue and blood will be carried out to help understand the mechanism of action of PF-06463922, as well as identify potential mechanisms of resistance. Such results may help in the future development of this drug as a single agent or in combination. These analyses may also result in the identification of potential biomarkers of response to PF-06463922, ultimately leading to development of a patient selection strategy for further clinical investigation. Collection of peripheral blood samples for biomarker assessments will be mandatory for all patients; samples should be obtained at the same time as PK samples whenever possible.

Tumor tissue from archived tissue specimens and/or a de novo biopsy (see Section 6.1.1 and Section 6.1.2) will be used to analyze candidate DNA, RNA or protein markers for their ability to predict or identify those patients who are most likely to benefit from treatment with the study drug. Markers that may be analyzed include, but may not be limited to ALK or ROS kinase domain mutation.

De novo tumor core biopsies collection in Phase 2 is mandatory unless it poses a safety risk to the patient, in the opinion of the Investigator, and only after discussion with the Sponsor. Examples of safety risks may include, but are not limited to: (a) pulmonary metastases deep within the thoracic cavity with high probability of bleeding or lung injury; (b) liver metastases located within the liver posing a high risk of bleeding if biopsied. In those cases,

every efforts should be made to collect fine needle aspiration (FNA) samples (2-3 pathes prepared as FFPE cell block) which are not preferred and should only be performed in the event a biopsy or pleural effusion cell pellet are not safe or feasible.

Table 16 summarizes the biomarker assessments currently planned for the study. Tumor specimens (archival tissue and de novo biopsy) will be analyzed for the presence of mutations affecting the kinase domain of ALK and/or for ROS1 rearrangment (for the patients enrolled in the ROS1+ arm). Additional pathway related markers (eg, EGFR, KIT) may be included as preclinical studies or literature reports further elucidate the mechanisms of resitance to ALK and/or ROS1 inhibition. Please refer to the Schedule of Activities for details pertaining to specific days of sample collection and to the Study Manual for details of sample preparation.

Table 16. Summary of Biomarker Assessments

Assay	Source
Circulating Nucleic Acid mutational analysis of ALK kinase domain mutations	Peripheral blood
CTC enrichment and/or profiling for ALK or ROS1 rearrangement/mutation (Phase 1 only; no longer required)	Peripheral blood
Profiling of ALK kinase domain mutations or ROS1 status confirmation	Archival tumor specimen and de novo tumor biopsies
Molecular profiling for mutations, gene copy number variant for candidate genes, RNA/miRNA profiling and/or expression/phosphorylation for candidate proteins involved in possible by-pass mechanisms relevant to sensitivity/resistance to treatment	Archival tumor specimen and de novo tumor biopsies

7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. CT scans of Chest Abdomen Pelvis [CAP] and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI must be used to assess CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size. For CNS lesions measuring between 10 mm and 40 mm gadolidium contrast enhanced MRI must be used with contingent slides of 5 mm. For patients who are without documented disease progression, CT and MRI scans will continue to be done at every 6 weeks ±1 week for the first 18 months in Phase 1 and first 30 months in Phase 2, and and then every 12 weeks ±1 week thereafter, and responses will be confirmed ≥4 weeks later (RECIST v1.1), until documented progression of disease. For patients who have documented disease progression, but are still receiving PF-06463922, tumor assessments are to be done according to local institutional standard of care. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients (regardless of bone involvement) and repeated every 12 weeks on study only if evidence of bone metastases are observed at baseline (however, if a patient has bone involvement, assessment of those sites via appropriate modality is required every 6 weeks ±1 week up to 18 months in Phase 1 and 30 months in Phase 2, and then every 12 weeks ±1 week thereafter. For all tumor assessments, the same method of assessment at baseline should be used

throughout the study. In Phase 2 patients with LM or CM not visualized on baseline MRI, a positive CSF cytology will be required at baseline (optional post baseline). Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks (more than 12 weeks beyond 18 months in Phase 1 and 30 months in Phase 2) have passed since the last evaluation. For patients enrolled in Phase 2, tumor assessments must continued until progression of disease or the start of a new anti-cancer therapy.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

[18F]-FLT-PET and [18F]-FDG-PET imaging for assessment of functional response may be used in addition to but not substitute the required radiology modalities listed above. Positron emission tomography (PET) imaging used to explore early signals of anti-tumor activity will be collected pre and post PF-06463922. The screening PET study will be used to determine evaluable index lesions for each patient. Tumor background ratios (TBR) and development of new sites of abnormality will be recorded.

Results of the PET studies will be scored according to methods developed by the American College of Radiology Imaging Network (*ACRIN; http://www.acrin.org/petcorelab.html*). All centers participating in the study will use the same PET methodologies and measures, to the extent possible, and one center will be designated as the central lab to be used for final interpretation of PET data.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, during treatment as specified in the Schedule of Activity, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 6 weeks or previous 12 weeks if beyond 18 months in Phase 1 and 30 months in Phase 2).

Assessment of response will be made using RECIST version 1.1 and the modified RECIST for intracranial response assessment (Appendix 3).[32] Confirmation of response will be required at least 4 weeks after initial response is observed.

All patients' files and radiologic images must be available for source verification and for potential peer/independent central radiology review as determined by the sponsor. Instructions for submission of these images will be provided in the Study Reference Manual.

Upon approval of Amendment 8, tumor assessments will be performed as per local clinical practice (see Table 1), tumor assessment information should be retained in the patient's file for documentation purposes.

7.5. Banked Biospecimens

7.5.1. Markers of Drug Response

Variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study ID number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical trial.

A 4 mL blood biospecimen Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis) will be collected at the screening visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations, patients will be asked to indicate on the consent form whether they will allow the Banked Biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in Markers of Drug Response Section will be used. Patients may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.6. Patient-Reported Outcome Assessments

7.6.1. EORTC QLQ-C30 and QLQ-LC13

Patients must complete all EORTC QLQ C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points. At Day -7 (lead- in period) site staff (eg, site coordinators) should instruct patients that the assessment should be completed without help from friends or family members and also recommend that this assessment be completed in the morning. The EORTC questionnaires do not have to be completed if the patient is blind, illiterate or if there is no appropriate translation is available at a site for a given patient. All scheduled assessments of the EORTC QLQ C30 and QLQ LC13 cannot be taken home and must be completed in the clinic prior to any other study or medical procedures.

The EORTC QLQ-C30 (Version 3.0) and its lung cancer module, QLQ-LC13 (Appendix 6 and Appendix 7, respectively) were selected for inclusion in the study as they are validated disease specific questionnaires and are also the two most commonly used patient reported measures in lung cancer clinical studies.[33]-[36] The EORTC QLQ-C30 consists of 30 questions which are incorporated into 5 functional domains (physical, role, cognitive, emotional, and social domains); a global quality of life (QOL) scale; 3 symptom scales (fatigue, pain, nausea and vomiting scales); and 6 single items that assess the additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and the perceived financial burden of treatment.[33,34] The QLQ-LC13 consists of one multi-item scale and 9 single items that assess the specific symptoms (dyspnea, cough,

hemoptysis, and site specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of lung cancer patients receiving chemotherapy.[35]

Both the EORTC QLQ-C30 and the QLQ-LC13 module require about 15 minutes to complete and are available in many languages. Patients will be requested to complete these questionnaires at baseline, Day 1 of each cycle until progression and at end of treatment. The EORTC QLQ-C30 and the QLQ-LC13 module are collected and evaluated in a different manner than the observed or volunteered adverse events. Given these differences, no attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected with the patient reported questionnaires. Additional data collected with the EORTC QLQ-C30 and the QLQ-LC13 module will be presented in separate tables, figures, and data listings, and will be reviewed in the final study report. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded on the Adverse Event pages on the Case Report Form (CRF*).*

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as a SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

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

- AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of investigational product through the patient's last visit.

