CLINICAL PROTOCOL

PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF PF-02341066, A MET/HGFR SELECTIVE TYROSINE KINASE INHIBITOR, ADMINISTERED ORALLY TO PATIENTS WITH ADVANCED CANCER

Compound:	PF-02341066
Compound Name:	Crizotinib
United States (US) Investigational New Drug (IND) Number:	CCI
Protocol:	A8081001
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 25	11 May 2021	Sections 5.2.1.1, 5.3 and Appendix 11 updated to allow usage of the PF-02341066 formulated capsules. (Japan specific amendment).
Amendment 24	26 March 2019	Sections 4.3 and 5.5.1 updated to clarify localized anticancer therapy (eg, topical treatment of skin malignancy, intravesical Bacillus Calmette-Guerin [BCG] treatment) may be acceptable upon prior Sponsor and Investigator agreement and prior written Sponsor approval. Section 4.5.1 updated to clarify laboratory confirmation (eg, a serum follicle stimulating hormone levels) may be indicated to confirm postmenopausal status but is not required. Inclusion Criterion #1 (Main study and Enriched Other Cohort) updated to include additional MET mutations potentially conferring sensitivity to PF-02341066. Exclusion Criterion #15 (Main study and Enriched Other Cohort) clarified to exclude patients with known presence of any grade interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis, but not a history of prior radiation pneumonitis. Exclusion Criterion #3 (Enriched Other Cohort) clarified to indicate MET-dependent tumors, prior therapy specifically directed against MET or HGF (Hepatocyte Growth factor); for ALK dependent tumors, prior therapy specifically directed against ALK; for ROS1 dependent tumors, prior therapy specifically directed against ROS1. Section 5.2.4 updated with guidance on

Document	Version Date	Summary of Changes and Rationale
		dosing compliance. MET Amplified NSCLC Cohort high amplification group closed to further enrollment, and remaining enrollment slots transferred to the MET Exon 14 alterations NSCLC subgroup within the Enriched Other cohort. Tumor scans for all patients enrolled in the MET amplification cohort will no longer be collected for and submitted to an independent radiology review laboratory. Added a Reduced Schedule of Activities (Appendix 13) for all ongoing patients to follow. Section 7.5.6 updated to remove requirement for collection of blood samples for plasma analysis of circulating nucleic acids. Section 7.2 updated to remove requirement for collection of blood samples for hypogonadism testing. Administrative changes: updated enrollment numbers; corrected typographical errors, formatting, and protocol inconsistencies; clarified protocol language; italicized text related to cohorts/substudies that are closed and/or no longer enrolling patients; formalized Protocol Administrative Clarification Letters previously issued since Amendment #23. Updated c-Met to MET throughout document. Updated ROS to ROS1 throughout document. Enrollment status as of Amendment #24 (patients treated): Dose Escalation (closed to enrollment): 66

Document	Version Date	Summary of Changes and Rationale
		Rifampin interaction sub-study (closed to enrollment): 18 Itraconazole interaction sub-study (closed to enrollment): 18 RP2D Midazolam Interaction Cohort (closed to enrollment): 15 RP2D Enriched Population Cohort (484 total planned slots for enrollment): ALK-marker positive NSCLC (closed to enrollment): 154 MET amplification NSCLC (closed to enrollment): 41 ROS1 marker positive NSCLC (closed to enrollment): 50 Enriched Other Cohort (closed to enrollment): 171 total planned slots for enrollment; 153 patients treated. ALK Marker Negative NSCLC Cohort #1 (closed to enrollment): 47 ALK Marker Negative NSCLC Cohort #2 (closed to enrollment): 21
Amendment 23	21 February 2017	Added a separate group of approximately 5 NSCLC patients whose tumors harbor MET Exon 14 alterations to be enrolled in clinical sites in Japan in Sections 9.1.3.4 and 9.2.1.4. For patients enrolled in clinical sites in Japan: Pharmacogenomic blood sampling is optional; will not participate in hypogonadism testing; will be followed for survival as a separate group; and female and male patients must be 20 years of age or older to be eligible for enrollment into the trial. Extended survival follow-up for ROS1 marker positive NSCLC patients, and NSCLC patients with tumors harboring

Document	Version Date	Summary of Changes and Rationale
		MET gene amplification or MET Exon 14 alterations to 2 years after the last patient in each of these cohorts has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor in Appendices 9, 10, and 11, respectively. In Appendix 10 (ROS1 Marker Positive NSCLC cohort): Removed requirement for collection and shipment of tumor scans to an independent radiology laboratory for central review for patients enrolled in the ROS1 marker positive NSCLC cohort as central review has been completed. In Appendix 11 (Enriched Other cohort): Added requirement for shipment of tumor scans to an independent radiology laboratory for central review for NSCLC patients whose tumors harbor MET Exon 14 alterations. Removed requirement to collect indirect bilirubin for new and ongoing patients as part of laboratory blood chemistry panel per updated Pfizer protocol template standards. Updated the protocol language to ensure consistency with Pfizer protocol template standards. Minor edits/clarifications to enhance clarity and to correct administrative inconsistencies. Modified the number of patients to be enrolled based upon number of treated patients in Protocol Amendment #23: Dose Escalation (closed to enrollment): 66 Rifampin interaction sub-study (closed to enrollment): 18 Itraconazole interaction sub-study (closed

Document	Version Date	Summary of Changes and Rationale
		to enrollment): 18 RP2D Midazolam Interaction Cohort (closed to enrollment): 15 RP2D Enriched Population Cohort (470 total planned slots for enrollment): ALK-marker positive NSCLC (closed to enrollment): 154 MET amplification NSCLC (low category closed to enrollment; medium and high categories open to enrollment): 68 planned slots for enrollment ROS1 marker positive NSCLC (closed to enrollment): 50 Enriched Other Cohort (open to enrollment): 130 planned slots for enrollment ALK Marker Negative NSCLC Cohort #1 (closed to enrollment): 47 ALK Marker Negative NSCLC Cohort #2 (closed to enrollment): 21
Amendment 22	27 April 2016	Added rationale for analysis of NSCLC patients with tumors harboring MET Exon 14 alterations in Protocol Summary and Section 1.2; added sample size justification for analysis of NSCLC patients with tumors harboring MET Exon 14 alterations in Section 9.1.3.4. Added analysis of NSCLC patients with tumors harboring MET Exon 14 alterations in Section 9.2.1.4. Changed "MET Exon 14 deletion" terminology to "MET Exon 14 alterations" throughout protocol to encompass various types of genetic alterations related to MET Exon 14. Closed enrollment of patients into the MET Low Amplification category and transferred