- If a patient begins a new anti-cancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

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

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

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor.

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

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see the Section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransfse (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

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

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

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

The investigator will use the following definitions of Severity in accordance with CTCAE v4.03 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event Report Form and Exposure in Utero (EIU) Supplemental Form regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

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

8.12. Withdrawal Due to Adverse Events (Also See Section on Patient Withdrawal)

At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuing treatment for progression of disease or for reasons other than progression of disease will enter the follow-up phase. The survival follow-up will be performed every 2 months and will include also the collection of information on subsequent anticancer therapies (telephone contact is acceptable).

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

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

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

- Full analysis set.

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

- Intention-To-Treat (ITT) analysis set.

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

- 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 (ie, 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 (ie, with Lesions having Disease Site=Brain) according to Independent Central Review

  - Evaluable for MTD (Phase 1 only): all enrolled patients who receive at least 75% of the planned PF-06463922 doses in the first cycle. 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.

- Safety analysis set.

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

- PK analysis set:

  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.

All other analysis sets will be documented in the SAP.

9.2. Statistical Methods and Properties

9.2.1. Methods

The Phase 1 portion of this study employs a modified CRM to estimate the MTD. The modified CRM algorithm utilizes the Bayesian methodology to continuously learn about the dose-toxicity relationship after each cohort's DLT data becomes available. The underlying model assumption is that DLT rate at each dose can be expressed as Pr (DLT|dose x)=f(x, β), where f is a monotonically increasing function in dose x and β is an unknown parameter with prior distribution placed on it at the beginning of the trial. The first 2 cohorts patients will be assigned to 10 mg/QD and 25 mg/QD respectively if the DLT data warrants dose escalation. After the DLT data of the 25 mg/QD cohort becomes available (~3 wks), the prior distribution of β is updated based on their DLT responses and becomes a posterior distribution. The current estimate of MTD is calculated as MTD=f^{-1} (0.33, β), given posterior information about β (ie, DLT data + modeling), and the next cohort's dose assignment is chosen as the dose closest to this estimated MTD but not exceeding it. This process is continued until 1 of the stopping rules below is triggered.

1. Maximum sample size of 36 patients has been reached.

2. MTD has been identified with sufficient accuracy: twelve (12) patients have been accumulated on a dose that is currently estimated to be the MTD likely to be the RP2D, and there are at least 12 patients overall enrolled in the trial.

3. All doses appear to be overly toxic and the MTD can not be determined in the current trial setting.

Starting from the third cohort and until the end of trial, the above described modified CRM algorithm constantly incorporates additional information about dose-DLT relationship learned from the data via modeling and that is reflected on the projected MTD. By design, such dose allocation procedure will eventually cluster dose assignments around the dose yielding a DLT rate closest to but no more than 33%. Additional patients may be enrolled to further explore doses below the MTD based on the totality of the safety data.

Once one of the aforementioned conditions for stopping the CRM is met, the dose identified as MTD will be evaluated together with information gathered from PK analyses and the overall safety profile in order to determine the RP2D. The dose(s) likely to be considered the RP2D will be expanded to 12 patients if not already tested within the CRM context in order to confirm the RP2D. Due to the variability of binary data in small samples, DLTs may be observed in a first cohort(s) assigned 10 mg simply by chance even when the true PR

(DLT|10 mg) is fairly low. This would result in the estimated posterior DLT rate at 10 mg (and all higher doses) to exceed the targeted 33% very early in the trial, triggering a futility stop when very few patients have been treated. To prevent stopping the trial prematurely for futility in such cases, a step-down option with a dose of 5 mg is added to the dose grid. This dose will be explored only if a high DLT rate (≥2/3) occurs in the first cohort assigned to 10 mg, ie, it will not be used as a starting dose and the algorithm will always assign the first cohort of patients to 10 mg.

9.2.2. Simulations for CRM Design in Phase 1

Several simulations were performed to fine-tune the CRM performance and to study operating characteristics of the chosen "best" CRM design. Below is a brief description of the simulation setup and key findings.

Different combinations of stopping rules (6, 9, and 12 patients on MTD) and maximum sample size were examined. Competing designs were evaluated against 6 different plausible scenarios of dose-toxicity profile varying in steepness of dose-DLT curve and location of the true MTD within the studied dose range. These scenarios are summarized in Table 17 below.

Table 17. Probability of DLT as a Function of Dose

	Dose-Toxicity Curve Scenario					
Dose	**Sc. 1: MTD= 25-flat**	**Sc. 4: MTD= 25-steep**	**Sc. 2: MTD= 100-flat**	**Sc. 5: MTD= 100-steep**	**Sc. 3: MTD= 400-flat**	**Sc. 6: MTD= 400-steep**
10 mg/QD	0.3	0.1	0.05	0.01	0.01	0.00
25 mg/QD	0.333	0.3333	0.1	0.02	0.02	0.00
50 mg/QD	0.4	0.6	0.175	0.05	0.03	0.00
75 mg/QD	0.45	0.85	0.25	0.15	0.04	0.00
100 mg/QD	0.5	0.95	0.333	0.333	0.05	0.00
150 mg/QD	0.6	1	0.5	0.7	0.08	0.00
200 mg/QD	0.7	1	0.65	0.9	0.12	0.00
300 mg/QD	0.8	1	0.85	1	0.22	0.10
400 mg/QD	0.9	1	1	1	0.333	0.333

For each of the competing designs (ie, CRM design variant), the following operating characteristics were assessed, by scenario, to further quantify the trade-off between precision of MTD estimation and design cost:

- Probability to select MTD.
- Design cost:
    - Average Sample Size;
    - Average Number of DLTs;
    - Average Proportion of DLTs.

These operating characteristics are summarized in Table 18 below for the final design selected based on 1000 trials simulated. The magnitude of trade-off between quality of MTD information obtained and design costs (such as sample size, and observed toxicities) varies depending on the underlying dose-toxicity relationship. A specific variant of CRM design (stopping rule with 12 patients on MTD) was chosen among multiple variants examined (6, 9, or 12 patients on MTD) as the most optimal in terms of MTD precision/design cost trade-off.

Table 18. Operating Characteristics of the CRM in Phase 1

	MTD Dose Selection Decision (Probability)											
Scenario	**10 mg/ QD**	**25 mg/ QD**	**50 mg/ QD**	**75 mg/ QD**	**100 mg/ QD**	**150 mg/ QD**	**200 mg/ QD**	**300 mg/ QD**	**400 mg/ QD**	**Average size**	**Average Num DLTs**	**Average DLTs (%)**
MTD 25 flat	0.142	0.107	0.091	0.043	0.009	0.001	0	0	0	12.9	4.6	0.4
MTD 25 steep	0.3	0.426	0.025	0	0	0	0	0	0	19.5	6.2	0.3
MTD 100 flat	0.003	0.017	0.15	0.305	0.356	0.089	0.004	0	0	26.6	7.2	0.3
MTD 100 steep	0	0	0.008	0.258	0.702	0.015	0	0	0	27.7	7.6	0.3
MTD 400 flat	0	0	0	0	0.001	0.02	0.138	0.497	0.327	27.9	4.2	0.2
MTD 400 steep	0	0	0	0	0	0	0	0.299	0.701	28.2	4.1	0.1

9.3. Sample Size Determination

Phase 1

Similar to the conventional 3+3 design, the exact sample size of the CRM design in the Phase 1 cannot be prespecified because of the dynamic feature of the design. The minimum and maximum sample sizes after which the Phase 1 can be stopped and MTD declared are 12 and 36 patients, respectively. The actual sample size of the Phase 1 will lie somewhere between 12 and 36 depending on the underlying dose-toxicity profile and variability in actual data realization.

Typically, at least 3 patients will be treated at each dose level tested. However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary from 0 to 12. At least 12 patients will be treated at the dose likely to be considered the RP2D.

Phase 2

For subpopulations EXP1-EXP-5 described in Section 3.1 the goal of the primary analysis of objective response will be to estimate the Objective Response Rates (ORR) and their 95% exact confidence intervals (Clopper-Pearson).

For EXP-1 the target sample size is 30 patients.

EXP-2 and EXP-3A+EXP-3B were considered similar; the subgroups were to be analyzed separately and also as a pooled set EXP-2:3A:3B for a combined efficacy analysis. As the population of patients receiving only crizotinib (EXP-2) was limited, a possible lower enrollment in this group was to be compensated with patients enrolled in EXP-3, targeting 80 patients in total between EXP-2 and EXP-3A+EXP3B combined.

For EXP-4, the target sample size is increased to 70 patients, allowing more precise estimation in this group with diverse prior treatments.

For EXP-5 the target sample size remains unchanged at 40 patients.

As EXP-4 and EXP-5 represent the more advanced line of treatment of patients treated in 3rd -4th line, a pooled analysis of efficacy will be conducted on the resulting target sample size of 110 patients treated with PF-06463922 after at least two prior ALK TKI.

Table 19 below shows possible estimated ORR and 95% CIs for different level of responses in populations of 30, 40 patients, 70 and 80 patients.

Table 19. 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% (57.7-0.90)
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% (23.3-46.6)
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 described in Section 3.1, the group-sequential two-stage design using an O'Brien-Fleming[40] non-binding stopping boundary for futility to test the null hypothesis that the response rate P ≤0.30 versus the alternative that P ≥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 will be terminated if ≤5 patients respond. If the trial proceeds to the second stage, a total of 39 patients will be studied. If the total number of responding patients is ≥16 for this subpopulation, then the null hypothesis will be rejected.

9.4. Efficacy Analysis

9.4.1. Primary Analysis

Phase 1

In Phase 1, anti-tumor activity is a secondary objective.

Phase 2

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

Objective Response Rate (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 ITT analysis set. ORR will be calculated for subgroups EXP-1:6 and will be provided along with the corresponding 95% exactconfidence intervals.

Waterfall plots displaying the best % change from baseline in tumor size and spider plots displaying the % change in tumor size from baseline across visits will also be presented.

Intracranial ORR (IC-ORR)

Intracranial ORR is defined as the percent of patients with intracranial response (ie, Best Overall Intracranial Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) considering only the Lesions having Disease Site=Brain) relative to patients with CNS metastases analysis sets. ORR will be calculated for subgroups EXP-1:6 and will be provided along with the corresponding 95% exact confidence interval.

Waterfall plots displaying the best % change from baseline in tumor size of intracranial lesions and a spider plots displaying the % change in tumor size of intracranial lesions from baseline across visits will also be presented.

For patients treated in EXP-3, ORR and IC-ORR will also be presented separately for subgroups EXP-3A and EXP-3B.

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).

A waterfall plot displaying the best percentage change in tumor size will also be provided for each pooled analysis set.

9.4.2. Analysis of Secondary Endpoints

Phase 1

For the Phase 1 all the analyses of efficacy endpoints but OS will be made according to both independent central radiology assessment and derived investigator assessment, respectively, and endpoints will be calculated pooling the populations from all of the dose escalation cohorts.

ORR

ORR is defined as the percent of patients with Best Overall Response as confirmed CR or PR according to RECIST version 1.1 relative to the ITT analysis set and will be provided along with the corresponding 95% exact confidence interval.

For Phase 1 only, in addition to the ORR based on confirmed responses a second ORR including Unconfirmed CR and Unconfirmed PR will also be calculated.

A waterfall plot displaying the best % change from baseline in tumor size and a spider plot displaying the % change in tumor size from baseline across visits will also be presented.

Intracranial ORR

Intracranial ORR is defined as the percent of patients with intracranial response (ie, Best Overall Intracranial Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) considering only the Lesions having Disease Site=Brain) relative to patients with CNS metastases analysis set, and will be provided along with the corresponding 95% exact confidence interval.

A waterfall plot displaying the best % change from baseline in tumor size of intracranial lesions and a spider plot displaying the % change in tumor size of intracranial lesions from baseline across visits will also be presented.

Phase 1 and Phase 2

In Phase 2, estimates of efficacy endpoints will be calculated separately for subgroups EXP-1:6; and for patients treated in EXP-3 also separately for subgroups EXP-3A and EXP-3B.

In addition, pooled estimates 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 more than one prior ALK TKI).

Disease Control Rate (DCR) at 12 and 24 Weeks

DCR at 12 and 24 weeks is defined as the percent of patients with Disease Control at 12 and 24 weeks (ie, having at week 12/24 or later a status of response [CR or PR] or of Stable Disease [SD]) relative to the patients in the ITT analysis set and will be provided along with the corresponding 95% exact confidence interval.

Time-to-Event Endpoints

PFS is defined as the time from first dose to first documentation of objective disease progression or to death on study due to any cause, whichever comes first.

OS is defined as the time from randomization to the date of death due to any cause. 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.

Censoring criteria will be described in details in the SAP.

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 as well as the 1-year and 18-month survival probabilities with related confidence intervals. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods.

Duration of Response

DR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. DR will only be calculated for the subgroup of patients with a confirmed objective tumor response, will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median will be provided. Since the number of patients with a confirmed CR or PR may be small, the use of Kaplan-Meier method may be limited and the DR may be summarized using descriptive statistics.

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

Time to Tumor Response

TTR is defined as the time from first dose to first documentation of objective tumor response (CR or PR). For patients whose OR proceeds from PR to CR, the onset of PR is taken as the onset of response. TTR will only be calculated for the subgroup of patients with a confirmed objective tumor response.

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

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

The probability of first event being a CNS progression, non CNS progression, or death will be estimated by using cumulative incidence functions relative to the analysis populations/subgroups based on both independent central review and investigator assessments.

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

Phase 2 Only

Time To Progression

TTP is defined as the time from first dose to first documentation of objective disease progression. Censoring criteria will be described in the SAP.

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, as well as the 1-year and 18-month survival probabilities with related confidence intervals. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods.

9.4.3. Analysis of Exploratory Endpoints

Phase 1

For patients in Phase 1 TTP will be analyzed. Estimates of the time-to-event curves from 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, as well as the 1-year and 18-month survival probabilities with related confidence intervals. The confidence intervals will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Single- and Multiple-Dose PF-06463922 PK Analysis

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 will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity (AUC_{inf}), 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.

For PF-06463922 concentrations, 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) using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. 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.

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.

Urine PK parameters (Ae%, CLr) for PF-06463922 will also be estimated and summarized.

9.5.1.2. Effect of PF-06463922 on MDZ Pharmacokinetics

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.

9.5.1.3. 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 $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ (if data permit) and C_{max} values will be analyzed using a mixed effects model with sequence and treatment (fed, fast) as fixed effects and patient within sequence as a random effect. 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.