Document	Version Date	Summary of Changes and Rationale
		remaining open enrollment slots to Enriched Other Cohort as described in Section 9.1.3.2, Appendix 9, and Appendix 11. Other conditions including, but not limited to, slow enrollment in the medium and/or high level MET amplification categories may trigger transfer of additional enrollment slots from these MET gene amplification categories to the Enriched Other cohort as described in Section 9.1.3.2. Added that with Sponsor written approval and IRB/EC notification, 10 to 15 additional patients may be enrolled (for a total overall enrollment of approximately 580 patients) to reach the target enrollment of approximately 40 to 50 NSCLC patients with tumors harboring MET Exon 14 alterations and approximately 20 to 25 male patients for hypogonadism evaluation in the event that overall enrollment is achieved prior to reaching these targets, as described in Sections 9.1.
		CCI [redacted]
		Clarified survival endpoints in Sections 2.1 and 9.2.1. Extended survival follow-up for ROS1 marker positive NSCLC patients, and NSCLC patients with tumors haboring MET gene amplification or MET Exon 14 alterations to 1 year after the last patient's End of Treatment visit in the cohort in Appendices 9, 10, and 11, respectively. In Appendix 11 (Enriched Other cohort):

Document	Version Date	Summary of Changes and Rationale
		Added text indicating that all tumor scans from all NSCLC patients with tumors harboring MET Exon 14 alterations will be collected and held at the investigative site. With Sponsor written approval and IRB/EC notification, the Sponsor may request tumor scans from these patients to be submitted to an independent radiology laboratory for review at a later date. In Appendix 9 (MET amplified NSCLC cohort): Added text indicating that all tumor scans from all NSCLC patients with tumors harboring MET gene amplification will be collected and held at the investigative site. With Sponsor approval and IRB/EC notification, the Sponsor may request tumor scans from these patients to be submitted to an independent radiology laboratory for review at a later date. Clarified that the use of medications known to prolong the QT interval and the use of bradycardic agents should be avoided to the extent possible during the study in Section 5.5.4. Removed respiratory rate assessment from Section 7.3, as this assessment was incorrectly required by the protocol. Removed single-multiple dose pharmacokinetic (PK) cohort from crizotinib-itraconazole drug-drug interaction substudy (Appendix 7) CCI [redacted] due to anticipated significant delays in completing this substudy as a result of dose interruptions and missed PK assessments (rendering patients unevaluable for PK) in an advanced cancer population. Clarified exclusion criterion #5 of crizotinib-itraconazole drug-drug interaction substudy (Appendix 7) to exclude patients

Document	Version Date	Summary of Changes and Rationale
		with history of or current evidence of congestive heart failure in accordance with the itraconazole United States Package Insert. Added clarification to crizotinib-itraconazole drug-drug interaction substudy (Appendix 7) that a total of approximately 25 patients will be enrolled to achieve at least 8 evaluable patients for multiple dose PK, and that patients who are enrolled but not treated may be replaced to obtain 8 evaluable patients for multiple dose PK. Removed expanded ophthalmology assessments (refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography) for NSCLC patients as the requirement for 30 evaluable patients with these assessments had been achieved. Clarified exploratory analysis of PF-06260182 (metabolite of PF-02341066) and definition of treatment periods in Itraconazole Substudy patients, as described in Section 9.2.2.5. Updated Serious Adverse Event reporting contact information in Appendix 1. Added text indicating that all sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose. Corrected typographical errors, administrative inconsistencies, and formatting; included clarification language; italicized text related to cohorts/substudies that are closed and/or no longer enrolling

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		patients.
Amendment 21	07 April 2015	Added details on hypogonadism testing to relevant Schedule of Activities (Appendix 9, 11, and 12), and in the body of the protocol. Testing was added to explore potential effects of PF-02341066 on testosterone levels in males. Additional detail on population PK/PD analyses were included in Section 9.2.4. for added clarity. CCI  Clarified repeat testing if ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2. Added language for PF-02341066 PK sampling at disease progression if patient is still taking PF-02341066. This is only for patients enrolled in the MET-amplified NSCLC, ROS1 marker positive NSCLC and Enriched Other cohorts. Updated survival data collection to every 3 months after discontinuing study treatment until at least one year after the first dose of the last patient enrolled into the MET-amplified NSCLC Cohort to obtain more robust survival data. A similar change to the survival follow-up period was made to the ROS1 marker positive NSCLC Cohort and Enriched Other Cohort (Met Exon 14 alterations NSCLC patients only). Clarified that patients with tumors harboring Met Exon 14 alterations may be eligible to enroll into the Enriched Other cohort. Criterion included to permit patients to

Document	Version Date	Summary of Changes and Rationale
		enroll in the Enriched Other cohort with molecular changes in other than ALK, Met and ROS1 if there are data supporting a biologic rationale for PF-02341066 treatment. Clarified reasons for pharmacogenomic testing at baseline. Updated pregnancy/contraception, medically qualified personnel, study drug storage, adverse event reporting, quality control/quality assurance and publication of study results language to be consistent with the Pfizer global template. Corrected typographical errors and administrative inconsistencies.
Amendment 20	30 June 2014	Administrative changes made: outdated information “italicized”. Replaced ketoconazole with itraconazole for the drug-drug interaction sub-study with a CYP3A strong inhibitor based upon FDA guidance and modified sub-study design. Clarified cohort requirements by adding Appendix 11 for the Enriched Other cohort. This cohort includes patients with cancer with molecular markers other than ALK marker positive NSCLC, ROS1 marker positive NSCLC and MET-amplified NSCLC that may confer sensitivity to PF-02341066. Cross referenced sections of main protocol to this appendix, as applicable. Clarified Dose Limiting Toxicity language and modified protocol language to indicate that the QD MTD cohort will not be expanded. For ALK-negative NSCLC Cohort #2, requirement for no MET or ROS1 testing to occur prior to enrollment was removed. A