9.5.1.4. 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, if performed, may be reported separately.

9.5.1.5. Metabolite Profiling

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

9.5.1.6. 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. Summary statistics may include the mean and standard deviation, median, and minimum/maximum levels of biomarker measures or frequency statistics, as appropriate.

Data from biomarker assays will be analyzed using graphical methods and descriptive statistics such as linear regression, t test, and analysis of variance (ANOVA). The statistical approach will 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.

9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint for the Phase 1 will be based on the per protocol analysis set. Summaries and analyses of safety parameters on Phase 1, Phase 2 and the DDI/Holter monitoring study will be based on the Safety Analysis Set.

9.6.1. Analysis of Primary Endpoint for Phase 1

- Dose-Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study). The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in the Study Design section. Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints for Phase 1, Phase 2, and the DDI/Holter monitoring study

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 both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

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

Vital Signs

Changes from baseline in vital signs, including body weight, blood pressure and heart rate will be summarized.

Left Ventricular Ejection Fraction (LVEF)

For patients with MUGA scans or echocardiograms, individual LVEF proportion (%) and its changes from baseline will be summarized by time point. The number of patients and the percentage whose maximum decrease from baseline in LVEF is equal or greater than 20% will be calculated.

Mini Mental State Examination (Phase 1 only):

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

9.6.3. ECG Analysis

The analysis of ECG results will be based on Safety Population patients with baseline and on-treatment ECG data. ECG collected prior to the first day of dosing will be considered the baseline ECG.

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 (ie, Bazett's, Fridericia's and possibly a study specific factor). 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. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time points. Outlier analysis of the QTc data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, 30-60, and ≥60 msec);
- The number of patients with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480-<500, and >500 msec).

Shift tables will be provided for baseline vs worst on study QTc (one or more correction method will be used) using Maximum CTCAE Grade V4.03. As well as tables of ECG abnormality at baseline (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on QTc change 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.

9.7. Pharmacodynamic Analysis

CTC-based pharmacodynamic analysis is an exploratory objective. For CTC enumeration, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline, end of C2/pre dose on C3D1 and end of study treatment. For each pair of specimens, the percent change from baseline of these same parameters might

also be calculated. The statistical approach may examine correlations of CTC results with pharmacokinetic parameters and measures of anti-tumor efficacy. Per Amendment 4, this analysis will no longer be performed and has been removed as a secondary endpoint.

9.8. Patient Reported Outcomes Analyses

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.

Rates of improvement will be evaluated over each cycle in the symptom scales, in the functioning scale and in the global QOL scale. In the symptom scales improvement is defined as decrease of at least 10 points. In the functioning and global QOL scales improvement is defined as an increase of at least 10 points.

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. Summary statistics (mean and SE), and median (range and 95% CI) of absolute scores will be reported for the items and scales of the QLQ-C30 and the QLQ-LC13. The mean change of absolute scores from baseline (and 95% CI) will also be assessed by dosing cohort/subgroups. Line charts depicting the means and mean changes of subscales 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 in a table. Additional analyses may be performed such as repeated measures mixed-effects modeling.

9.9. Cognitive, Mood and Suicidal Ideation and Behavior Analyses (Phase 2 only)

For Mood assessment via the Beck Depression Inventory-II (BDI-II), frequencies and percentages on items capturing mood, suicidal ideation, cognitive signs as well as somatic signs will be summarized.

For each of the 5-part battery test of the Cogstate assessment of Cognitive Function, the change from baseline scores at all post-baseline assessment will be calculated and summarized using descriptive statistics.

For Suicidal Ideation and Behaviors via the Columbia Suicide Severity Rating Scale (C-SSRS), frequencies and percentages will be displayed for patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent.

Further details are provided in the SAP.

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

Japanese patients enrolled into the LIC will be analyzed separately from patients enrolled in the main part of the study.

9.11. Patients Receiving Crizotinib after PF-06463922

The analysis of data on patients receiving crizotinib after PF-06463922 will focus on the efficacy endpoints as described in Section 2.2 (ORR, PFS, DR, TTR, OS), on AEs and Laboratory assessments and on Duration of Treatment.

Efficacy Endpoints definition follow the definition of same endpoints already provided in Section 9.4.2 for EXP-1 through EXP-6, with the following caveats:

- For tumor assessments, the baseline assessment will be the re-baselined assessment as described in Appendix 11;
- The starting date for the calculation of PFS, TTR, and OS will be the treatment start date of crizotinib;
- The analysis set definition for this population will be documented in the Statistical Analysis Plan.

AEs and laboratory endpoint definitions follow the definition of the same endpoints already provided in Section 9.6.2, with the following caveats:

- The baseline assessment will be the tumor assessment within 2 weeks after the last dose of PF-06463922, as described in Appendix 11;
- The first dose of study medication will be defined as the treatment start date of crizotinib.

9.12. 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. However, a sample size of 6 subjects will provide 90% CI for the difference between treatments of ±0.5338 on the natural logarithm scale for Cmax, with 80% coverage probability.

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 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 AUC_{24}, AUC_{inf} (if data permits), and C_{max} for the probe substrates and their relevant metabolites will be analyzed using a mixed effect model with treatment as fixed effect and subject as a random 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}, $MRAUC_{inf}$, 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. Plasma concentrations for the probe substrates, their metabolites (as appropriate), PF-06463922 and its 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 in these patients.

Safety and Efficacy in patients entering the DDI and Holter monitoring study will be analyzed separately from the Phase 2 efficacy population, as outlined in the statistical analysis plan.

9.13. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Discussions between the Investigators and the Sponsor of AEs and laboratory tests alterations seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and benefit/risk ratio and decide if further enrollment is appropriate.

9.14. Independent Central Radiological Review

An independent core imaging laboratory will be used in Phase 2. All sites will be required to submit images to the core imaging laboratory for independent central review (ICR) as soon as they are performed at the site so that imaging scans may be read in real time. The requirements of submitting images will be provided to sites by the core imaging laboratory. For those patients who receive crizotinib after PF-06463922, submission of scans to the core imaging laboratory is no longer required (ie, only required during treatment with PF-06463922). Additionally, all sites in Phase 1 will be required to submit images to the core imaging laboratory for retrospective ICR.

The independent central radiology review will be stopped when the data collection required for the primary and secondary endpoints is deemed sufficient.

Upon approval of Amendment 8, the radiologic assessments will be performed according to local practice.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the Sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

The End of Trial is defined as the date of the "last patient last visit" (LPLV) in the study. Study Completion is defined when 2/3 of OS events (deaths) have occurred.

The End of Trial will occur after 36 months of treatment of the "last patient first visit" (LPFV) or upon Study Completion, whichever comes first.

If the Study Completion occurs before the 36 month treatment period and a patient is still experiencing clinical benefits, a number of options for extending the study treatment will be considered based on the local availability of the treatment and local country laws/regulation.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06463922 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a time defined by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

If the study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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Appendix 1. Phase 1 Required Laboratory Assessments

	Phase 1 Dose Escalation Single Agent				
Hematology	**Chemistry**	**Coagulation**	**Lipids**	**Urinalysis**	**Pregnancy Test**
Hemoglobin	ALT	PT or INR	Total Cholesterol	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	Serum from female patients of childbearing potential
Platelets	AST	PTT	LDL		
WBC	Alk Phos		HDL		
Absolute Neutrophils	Sodium		Triglycerides		
Absolute Lymphocytes	Potassium			Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	
Absolute Monocytes	Magnesium				
Absolute Eosinophils	Chloride				
Absolute Basophils	Total Calcium				
	Total Bilirubin *				
	BUN or Urea				
	Creatinine				
	Uric Acid				
	Glucose -				
	Albumin				
	Phosphorous or Phosphate				
	Serum total amylase (pancreatic isoenzyme required if serum total amylase not within normal limits per local institutional ranges).				
	Serum lipase				

**For potential Hy'sLlaw cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.*

Appendix 2. Phase 2 Required Laboratory Assessments

	Phase 2 Laboratory Assessments				
Hematology	**Chemistry**	**Coagulation**	**Lipids**	**Urinalysis**	**Pregnancy Test**
Hemoglobin	ALT	PT or INR	Total Cholesterol	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	Serum from female patients of childbearing potential
Platelets	AST	PTT	LDL		
WBC	Alk Phos		HDL		
Absolute Neutrophils	Sodium		Triglycerides		
Absolute Lymphocytes	Potassium			Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	**Hypogonadism blood sampling between 08:00-11:00 in male patients only**
Absolute Monocytes	Magnesium				Total Testosterone (TT)
Absolute Eosinophils	Chloride				Free Testosterone (Free T)
Absolute Basophils	Total Calcium				Lutenizing Hormone(LH)
	Total Bilirubin *				Follicle Stimulating Hormone (FSH)
	BUN or Urea				Sex Hormone Binding Globulin (SHBG)
	Creatinine				Prolactin
	Uric Acid				Dehydroepiandrosterone sulphate (DHEA-s)
	Glucose (non-fasted)				Estradiol
	Albumin				
	Phosphorous or Phosphate				
	Serum total amylase				
	Serum lipase				

**For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.*

Appendix 3. RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 Modified to Include Assessment of CNS Metastases

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below.[39]

Measurable Lesions

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

- 10 mm for all lesions including CNS lesions, but excluding lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- **5 mm for CNS lesions provided gadolidium contrast enhanced MRI is perfomed with contingent slices of 1mm.**
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-Measurable Lesions

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

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

Special Considerations Regarding Specific Lesions

Bone lesions:

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

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

Solitary lesions:

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

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. **Exception to this rule is in the presence of CNS metastases ≥5 mm in diameter assessed by gadolidium contrasted MRI with slices of 1 mm; up to 5 CNS lesions will be permitted in addition to 5 extracranial lesions previously noted.**[32] Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

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

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

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

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

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

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

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

Non-Target Lesions

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

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Cytology, Histology

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

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

New Lesions

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up.

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

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

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

Confirmation of Tumor Response

Confirmation of response will be required at least 4 weeks after the initial response is observed.

Determination of Overall Response by the RECIST v1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 20.

Table 20. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best Overall Response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trails) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

For CR and PR, confirmation is required at least 4 weeks after the initial response is observed. Therefore, CR and PR may only be claimed as the best overall response provided this confirmation is met.

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

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

Appendix 4. ECOG Performance Status

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

Appendix 5. Bone Marrow Reserve in Adults

Bone	Relative red bone marrow content (%)
Cranium	7.3
Mandible	0.8
Scapulae	6.4
Clavicles	1.4
Sternum	1.8
Ribs	15.8
Cervical vertebrae	2.2
Thoracic vertebrae	11.8
Lumbar vertebrae	9.3
Sacrum	6.5
Pelvis	19.7
Femurs (upper half)	11.1
Humeri (upper half)	5.8
Total skeleton	**100.0**

Adapted from:

Zankle M, Wittman A.

The adult male voxel model "Golem" segmented from whole body CT patient data.

Rad Environ Biophysics 40:153 62, 2001

Appendix 6. EORTC QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7. EORTC QLQ-LC13 Questionnaire

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 8. Mini Mental State Examination

For copyright reasons, the MMSE may not be reproduced here. The tool and instructions may be found in the following publication:

Folstein M et al. Mini-Mental State a practical method for grading the cognitive state of patients for the clinican. Journal of Psychiatric Research 1975; 12 (3):189-198.

The Forms and Instructions will be provided as paper copies to the participating investigational sites in the Site Study Manuals.

Appendix 9. Japanese Patient-Only Lead-In Cohort (LIC) Schedule of Assessments

Note: The current table is no longer applicable after the approval of Amendment 8, please refer to Table 1.

		CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3 –25 (Up to Month 18) (21 days)	CYCLES >25 (Months >18) (21 days)		
Protocol Activity	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[25]**	**Follow- Up[24]**
Visit Window (days)	**N/A**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Informed consent[2]	X								
Tumor history	X								
Medical history	X								
Physical examination	X	(X)			X	X	X		
Baseline signs and symptoms[3]		X							
Height	X								
Weight	X	X			X	X	X		
Vital signs[4]	X	X	X	X	X	X	X	X	
Performance status[5]	X	X			X	X	X	X	
Contraception check (as appropriate)		X			X	X	X		
Laboratory									
Hematology[6]	X	(X)	X	X	X	X	X	X	
Blood Chemistry[7]	X	(X)	X	X	X	X	X	X	
Lipids[8]	X	(X)	X	X	X	X	X	X	
Hypogonadism (male patients)[9]	X			X	X	C5D1 and Q 4 cycles thereafter	Q 4 cycles	X	
Coagulation[10]	X	(X)						X	
Urinalysis[11]	X	(X)	X	X				X	
Pregnancy test[12]	X	(X)			X	X	X	X	
(12 lead) ECG[13]	X	X	X	X	X	X (up to Cycle 5)		X	
Pulse Oximetry[27]	X	X	X	X	X	X (up to Cycle 5)		X	
Chest X-ray or Chest CT[28]	X								
LVEF assessment (Echocardiogram or MUGA)[26]	X				X	X	Every 4 cycles	X	
Registration and Treatment									
Registration[14]		(X)							
PF-06463922 Treatment[15]			Once a day or twice a day, continuously						

		CYCLE 1 (21 days)			CYCLE 2 (21 days)	CYCLES 3 –25 (Up to Month 18) (21 days)	CYCLES >25 (Months >18) (21 days)		
Protocol Activity	**Screen[1] (≤28 days)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1 of Every Other Cycle**	**End of Treatment[25]**	**Follow- Up[24]**
Visit Window (days)	**N/A**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Tumor Assessments									
CT or MRI Scan or Equivalent[16]	X					X and then every 6 weeks ±1 week	Every 12 weeks ± 1 week	(X)	(X)
Cerebrospinal fluid if leptomenigeal/carcinomatous meningitis [LM/CM]disease is present[17]	X					As indicated	As indicated		
Other Clinical Assessments									
Adverse Events[18]		X	X	X	X	X	X	X	X
Concomitant medications and non drug supportive interventions[19]	X	X			X	X	X		X
EORTC QLQ-C30, QLQ-LC13[23]		X			X	X	X	X	
Cognitive Assessment[29]	X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Mood Assessment[30]	X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Suicidal Ideation and Behavior[31]	X	X			X	X up to Cycle 6 and then D1 of every other cycle	X	X	
Survival Follow-up									X
Other Samples									
Archival Tumor Tissue Specimen[20]	X								
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[21]	X					X		X	
Banked Biospecimen[22]	X								

Footnotes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required. For example, if a patient will not have the Lead-In (Day -7) Visit, some assessments may be required on Cycle 1 Day 1 instead of Day -7 and vise versa.