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		Note to File was issued 19 June 2012. Yearly ophthalmologic testing (±2 weeks) added for NSCLC patients who have the expanded ophthalmology testing. Clarified that intraocular pressure testing should be done twice for each eye and if test results deviate by more than 2 mmHg of each other a third reading must be obtained. Added chemistry laboratory testing at Cycle 2 Day 15 to be consistent with the product label. Updated the protocol language of several exclusion criteria to ensure consistency with the current version of the Investigator's Brochure and Pfizer standards. In addition, the exclusion criteria for QTc was modified to allow patients with a QTc >470 msec but <490 msec in the presence of a right bundle branch block or with an implanted cardiac pacemaker to enroll into the study upon agreement between the Investigator and Sponsor. For sites using the Western Institutional Review Board, patients who lack capacity to consent for themselves will be excluded from this study. Clarified that if tumor imaging was done within 6 weeks of last dose of PF-02341066, it will not be required to be repeated at the End of Treatment visit. Removed requirement for collection and shipment of tumor scans to an independent radiology laboratory for central review for the ALK-negative NSCLC Cohort #1 and the ALK-positive NSCLC cohort. Note to File was issued 25 October 2012. Added requirement for collection and shipment of tumor scans to an independent radiology laboratory for central review for

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		the ROS1 marker positive NSCLC cohort. Increased sample size for ROS1 marker positive NSCLC cohort from 30 to 50 patients and provided the rationale for change. Note to File was issued 12 November 2012. Increased the number of patients enrolled for both the rifampin and itraconazole drug-drug interaction sub-studies from 15 to a maximum of 25 in order to obtain 8 evaluable patients each. Increased the overall sample size to approximately 550 patients based on additional patient enrollment into the ROS1 marker positive NSCLC cohort, the Enriched Other cohort and the rifampin and itraconazole drug-drug interaction sub-studies. Protocol template language updated to be consistent with Pfizer standards. Corrected typographical errors.
Amendment 19	27 April 2012	Starting dose of PF-02341066 reduced from 200 mg BID to 250 mg QD for ketoconazole sub-study. In addition, clarified dose administration instructions. For rifampin and ketoconazole sub-studies clarified that on days of PK sampling patients must take their morning doses at the clinic. Administrative changes made: outdated information "italicized". Text previously italicized, was bolded and text previously bolded was underlined. Clarified cohort requirements by adding Appendices for: cMET-amplified NSCLC, ROS1-positive NSCLC, and ALK-negative NSCLC #2 cohorts. Cross referenced

Document	Version Date	Summary of Changes and Rationale
		sections of main protocol to appendices, as applicable. Removed requirement for tumor assessments for rifampin and ketoconazole sub-studies. Clarified that patients with Gilbert's syndrome are permitted to enter the study with Sponsor approval. Patients will be eligible to enter the study if they experienced any of the following within 6 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus. For MET-amplified NSCLC cohort eligibility, removed reference to the test needing to be FISH.
Amendment 18	24 February 2012	Added 2 drug-drug interactions sub-studies: rifampin, ketoconazole. Included rationale for the number of ROS1-positive (positive for chromosomal translocations in the ROS1 gene) NSCLC patients to be enrolled. Clarified the MET-amplified NSCLC cohort; enrolling 3 patient categories based on degree of MET amplification (low, medium, high). Rationale for the numbers of patient updated in each category. Updated concomitant medications for consistency across all PF-02341066 studies. Clarified required imaging frequency should renal cysts be diagnosed. Updated adverse event guidelines to be

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		consistent with Pfizer standards.
Amendment 17	27 September 2011	Added a second cohort of ALK-marker negative NSCLC. Added more detailed ophthalmology testing for NSCLC patients. Defined MET-amplified NSCLC and provided the rationale for the number of patients required.
Amendment 16	08 August 2011	Added monitoring guidance for patients developing renal cysts and guidelines to manage potential cases of drug-induced liver injury. Increased the number of patients enrolling in the dose escalation cohort and enriched population cohort. Removed the Day -7 dosing requirement for all patients except those enrolled in the dose escalation cohort. Modified the minimal acceptable platelet count eligibility criterion only for patients enrolled into the enriched population cohort. Clarified the dose reduction levels for patients enrolling into the enriched population cohort. Updated and clarified the dose modification guidelines. Allowed solution dosing as an alternative to tablet dosing. Clarified ophthalmology examination guidelines. Updated adverse event guidelines to be

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		consistent with Pfizer standards.
Amendment 15	5 August 2010	Safety monitoring for potential AEs of pneumonitis was added, exclusion criteria were updated to exclude patients with interstitial fibrosis or interstitial lung disease, and treatment guidelines of selected crizotinib-related AEs was added.
Amendment 14	1 June 2010	The survival monitoring period was modified, the food restriction criteria for prior to Cycle 2 Day 1 was removed, and evaluation of active metabolites in addition to the parent was added.
Amendment 13	8 April 2010	Atrial fibrillation criteria were modified to only exclude uncontrolled atrial fibrillation, Coumadin dosing restriction was removed, PK sampling time points for ALK-negative, Asian, and QD patients were modified.
Amendment 12	9 November 2009	An ALK-negative NSCLC cohort with a cycle length of 3 weeks was added. This cohort consisted of NSCLC patients who were negative for the ALK translocation as determined by the Abbott Molecular ALK break-apart FISH IUO assay used in Protocols A8081007 and A8081005. A minimum of 25 to a maximum of 40 evaluable patients were planned to be enrolled into this cohort. The dose-escalation cohort was reopened in order to determine a QD MTD. The creatinine eligibility criteria were widened from ≤1.5 x ULN to ≤2 x ULN. Day -7 dosing for all patients (except dose escalation and Asian patients) was waived. 50-mg and 100-mg tablets were to replace the 50-mg and 100-mg capsules once the capsule supply was depleted. A screening ophthalmology examination was added, with any follow-up as clinically

Document	Version Date	Summary of Changes and Rationale
		indicated. Crizotinib was allowed to be taken without regard to meals after Cycle 2 Day 1. Increased the number of patients to be allowed to enter the study. Patients with tumors having an ROS1 gene translocation were added as an option to the RP2D-enriched population cohort.
Amendment 11	30 June 2009	Patients with documented Gilbert's syndrome were allowed to enter the study.
Amendment 10	14 May 2009	PET by both FDG-PET and FLT-PET was added as a new substudy, added an optional biopsy at time of disease progression, increased the number of patients allowed to enter, and modified PK collection criteria for Asian patients.
Amendment 9	5 March 2009	Patients with pulmonary embolism within 6 months prior to starting study treatment were allowed to enter the study on a case-by-case basis.
Amendment 8	18 August 2008	Patients with stable brain metastases were allowed to enter the study.
Amendment 7	23 June 2008	Patients with ECOG performance status scores of 2 were allowed to enter the RP2D-enriched population cohort, modified PK sampling time points, added MET translocation/fusions as an option for the RP2D-enriched population cohort, and modified Cycle 1 Day 1 PK sampling for patients exempted from Day -7 dosing.
Amendment 6	4 March 2008	Patients with cytogenetic abnormalities defined in the RP2D-enriched population cohort could enter a lower cohort in the dose-escalation cohort that was shown to be tolerated (without Day -7 dosing) but were not considered evaluable for dose limiting toxicity assessment, criteria were added for

Document	Version Date	Summary of Changes and Rationale
		top dose to be evaluated, exempted patients enrolled in the RP2D-enriched population cohort from Day -7 dosing on a case-by-case basis, allowed dosing with a small amount of food starting on Cycle 2 Day 2, and modified PK sampling time points.
Amendment 5	23 January 2008	Eligibility criteria for albumin were removed, and PK time points were added to better characterize the half-life of crizotinib.
Amendment 4	29 October 2007	EML4-ALK-positive NSCLC patients were allowed to enter, QTc eligibility criteria were modified from >450 msec for males and >470 msec for females to >470 msec for both males and females, and the exclusion criterion of "prior radiotherapy to >25% of bone marrow" was removed.
Amendment 3	27 April 2007	Two RP2D cohorts were added: one to evaluate the effect of an MDZ drug-drug interaction and 1 to evaluate clinical activity in an enriched population (enriched population included patients with tumors harboring MET gene amplification or mutation, or anaplastic large cell lymphoma cases with ALK translocation) to obtain early evidence of clinical activity. In addition, [^{18}F] FLT-PET was evaluated in a small subset of patients in the RP2D-enriched cohorts (N=6) as a noninvasive measure of tumor inhibition. Lastly, 12 patients in this RP2D-enriched cohort were to participate in a fed/fasted study to characterize the effect of food on the PK of crizotinib.
Amendment 2	30 August 2006	Lymphoma/myeloma patients were allowed to enter, and indirect bilirubin, bicarbonate, and lactate dehydrogenase were added as part of the clinical laboratory test battery.
Amendment 1	19 January 2006	Minor changes were made in PK time points.

Document	Version Date	Summary of Changes and Rationale
Original protocol	05 December 2005	N/A

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

ITALICIZED TEXT IS OUTDATED INFORMATION AND SHOULD BE DISREGARDED

SUMMARY

Indication:

Advanced malignancies (with the exception of leukemia) refractory to standard of care therapy, or for whom no standard of care therapy is available.

Rationale:

Cancer remains an area with tremendous unmet medical need. Each year, an estimated 23 million people worldwide are diagnosed with the disease and more than half die from it. Across the seven major markets (US, 5 EU and Japan), three million individuals are diagnosed with cancer annually, and 1.5 million died from it in 2002. The three cancers representing the largest frequency include non-small cell lung cancer (NSCLC), breast cancer, and colorectal cancer. Taken together, these cancers account for more than 1 million cases of cancer per year in the major geographic markets.

An emerging paradigm in oncology is that robust clinical efficacy can be obtained with well-tolerated kinase inhibitors directed towards oncogenic kinases bearing activating mutations or other signal transduction perturbations. Recent examples include Gleevec® in Gastrointestinal stromal tumors (GIST) with mutant c-Kit, Tarceva® and Iressa® in NSCLC with mutant epidermal growth factor receptor (EGFR), and SU11248 targeting the VHL-dependent vascular endoethelial growth factor (VEGF) pathway in renal cell carcinoma (RCC).

MET/Hepatocyte growth factor receptor (HGFR) has been well characterized for its role in regulation of cell growth, migration, and invasion of both tumor cells and endothelial cells. An extensive body of literature indicates that MET/HGFR is one of the receptor tyrosine kinases (RTKs) most frequently mutated or otherwise abnormally activated in late-stage human cancer. When activated, MET/HGFR plays a critical role in regulation of tumor oncogenic processes such as mitogenesis, survival, and invasive growth, and especially in the metastatic process. Additionally, the emerging role of MET/HGFR in the regulation of tumor angiogenesis indicates potential for dual anti-tumor and anti-angiogenic mechanisms. Activating mutations in MET/HGFR have been identified in multiple patient populations, including NSCLC, small cell lung cancer (SCLC), renal cancers, head and neck cancers, and hepatocellular cancer. In addition to activation driven by mutation, MET/HGFR gene amplification/ overexpression resulting in increased kinase activity has been frequently observed in gastric and colorectal cancer patients. Furthermore, MET/HGFR is also activated in human tumors by other mechanisms (eg, autocrine loops, paracrine activation from tumor-associated stroma). Collectively, the dysregulation of MET/HGFR in tumors by multiple mechanisms along with the potential role of MET/HGFR in tumor angiogenesis comprises a large potential patient population. Most importantly, in preclinical proof of concept studies, both neutralizing monoclonal antibody and RTK inhibitor exhibit convincing antitumor activity in several xenograft models, which supports the concepts that MET is a valid target for treatment of cancer.

Mutations in Met Exon 14 were previously reported to be oncogenic drivers in preclinical models of lung cancer (Ma et al, 2003; Ma et al, 2006; Kong-Beltran et al, 2006).[22,23,24] Given the role of MET/HGFR in regulation of cell growth, migration, and invasion of both tumor cells and endothelial cells, there is increasing interest in understanding the potential effectiveness of tyrosine kinase inhibitors as a treatment in NSCLC patients with tumors harboring MET Exon 14 alterations. Paik et al (2015)[21] reported on 3 crizotinib-treated patients with NSCLC harboring alterations leading to MET exon 14 skipping. All 3 patients were shown to have a partial response.

Mechanism of Action and Pharmacodynamic Relationship to Anti-Tumor Efficacy:

PF-02341066 is a selective MET/HGFR aminopyridine tyrosine kinase inhibitor and a potent ATP-competitive inhibitor of recombinant, human MET/HGFR kinase activity with a mean K_i of 4 nM.

The potency of PF-02341066 against MET/HGFR and selectivity against kinases identified in preliminary biochemical screens was further addressed in cellular kinase phosphorylation ELISAs. In these studies, PF-02341066 inhibited HGF-stimulated or constitutive total tyrosine phosphorylation of wild type MET/HGFR with a mean IC_{50} value of 11 nM across a panel of human tumor cell lines and demonstrated similar values in mouse or canine epithelial cell. PF-02341066 demonstrated minimal variation (<4-fold variance) across the panel of cell lines, which were selected for these studies by virtue of increased expression of the ABC family of transporters that are implicated in tumor multidrug resistance. These data indicate a moderate but manageable potential for intrinsic resistance to PF-02341066 due to expression of efflux transporters.