1. **Screening:** To be obtained within 28 days prior to registration.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures not considered standard of care.
3. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening Baseline signs and symptoms will be recorded on the Adverse Events CRF page.
4. **Vital signs:** blood pressure and pulse rate to be recorded in sitting position.
5. **Performance Status:** use ECOG – see Appendix 4.
6. **Hematology:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, hematology labs may be done within 72 hours of dosing with results checked prior to dosing.
7. **Blood Chemistry:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, chemistry labs may be done within 72 hours of dosing with results checked prior to dosing.
8. **Lipids:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after C1D1, lipid labs may be done within 72 hours of dosing with results checked prior to dosing.
9. **Hypogonadism Laboratory Test:** to be performed in male patients only. The required blood tests are reported in Appendix 2. Blood draws MUST be done between 08.00-11.00 AM. Should a decrease of ≥25% from baseline be observed in total testosterone or free testosterone a repeat laboroatory analysis of both these parameters must be performed at the next clinical visit to confirm hypogonadism.
10. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2. For those visits after Cycle 1 Day 1, coagulation labs may be done within 72 hours of dosing with results checked prior to dosing.
11. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. See Assessments section for Laboratory Tests in Appendix 2.
12. **Serum Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period (every other cycle beyond 18 months), at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
13. **Triplicate 12-lead ECGs:** At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected as follows: a) at Screening, b) Cycle 1 Day 1 pre-dose and 1 hr, 2 hr and 4 hr post-dose), c) Cycle 1 Day 8 and Day 15 at pre-dose, 1 hr and 2 hr post dose, d) Cycles 2-5 Day 1 at pre-dose, 1 hr and 2 hrs post dose and e) End of Treatment. If at any of these timepoints the mean QTc is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

    When an ECG and PK sample are scheduled at the same time, ECG assessments should be performed prior to PK sample such that the PK sample is collected at the nominal time (but regardless, the exact time of ECG assessment and PK collection should always be recorded).
14. **Registration:** Registration will be within 2 days prior to lead-in or study treatment start.
15. **Trial Treatment:** described in the Study Treatments section.

16. **Tumor Assessment:** Tumor assessments will include all known or suspected disease sites. CT or MRI scans of Chest Abdomin Pelvis [CAP] and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI for must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5mm for lesions greater than 10mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases are observed at baseline. For patients who are without documented disease progression, CT and MRI scans to be done at every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ±1 week beyond 18 months, and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment will be done every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ±1 week beyond 18 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses will be confirmed ≥4 weeks later (RECIST v1.1) until documented progression of disease. For patients who have documented disease progression, but are still receiving treatment with PF-06463922, tumor assessments should be done according to local institutional standard of care. For all tumor assessments, the method of assessment used at baseline should be the same method used throughout the study. Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1 especilaly if there are dosing cycle interruptions due to toxicities. Tumor assessment should be repeated at the end of treatment and study visits if more than 6 weeks have passed (more than 12 weeks beyond month 18) since the last evaluation. Tumor assessments will continue until progression of disease or a new anti-cancer therapy has commenced.
17. **Cerebrospinal fluid (CSF)** CSF analysis will not be required unless patients have suspected or confirmed leptomeningeal carcinomatosis not visualised on MRI. When applicable, CSF sample will be collected at Screening (optional CSF collection post-Screening). See PK assessments for PF-06463922 CSF concentration sampling (optional).
18. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
19. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
20. **Archival Tumor Tissue Specimens:** All patients will provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen, specifically a FFPE tissue block that contain sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that are 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block cannot be submitted. If an archival tumor tissue sample is not available, a de novo tumor specimen must be obtained. Specimens will be sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to PF-06463922 (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1+ NSCLC patients specimens will be sent to the Sponsor-designated central laboratory for ROS1 status confirmation.
21. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling:** 10 ml blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at screening, at the end of Cycle 2 matching the first tumor restaging (in practical terms, this may be C3D1 pre-dose) and at end of treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
22. **Banked Biospecimens**: Unless prohibited by local regulations, a blood sample (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, will be collected at screening.
23. **EORTC QLQ-C30 and QLQ-LC13:** Patients must complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points prior to dosing. At Cycle 1 Day 1 site staff (eg, site coordinators) should instruct patients that the assessment should be completed without help from friends or family members and also recommend that this assessment be completed in the morning. All scheduled assessments of the EORTC QLQ-C30 and QLQ LC13 cannot be taken home and must be completed in the clinic prior to any other study or medical procedures.

24. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuating treatment for reasons other than progression of disease will continue to perform tumor assessments until PD or a new anti-cancer therapy is commenced. Bimonthly survival followup after PD or new anti-cancer therapy has commenced will be performed (telephone contact is acceptable).
25. **End of Treatment Visit:** Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments if during first 18 months, then last 12 weeks if beyond month 18).
26. **LVEF Assessment**: Echocardiogram or MUGA will be performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every two cycles thereafter up to approximately 18 months, and then every 4 cycles thereafter, and at the End of Treatment visit (a ±2 days time window is allowed at all time-points applicable at the discretion of the investigator). The same method should be used at each time point.
27. **Pulse Oximetry:** Pulse oximetry will be performed within 14 days prior to the first dose of study treatment, and during treatment as described in the table above. Pulse oximetry should be repeated if clinically indicated.
28. **Chest X-ray or Chest CT:** Chest X-ray or Chest CT will be performed within 14 days prior to the first dose of study drug. Chest X-ray or CT should be repeated if clinically indicated and at the discretion of the investigator. Patients who have had a CT scan including chest for the purpose of tumor assessment for this study will not need to be repeated at baseline.
29. **Cognitive Assessment:** A computerized cognitive test compromised of verbal learning, psychomotor function, attention and memory will be administed to patients prior to study drug dosing. This test will take approximately 10-20 minutes to complete and will be administered via a qualified site personnel. A practice test will be performed at Screening and a baseline test will be done prior to dosing on C1D1and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this will be administed prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).
30. **Mood Assessment:** An assessment of mood via the Beck Depression Inventory-II (BDI-II) scale will be administered to patients prior to study drug dosing. The assessment will be given prior to dosing on C1D1 and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this will be administed prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).
31. **Suicidal Ideation and Behavioral Assessment:** An assessment of suicidal ideation via the Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to patients prior to dosing on C1D1 and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After C6D1, this will be administed prior to dosing on D1 of every other cycle ±1 week (ie, C8D1, C10D1, etc.).

Japanese Patient-Only Lead-In Cohort (LIC) Pharmacokinetic Sampling Schedule

	CYCLE 1 (21 days)			CYCLE 2-5 (21 days)	CYCLE 6, Cycle 8 and Cycle 10 (21 days)
Protocol Activity	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**
Visit Window	**±1**	**±1**	**±1**	**±2**	**±2**
All Patients					
Plasma sampling for PF-06463922 PK[1]	X	X	X	X	X
PF-06463922 metabolite profiling blood sample[2]			X		
Cerebrospinal fluid (CSF) for PF-06463922 concentration (optional)[3]			Any time during steady state ideally 4-6 hrs and 8-9 hrs post-dose		
Blood sample (when CSF for PF-06463922 is collected)[4]			Same time as CSF PF-06463922 concentration sample collected		

Footnotes

1. **PF-06463922 PK Sampling (Japanese LIC patients):** Blood samples will be collected on Cycle 1 Day 1 and Cycle 1 Day 15 at pre-dose, 0.5, 1, 2,3, 4, 6, 8, 9 and 24 hours post dose. On Cycle 1 Day 8, a blood sample will be collected at pre-dose, 1, 2 and 4 hrs post-dose. Cycles 2-5: Pre-dose, 1 and 2 hrs post dose. Day 1 of Cycle 6 and Day 1 of Cycles 8 and 10: Pre-dose. Patients will be hospitalized for PK sampling for at least the first two days on Cycle 1 Day 1 and Cycle 1 Day 15.
2. **PF-06463922 Metabolite profiling (Japanese LIC patients):** Blood samples will be collected at steady-state, Cycle 1 Day 15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hrs post-dose.
3. **CSF PF-06463922 Concentration Sample (Optional):** If a patient undergoes a lumber puncture, a sample of CSF should be collected for exploratory analysis of PF-06463922 concentration, if possible. If scheduling permits, one CSF sample should be taken between 4 and 6 hours post dose. If it is possible to take a second sample, collection should be between 8 and 9 hours post-dose.
4. A blood sample for PK analysis should be collected at approximately the same time as the CSF PF-06463922 concentration sample.