The selectivity of PF-02341066 was evaluated in a panel of cell-based assays for selected kinases that were closely related to MET/HGFR and/or were identified in biochemical assays. In these studies, PF-02341066 selectivity for MET/HGFR (IC_{50} = 11 nM) was greater than 1000-fold relative to CCI or Sky RTKs, greater than 200-fold relative to IRK and Lck, approximately 40- to 60-fold relative to Axl, Tie2, TrkA, and TrkB, and approximately 20- to 30-fold relative to RON kinase. Further studies to investigate the likelihood of inhibition of selected targets (ie, Tie-2) in pharmacodynamic assays in vivo indicated that pharmacologically relevant inhibition of these kinases by PF-02341066 would be unlikely at efficacious dose levels. In contrast, PF-02341066 demonstrated potent activity against nucleophosmin (NPM)-anaplastic lymphoma kinase (-ALK), an oncogenic fusion protein variant of the ALK RTK, which results from a chromosomal translocation and is implicated in the pathogenesis of human ALCL (Pulford et al, 2004).[4] These data indicate that the pharmacological activity of PF-02341066 is likely mediated by inhibition of MET/HGFR and ALK RTKs and their oncogenic variants.

To also investigate for potential antiangiogenic activity, PF-02341066 was shown to inhibit HGF-mediated HUVEC endothelial cell survival (IC_{50} = 11 nM) and matrigel invasion (IC_{50} = 35 nM) as well as HMVEC endothelial cell tubulogenesis in fibrin gels (IC_{50} = ~80 nM). These data suggest that antitumor efficacy of PF-02341066 may be mediated by both direct effects on tumor cell growth or survival as well as antiangiogenic mechanisms.

To evaluate the pharmacodynamic (PD) inhibition of MET/HGFR by PF-02341066, GTL-16 gastric carcinoma tumors were harvested at several time points following oral administration of PF-02341066 in both single-dose and repeat-dose (steady-state) studies. MET/HGFR phosphorylation status in tumors was quantitated by ELISA over a range of doses. With focus on steady-state PD studies (11-day administration) to draw a correlation with tumor growth inhibition, PF-02341066 demonstrated the following:

- At 50 mg/kg/day: 100% tumor growth inhibition correlated with complete inhibition of MET/HGFR phosphorylation in GTL-16 tumors sustained for 24 hours. (25 mg/kg: near complete inhibition of both phosphorylation and tumor growth). At 12.5 mg/kg/day: 60% tumor growth inhibition correlated with 80 to 90% inhibition of MET/HGFR phosphorylation at 1 to 8 hours which decreased to 50% to 60% inhibition by 16 to 24 hours.

- At 6.25 mg/kg/day: non-significant trend toward tumor growth inhibition correlated with 30% to 50% inhibition of MET/HGFR phosphorylation at 1 to 8 hours with full recovery by 16 hours.

In summary, MET has been shown to be a valid target, and PF-02341066 is a potent and selective inhibitor of MET. PF-02341066 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window, providing increased confidence that mechanism-based toxicity will not be limiting in the clinic.

Objectives:

1. Determine the safety profile of PF-*02341066 including identification of dose limiting toxicity (DLT) and maximum tolerated dose (MTD).*

2. *Determine the recommended Phase 2 doses (RP2D) and regimens of PF-02341066.*

3. Determine pharmacokinetic profile of PF-02341066 following oral administration *including the effect of food*.

4. *Perform initial evaluation of PF-02341066 related CYP3A4 inhibition using midazolam (MDZ) as a probe.*

5. *Determine the effect of the co-administration of rifampin on the multiple-dose plasma pharmacokinetics of PF-02341066.*

6. *Determine the effect of the co-administration of itraconazole on the plasma pharmacokinetics of PF-02341066.*

CCI [redacted]

8. Document any evidence of anti-tumor activity of PF-02341066.

CCI [redacted]

10. Evaluate the effect of PF-02341066 on parameters related to hypogonadism in males.

Trial Design:

Open label, multi-center Phase 1 dose escalation, safety, pharmacokinetic CCI [redacted] study.

Endpoints:

1. *To determine the MTD and potential phase 2 dose(s) of PF-02341066.*

2. To characterize the plasma pharmacokinetic (PK) profile following oral administration of PF-02341066, *including the effect of food and a midazolam study to evaluate the potential for time-dependent inhibition (TDI) of CYP3A4 at different PF-02341066 dose levels.*

3. To determine the safety, tolerability *and the DLT* of PF-02341066.

4. *Plasma PK parameters of PF-02341066 and its metabolite(s) following multiple oral doses of PF-02341066 alone and when co-administered with rifampin.*

5. *Plasma PK parameters of PF-02341066 and its metabolite(s) following single (if possible) and multiple oral doses of PF-02341066 alone and when co-administered with itraconazole. As of Protocol Amendment #22, the Single and Multiple-Dose Design will no longer be performed.*

CCI [redacted]

7. To document evidence of anti-tumor activity, including tumor response rate (by RECIST for solid tumors and response criteria for lymphomas and multiple myelomas), duration of response, time to response, progression free survival, overall survival, probabilities of survival at 6 and 12 months and others as appropriate.

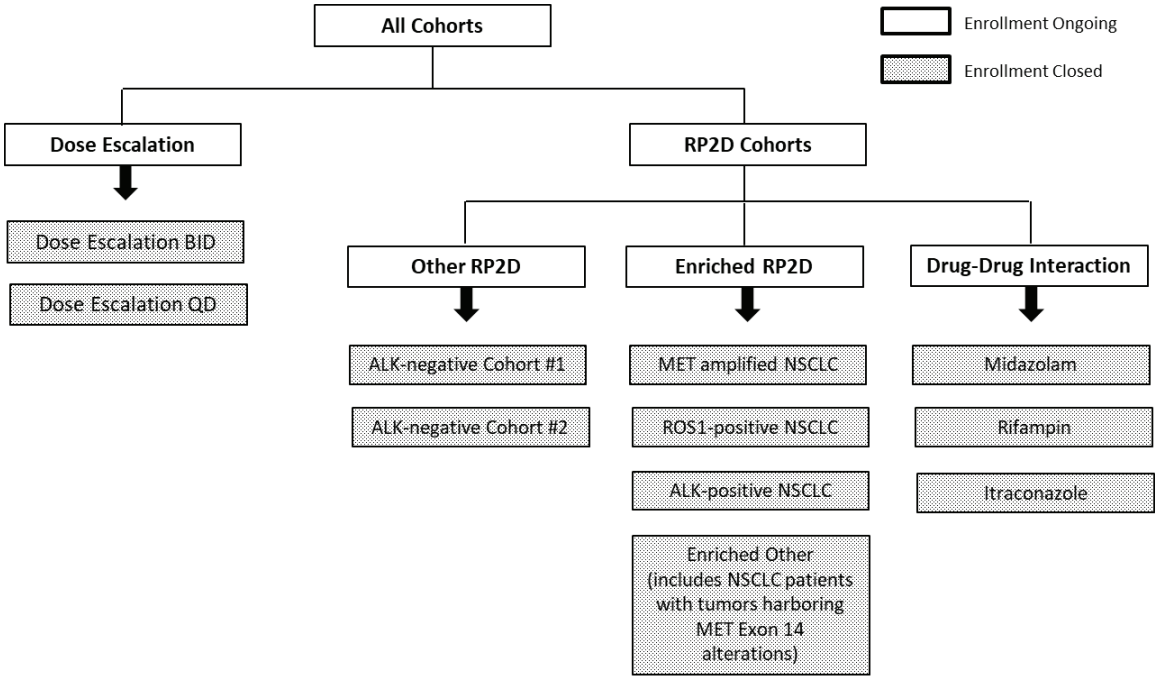
CCI

9. Blood testosterone and other blood parameters associated with detecting hypogonadism in males [*Appendix 12*].

Trial Treatments:

Figure 1 provides the status of each of the RP2D cohorts of this study, based on Protocol Amendment #24.

Figure 1. Summary of RP2D Cohorts Based on Protocol Amendment #24



Dose Escalation:

PF-02341066 will be administered orally on an empty stomach once a day (QD) or twice a day (BID) in continuous 28-day cycles (see Schedule of Activities). However, with the approval of Amendment #14, PF-02341066 may be administered without regards to meals. *There will be a lead-in period in which single-dose pharmacokinetics of PF-02341066 or MDZ (for patients participating in the MDZ sub-study) will be characterized prior to initiation of continuous dosing in the first cycle of treatment unless patients who are exempted from the Day -7 lead-in dose (see below). With the exception of cohorts in which the evaluation of a MDZ interaction is scheduled for patients who are exempted from the Day -7 lead-in dose (see below), all other patients will receive a single dose of PF-02341066 seven days prior to the start of Cycle 1 (Day –7) in order to characterize the complete PK profile of PF-02341066 after a single dose. With the approval of Amendment #13, only patients enrolled in the QD dose escalation part of the study or Asian patients enrolled in*

any cohort will have the Day -7 lead-in dose. 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-02341066 on Cycle 2 Day 1. During the study, real-time pharmacokinetic monitoring will be conducted as much as possible.

After approval of Amendment #16, Day -7 dosing will only be required for dose escalation cohorts.

The PF-02341066 dose regimen may be changed if the pharmacokinetics and safety data suggest that a discontinuous regimen or another dosing frequency may be preferable. Dosing of oral PF-02341066 will be based on flat milligram increments without adjustment for body size. The dose will be 50 mg QD in the initial cohort.

Patients will be successively assigned to the next available treatment slot within a dose level.

Each dose cohort will initially include a minimum of 3 evaluable patients for assessment of toxicity within the first cycle. Dose escalation will occur in 100% increments until either of the following occurrences: (1) drug related toxicity of Grade 2 severity occurs in 2 or more patients within a dose level; or (2) mean unbound $AUC_{0\text{-}24}$ exceeds 2.4 μg·h/mL (the highest unbound AUC tested in the one-month toxicology studies). Escalation increments will then become 40%. In any cohort, if 1 patient experiences a DLT, 3 additional patients will be enrolled to that dose level. If 2/3 or 2/6 patients experience a DLT, no further dose escalation will occur.

If the highest cohort being evaluated is closed to new enrollment, additional patients who have a cytogenetic abnormality as described in Section 4.1 (Inclusion #1) may enter the study at the previous dose level. These patients will not participate in the midazolam sub-study and will not have the Day -7 lead-in dose of PF-02341066 or any corresponding PK assessments. They will be evaluated for safety but will not contribute to the DLT assessments. These patients will enter the study on Day 1 of Cycle 1. Additionally, patients scheduled to enroll in the RP2D enriched population cohort (see RP2D Cohorts Section) may be exempted from the Day -7 lead-in dose depending on the their overall medical condition. This exemption will be granted on a case-by-case basis as agreed upon by the investigator and Sponsor. Upon Institutional Review Board/Ethics Committee (IRB/EC) approval of Amendment #12, non-Asian patients will also be exempt from the Day -7 lead-in dose. Amendment #13 extends the requirements as described in the first paragraph of this section.

Doses may not be modified until a DLT has been reached. The study investigator may implement dose suspension in order to ensure patient safety; this will be considered dose-limiting toxicity for the purpose of dose-escalation if PF-02341066 has to be suspended for more than 3 days. Patients who discontinue treatment before completing Cycle 1 (DLT evaluation) for reasons other than treatment-related toxicity will be replaced.

One or more lower dose level(s) may be tested in search of the MTD, defined as the dose level immediately below that in which 2/3 or 2/6 patients experience DLTs. Dose escalation

may be stopped if 1) the maximum administered dose (MAD) produces PF-02341066 concentrations that are at least 5-fold greater than the projected target concentration, 2) exposure plateaus as the dose is increased and 3) MTD cannot be reached within a reasonable dose range (up to 2000 mg). The MTD for both QD and BID dosing may be determined.