Appendix 10. Safety Review Process for Japanese Only Patient LIC

Following 1 cycle (21 days) of treatment, a safety review will be performed by Japanese investigators, Pfizer Japan, and the global Pfizer Team to determine Japan site participation in Phase 2. Emerging Phase 1 safety/PK data in Western patients will also be used as a reference.

Appendix 11. Patients Receiving Crizotinib Following PF-06469322

Patients in EXP-1 who discontinue PF-06463922 for reasons other than withdrawal of consent may be eligible to receive single-agent crizotinib. At the time of PF-06463922 discontinuation, patients will undergo a brief Screening period to ensure inclusion and exclusion criteria are met and required assessments are performed. Patients may initiate crizotinib within 5 days after discontinuing treatment with PF-06463922. In situations of disease-related tumor flare, patients may initiate crizotinib sooner per investigator discretion for appropriate and necessary patient management. The last tumor assessment performed prior to initiating treatment with crizotinib will be considered the baseline tumor assessment for crizotinib therapy. Adverse event reporting should follow the same guidelines as described in Section 8 of the protocol. Data for patients receiving crizotinib following PF-06463922 will be collected in a separate CRF and analyzed separately.

1. Patient Selection

Inclusion Criteria:

1. ECOG Performance Status (PS) 0. 1 or 2.
2. Adequate Bone Marrow, Pancreatic, Renal and Liver function as defined by:
   - Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L;
   - Platelets ≥100 x 10^9/L;
   - Hemoglobin ≥9 g/dL;
   - Serum lipase ≤1.5 ULN;
   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution;
   - Total serum bilirubin ≤1.5 x ULN;
   - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver metastases involvement.
3. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator' judgment do not constitute a safety risk for the patient.
4. Serum pregnancy test (for females of childbearing potential) negative at screening. A patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active.

5. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study (reconseting is not necessary if the patient already consented to receiving crizotinib following PF-06463922).

6. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

7. Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of the first negative pregnancy test at screening, throughout the study and for 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Exclusion Criteria:

All Section 4.2 Exclusion Criteria apply plus:

1. Anticancer treatment except palliative radiation therapy between last PF-06463922 dose and first crizotinib dose.

2. Any history of pneumonitis or interstial lung disease.

2. Life Style Guidelines for Crizotinib:

2.1. Contraception

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and continued for 90 days after the last dose.

The investigator, in consultation with the patient, will select an appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator, at each study visit, will discuss with the patient the need to use a highly effective contraception consistently and correctly and document such conversation in the patient chart. The patient may be contacted by phone to confirm contraception is still appropriate per the protocol. In addition, the investigator will instruct the patient to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the patient remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom must be used in association with a female highly effective method of contraception. .

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

2.2. Sunlight Exposure

Patients treated with crizotinib should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period.

3.0. Concomitant Treatments

All concomitant treatments, blood products, as well as non drug interventions (eg, paracentesis) received by patients from the first dose of crizotinib to 28 days after the last dose of study treatment will be recorded on the CRF as detailed in Table 23. Anticancer therapy with agents other than crizotinib is not allowed. The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of potent CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, telithromycin, troleandomycin, saquinavir, voriconazole, and grapefruit or grapefruit juice, are not allowed in the study. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

In vitro data indicate that the most pronounced inhibitory potential of crizotinib was observed toward CYP3A4 (testosterone)-mediated drug metabolism. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6. Crizotinib also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A. Caution (excluding those restricted medications mentioned above) must be exercised in patients receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A such as alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. In particular, co-administration of crizotinib with

CYP3A4 substrates with narrow therapeutic indices including, but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation.

Additionally, the concurrent use of non-prescription drugs, complementary medicines (excluding vitamins) or herbal supplements is not recommended.

3.1. Antiemetic and Antidiarrheal Therapy

Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. Patients may receive prophylaxis of treatment-induced diarrhea. Taking the medication with food may reduce nausea. Prophylactic use of antiemetics should be considered.

3.2. Hematopoietic Growth Factors

The use of hematopoietic growth factors is at the discretion of the treating physician. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician. However, in Japan, erythropoietin and darbepoietin will not be allowed to be used for chemotherapy-related anemia because these drugs have not been approved for this indication. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

3.3. Other Concomitant Medications

Anti-inflammatory or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated. Patients on this trial may be supported with appropriate hormone replacement therapy as clinically indicated in the absence of disease progression or unacceptable treatment-associated toxicity. Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited. Medications that are known to prolong the QT interval and bradycardic agents (eg, betablockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be used with caution during the study.

3.4. Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Crizotinib treatment should be interrupted during palliative radiotherapy; stopping 1 day before and resuming treatment 1 day after.

The effect of crizotinib in wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect) for any surgical procedures during the study. The appropriate interval of time between surgery and crizotinib required to minimize the risk of impaired wound healing and bleeding has not been determined. In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery. Postoperatively, the decision to reinitiate crizotinib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

4. Study Treatment

Patients will receive a starting dose of crizotinib 250 mg BID which will be administered orally at approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing. Crizotinib can be dosed without regard to meals. Cycles are defined as 21 days in length.

4.1. Allocation to Treatment

Patient registration will be same automated registration system as used for PF-06463922.

4.2. Formulation and Packaging

Crizotinib will be provided as capsules containing 250 mg and 200 mg of study medication and will be packaged in HDPE bottles. Study medication will be supplied by Pfizer.

4.3. Preparation and Dispensing

Crizotinib will be supplied as 200 mg and 250 mg capsules for oral administration. Crizotinib will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Administration Cards and Patient Diaries. In addition, administration instructions will be detailed in the Investigational Product (IP) Manual.

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

4.4. Compliance

See Section 5.2.8 of the protocol. Same instructions apply for crizotinib.

4.5. Drug Storage and Drug Accountability

Crizotinib should be stored in its original container and in accordance with the drug label. See Section 5.2.9 of the protocol for details on drug accountability for crizotinib, as the same instructions for PF-06463922 apply for crizotinib.

4.6. Temperature Excursions

See Section 5.2.10 of the protocol. Same instructions apply for crizotinib.

4.7. Dose Modifications for Crizotinib

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

In the event of significant toxicity, dosing may be delayed and/or reduced as described below in Table 21 and Table 22. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify their investigators at the first occurrence of any adverse event.

Dose modifications may occur in 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as indicated in the dose modification table below (Table 21).

Table 21. Dose Modifications for Crizotinib

Current Dose Level	Dose Level -1	Dose Level -2
250 mg BID	200 mg BID	250 mg QD

Patients requiring more than 2 dose reductions due to treatment-related toxicity will be discontinued from the study.