MDZ interaction sub-study: *The potential for CYP3A inhibition due to PF-02341066 will be evaluated using MDZ as a CYP3A4 substrate probe at 3 dose levels of PF-02341066: the next higher dose after the initial dose, the efficacious dose, and the RP2D (see Figure 4). The MDZ interaction study will be conducted starting in the second dose cohort, and will be conducted in a higher dose in which the trough unbound plasma concentration of PF-02341066 at the steady state will equal or exceed the projected target unbound concentrations (8.1-12.8 nM) if target unbound plasma concentrations of PF-02341066 are not achieved in the second cohort. In the second cohort or the efficacious dose cohort, at least 3 evaluable patients per cohort will be assessed for the effect of repeat PF-02341066 administration on the pharmacokinetics of midazolam. If a significant change in MDZ clearance (>3-fold increase in MDZ AUC in all 3 patients, or > 5-fold increase in 2 or more patients) is observed at any PF-02341066 dose level, further dose escalation may be terminated. The effect of PF-02341066 on CYP3A activity will be evaluated at the RP2D. Eight evaluable patients will be required for the MDZ interaction study in one of the RP2D cohorts (see RP2D Cohorts Section). Patients enrolled in the MDZ interaction sub-study 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-02341066 on Cycle 2 Day 1.*

Rifampin interaction sub-study:

This sub-study is to determine the effect of the co-administration of rifampin on the multiple-dose plasma pharmacokinetic profile of PF-02341066. The starting dose of PF-02341066 will be 250 mg BID and the dose of rifampin will be 600 mg QD. Approximately 25 patients with advanced malignancies refractory to standard of care therapy, or for whom no standard of care therapy is available will be enrolled into this sub-study to obtain 8 evaluable patients. The rationale for the PF-02341066 starting dose of 250 mg BID is provided below.

In vitro studies demonstrated that CYP3A4/5 are the major enzymes involved in the metabolic clearance of PF-02341066. Co-administration of a single 250 mg PF-02341066 dose with rifampin (600 mg QD), a strong CYP3A inducer, resulted in 81.8% and 68.5% decreases in PF-02341066 AUC_{inf} and C_{max}, respectively, compared to when PF-02341066 was given alone. As PF-02341066 is also a CYP3A inhibitor, the magnitude of the effects of CYP3A inducers on steady state PF-02341066 exposures may differ from those seen after single doses. A mathematical modeling approach based on preclinical and clinical data indicate that rifampin co-administration is likely to result in an approximately 36% decrease in the PF-02341066 AUC. Based on these findings no safety issues in using a 250 mg BID PF-02341066 dose in combination with rifampin are anticipated.

Please see Appendix 6 for further details.

Note that the Rifampin interaction sub-study will be enrolled prior to the enrollment of patients on the itraconazole interaction sub-study.

Itraconazole interaction sub-study:

This sub-study is to determine the effect of itraconazole on the multiple-dose plasma pharmacokinetics of PF-02341066 when itraconazole is co-administered. If multiple-dosing of PF-02341066 in combination with itraconazole is tolerable (as defined in the TRIAL DESIGN Section), a cohort of patients may be also enrolled to determine the effect of itraconazole on single and multiple-dose plasma pharmacokinetic profiles of PF-02341066. As of Protocol Amendment #22, the Single and Multiple-Dose Design will no longer be performed. The starting dose of PF-02341066 will be 250 mg QD and approximately 25 patients will be enrolled to obtain at least 8 evaluable patients for multiple-dose PK.

The magnitude of the effects of CYP3A inhibitors on steady state PF-02341066 exposures may differ from those seen after a single dose of PF-02341066 as PF-02341066 is also a CYP3A inhibitor. An autoinhibition-mediated change in apparent clearance of PF-02341066 was observed during chronic PF-02341066 treatment. There are limited data with single doses of PF-02341066 administered with ketoconazole (200 mg BID), a strong CYP3A inhibitor. Co-administration of a single 150 mg oral dose of PF-02341066 in the presence of ketoconazole, resulted in increases in PF-02341066 systemic exposure, with PF-02341066 AUC_{inf} and C_{max} values that were approximately 3.2 fold and 1.4 fold higher, respectively, than those seen when PF-02341066 was administered alone. SIMCYP (a population based pharmacokinetics modeling simulator) modeling based on preclinical and clinical data, predict a 2-fold increase in PF-02341066 AUC when PF-02341066 at steady state is co-administered with ketoconazole. The effect of itraconazole on PF-02341066 exposure cannot be properly predicted due to the lack of a validated physiologically based pharmacokinetic model. Based upon recent FDA guidance[15] on the use of ketoconazole, ketoconazole was replaced with another CYP3A strong inducer, itraconazole. However, it is expected that the magnitude of the effect of itraconazole would be no greater than that of ketoconazole given that itraconazole had a smaller inhibitory effect on the exposure of midazolam, a CYP3A probe, than ketoconazole. Therefore, the PF-02341066 exposure at 250 mg QD when administered with itraconazole is expected to be similar or lower than the PF-02341066 exposure at the maximum tolerated dose of 250 mg BID when administered alone. For these reasons, the same starting dose of PF-02341066 proposed for the ketoconazole drug-drug interaction, will be used for the itraconazole drug-drug interaction, ie, 250 mg QD. However, should additional data arise impacting this assumption, the Sponsor will adjust the starting dose of PF-02341066 accordingly.

Please see Appendix 7 for further details.

RP2D Cohorts: *The RP2D will be determined as a dose below or equal to MTD, at which PF-02341066 is unlikely to cause an inhibition of CYP3A4 activity.* There will be two RP2D cohorts:

1. The first RP2D cohort will evaluate drug-drug interactions. This includes the MDZ, rifampin and itraconazole interaction sub-studies noted above.

a. The MDZ interaction sub-study requires 8 evaluable patients. Enrollment is closed with a total of 15 patients treated.

b. The Rifampin interaction sub---study requires 8 evaluable patients. Enrollment is closed with a total of 18 patients treated.

c. The Itraconazole interaction sub--study requires 8 evaluable patients. Enrollment is closed with a total of 18 patients treated.