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Table 22. Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic General (except as noted below), eg, neuropathy, edema (including peripheral edema and localized edema), fatigue, and skin rash (including erythematous, macular, papular, and pruritic rash).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.*	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.*
ALT or AST elevation with total bilirubin <2 X ULN (in the absence of cholestasis or hemolysis).§	Continue at the same dose level.	Continue at the same dose level. Obtain repeat ALT or ALT and total bilirubin when symptomatic or within 7 days. **For France only:** Consult with Sponsor (according to letter provided under separate cover) to determine whether (1) to continue with same dose, level; (2) withhold dose until toxicity is Grade ≤1 or has returned to baseline, then resume treatment at the same dose level; or (3) withhold dose until toxicity is Grade ≤1 or has returned to baseline, then reduce the dose by 1 level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment by reducing the dose by one dose level. If Grade 3 ALT or AST elevation recurs reduce further (at most by 2 dose levels from initial dose level). If recurrence at dose level -2, discontinue permanently. If Grade 3 ALT or AST elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level. **For France only:** Discontinue treatment and do not retreat.	See Grade 3. **For France only:** Discontinue treatment and do not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT or AST elevation concurrent with total bilirubin elevation ≥2 X ULN (in the absence of cholestasis or hemolysis).	Continue at the same dose level. Obtain repeat ALT or AST and total bilirubin within 48 hours, then repeat every 48-72 hours until ALT/AST < grade 1.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Left ventricular systolic dysfunction.	Continue at the same dose level.	Continue at the same dose level.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Prolonged QTc	Continue at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities.	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily. In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade ≥3 recurrence.	Discontinue treatment and do not retreat.
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect).	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Bradycardia (heart rate less than 60 beats per minute).	Continue at the same dose level.	Withhold until recovery to Grade ≤1 or to heart rate ≥60. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications.	Same as for Grade 2 bradycardia.	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate ≥60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60.		250 mg once daily upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring. Permanently discontinue for recurrence.
Visual disturbance.	Continue at the same dose level.	Continue at the same dose level.	Interrupt crizotinib until recovery. Resume treatment by reducing by one dose level.	Discontinue treatment and do not retreat.
Hematologic (excluding lymphopenia**).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 level after discussion with the Sponsor.**	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment.**

* Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

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

§ Patients entering with ALT and/or AST ≥5 x ULN (ie, Grade ≥3) due to underlying malignancy will be monitored for potential drug related increases at which point dose modifications will be discussed with the Sponsor (Note: this option does not apply for France).

Table 23. Schedule of Assessments for Patients Receiving Crizotinib Following PF-06463922

Protocol Activities	Within 2 Weeks of First Crizotinib Dose	Cycle 1	Every other Cycle	End of Treatment[12]	Follow-up[13]
		Day 1	Day 1 of Every other Cycle (±4 days)	±2 days	±7 days
Physical Examination	X	X			
Blood Pressure and Pulse Rate	X	X			
ECOG Performance Status	X	X			
Laboratory Studies					
Hematology, Blood Chemistry[1]	X	X	As per local practice		
Coagulation[2]	X				
Urinalysis dipstick and Reflex Microscopy[4]	**Korea only**: X (all other countries: as clinically indicated)	**X**	**Korea only**: X (all other countries: as clinically indicated)	**Korea only:** X (all other countries: as clinically indicated)	
12-lead Electrocardiogram[3]	X				
Female patients: Pregnancy Test (as appropriate)[5]	X		(every cycle ±2 days)	X	X
Contraceptive Check (as appropriate)[6]			(every cycle ±2 days)	X	X
Disease Assessments					
Tumor Assessments[7]	X		As per local practice		X
Other Assessments					
Tumor tissue for molecular profiling[8]	X			X	
Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[9]	X			X	
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram (France and Japan only)	**France and Japan only**		**France and Japan only:** every 4 cycles		
Adverse Events[10]	X	X	X	X	
Concomitant Medications/Treatments[11]	X				
Survival Follow-up					X
Study Treatment					
Crizotinib		Twice daily			

Footnotes for Schedule of Activities

1. **Hematology:** hemoglobin, platelet count, white blood count and differential. Labs may be collected within 72 hours of cycle.
   Chemistry: total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, total calcium, phosphorus, blood urea nitrogen (BUN) for EU-only sites, creatinine, uric acid magnesium, glucose, LDH.
2. **Coagulation:** protime INR. Labs may be collected within 72 hours of cycle.
3. **12-Lead ECG:** Collect within 2 weeks of last PF-06463922 dose.
4. **Reflex Microscopy** required if urine dipstick is positive for blood or protein. Dipstick may be collected within 72 hours of cycle.
5. **Pregnancy Test**: it will be routinely repeated at every cycle (±2 days) during the active treatment period, at the end of study therapy (±- 2 days), at first follow-up visit (± 7 days), and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations. Patients will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.
6. **Contraceptive check**: patient may be contacted by phone to confirm contraception is still appropriate per the protocol. Males and females of childbearing potential must be contacted post-study to ensure that they continue to use appropriate contraception for at least 90 days after the last dose of study drug.
7. **Tumor Assessments**: Patients who are coming off treatment with PF-06463922 will be re-baselined using the last set of tumor assessments performed and will be performed using RECIST 1.1. If the last set of tumor assessments is not performed within the past 6 weeks, a new baseline will need to be obtained. Tumor assessments will include all known or suspected disease sites. Imaging will include brain (even if brain metastases not suspected) chest, abdomen and pelvis CT or MRI scans. CT scans are recommended for assessment of thorax, abdomen and pelvis lesions. Gadolinium contrast enhanced MRI must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5 mm for lesions greater than 10 mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all patients and repeated as per local practice. Subsequent tumor assessments will be performed as per local practice.
8. **De Novo Tumor Specimens**: If feasible and if consent is given, a de novo biopsy will be performed prior to initiating treatment with crizotinib, if not collected at End of Treatment with PF-06463922. Pleural effusions (PE) cell pellets may substitute for tumor core biopsy as appropriate. Fine needle aspiration (FNA) samples are not acceptable. If local country regulations do not allow for tumor biopsy block to be submitted, 5-micon FFPE tumor slides (at least 12 slides) are acceptable. Samples will be sent to a dedicated laboratory as defined by the study sponsor and outlined in the study manual.
9. **Blood Specimens for Circulating Nucleic Acid (CNA) Profiling**: 10 ml blood specimen optimized for plasma preparation for nucleic acid analysis (eg, circulating free DNA (cfDNA) or RNA (cfRNA)) will be collected at screening, and at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
10. **Adverse Events**: A new Adverse Event log will be used for patients receiving crizotinib following PF-06463922. Patients must be followed for adverse events until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. SAEs will be collected For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
11. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be collected at screening. During the treatment, concomitant medications will be assessed by investigator, recorded in the patient's file but not collected in CRF.
12. **End of Treatment Visit:** Obtain these assessments if not completed in the last week.
13. **Follow up:** At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo assessment for resolution of any treatment-related toxicity, and pregnancy test for female patients. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. After study discontinuation the survival follow-up will be performed every 2 months and will include also the collection of information on subsequent anticancer therapies (telephone contact is acceptable).

Appendix 12. Drugs Known to Prolong PR Interval

The following table provides a list of examples and should not be considered an all-inclusive listing:[49]

Drug	Action	Indications
Affecting AV nodal conduction (PR interval)		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyarmide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-1 protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		
Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT3 receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial

Appendix 13. Country Specific Appendix for France

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.