2. The second RP2D cohort will be composed of an enriched population of approximately 484 patients:

a. A group of ALK marker positive NSCLC patients. Enrollment is closed with a total of 154 patients treated.

b. Three categories of NSCLC patients with MET amplification defined as:

a. *MET/CEP7 (centromeric region of chromosome 7) ratio of ≥5.0 (Group 1);* As per the Protocol Administrative Clarification Letter (PACL) dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to ≥4.0. As per the PACL dated 11 September 2018, this group was closed to further enrollment. The remaining 14 enrollment slots were transferred to the MET exon 14 alterations subgroup within the Enriched Other cohort.

b. *MET/CEP7 ratio of >2.2 to <5.0 (Group 2);* As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to >2.2 to <4.0 and this group was closed to further enrollment. The remaining 13 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort;

c. *MET/CEP7 ratio of ≥1.8 to ≤2.2 (Group 3);* As per the PACL dated 12 October 2015, this group was closed to further enrollment.

c. *A total of 68 slots are planned for enrollment.* As of IRB/EC approval of Protocol Amendment #24, enrollment is closed with 41 patients treated. Further details for the MET amplified NSCLC cohort are provided in Appendix 9.

d. A group of 50 NSCLC patients positive for chromosomal translocations at ROS1 gene, including but not limited to CD74-ROS1 and SLC34A2-ROS1 fusion events, will be enrolled. Enrollment is closed with 50 patients treated. Further details for the ROS1 marker positive NSCLC cohort are provided in Appendix 10.

e. Approximately 171 patients with disease with molecular markers (other than ALK marker positive NSCLC and ROS1 marker positive NSCLC) that may confer sensitivity to PF-02341066 may also be enrolled into an 'Enriched

Other' cohort. This cohort also includes NSCLC patients with tumors harboring MET Exon 14 alterations. Sponsor approval is required for enrollment. Further details for the Enriched Other cohort are provided in Appendix 11. After IRB/EC approval of Amendment #18, patients with NSCLC that is positive for ALK chromosomal translocations or gene amplifications will not be allowed to enter the Enriched Other cohort. As of the PACL dated 07 December 2017, the remaining 13 open enrollment slots in the Enriched Other cohort were assigned specifically to NSCLC patients with tumors harboring MET Exon 14 alterations rather than the broader Enriched Other cohort. Thus, the Enriched Other cohort will be open only for enrollment of NSCLC patients with MET Exon 14 alterations. As of the Investigator Communication Letter dated January 7, 2019, further enrollment of NSCLC patients with tumors harboring MET exon 14 alterations is closed.

f. *ALK Marker Negative NSCLC Cohort #1: This cohort will consist of NSCLC patients who are negative for the ALK translocation as determined by the ALK break apart fluorescence in situ hybridization (FISH) assay used in Protocols A8081007 and A8081005. A minimum of 25 to a maximum of 50 evaluable patients will be enrolled into this cohort. Patients will be dosed at the RP2D, ie, 250 mg BID of PF-02341066, with a cycle length of 3 weeks. Enrollment is closed with 47 patients treated.*

g. *ALK Marker Negative NSCLC Cohort #2: This cohort will consist of NSCLC patients who are negative for the ALK translocation as determined by the ALK break apart fluorescence in situ hybridization (FISH) assay as determined by the central laboratory selected by the Sponsor. Patients may have been pre-screened and determined to have ALK-marker negative NSCLC by a local test but no molecular testing for MET or ROS1 should have occurred prior to enrollment. As of Note to File dated 19 June 2012, the requirement that no molecular testing for MET or ROS1 was to occur prior to enrollment was removed. Thus, MET or ROS1 testing may have been performed prior to patient entry into this cohort. However if the test result for either MET or ROS1 was positive, then the patient could not be enrolled into this cohort. At least 20 patients will be enrolled into this cohort. Patients will be dosed at the RP2D, ie, 250 mg BID of PF-02341066, with a cycle length of 3 weeks. Enrollment is closed with 21 patients treated. Please see Appendix 8 for further details.*

CCI [redacted]

CCI [redacted] *In addition, if possible, up to 6 patients will undergo pre- and post-dose [^{18}F]-fluorothymidine (FLT)-positron emission tomography (PET). Also, if possible, the same patients who have biopsies performed, will undergo [^{18}F]-FLT-PET.*

A separate sub-study with at least 6 evaluable patients with MET mutation or amplification will undergo pre- and post-dose [^{18}F]-FLT-PET and [^{18}F]-fluorodeoxyglucose (FDG)-PET. With the approval of Amendment #13 by the IRB/EC, no additional patients will undergo

PET imaging. Finally, 12 evaluable patients in this cohort will participate in a fed/fast sub-study. Clinical sites in Korea will not participate in this sub-study. Depending upon the overall results from the RP2D cohorts, a different dose/schedule may be tested in additional cohorts.

Statistical Methods:

This is a Phase 1, open-label, multi-center, dose escalation study. The number of patients to be enrolled will depend upon the observed safety profile and study objectives, which will determine the number of patients per dose level, the number of dose escalations and the number of cohorts. Approximately 600 patients will be enrolled in the study including patients in the dose escalation and RP2D cohorts [see Figure 1]. All patients who receive at least 1 dose of PF-02341066 will be included in the study analyses. All data will be tabulated and summarized using descriptive statistics.

The plasma concentration-time data of PF-02341066 will be analyzed using non-compartmental methods to derive standard pharmacokinetic (PK) parameters including $AUC_{0\text{-last}}$, C_{max} and T_{max} for individual patients. Descriptive statistics of the PK parameters will be provided in tabular form. *The plasma concentration-time data of MDZ will be analyzed using non-compartmental methods to derive standard PK parameters including $AUC_{0\text{-last}}$, C_{max} and T_{max}. In the RP2D cohort, a mixed effects model will be used to analyze log-transformed MDZ $AUC_{0\text{-last}}$ for evaluation of the potential CYP3A4 inhibition due to PF-02341066. In the rifampin and itraconazole drug-drug interaction sub-studies, a mixed effect model will be used to analyze log-transformed PF-02341066 $AUC_{0\text{-tau}}$ to assess the interaction.*

Inferential statistics will be provided for assessing food effect, inhibition of CYP3A and the comparison of anti-tumor effects in ALK marker negative NSCLC patients and ALK marker positive NSCLC patients (from Protocols A8081007 and/or A8081005, as appropriate). In the food effect sub-study, a mixed effect model will be used to analyze log transformed $AUC_{0\text{-last}}$ between fasting and fed conditions for the evaluation of the food effect.

Schedule of Activities

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

*** See Appendix 6 (Rifampin Sub-study) and Appendix 7 (Itraconazole Sub-study), Appendix 8 (ALK-Negative NSCLC Cohort #2), Appendix 9 (patients with MET-amplified NSCLC), Appendix 10 (ROS1 marker positive NSCLC patients), and Appendix 11 (Enriched Other cohort).

Note: Upon IRB/EC approval of Protocol Amendment #24, ongoing patients will follow a Reduced Schedule of Activities as indicated in Appendix 13.

Protocol Activity	**Screening***	**Lead-in PK Period[31]**	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks******	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day -7**	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Informed consent[1]	X								
Medical history[2]	X								
Physical examination[3]	X		X		X		X		X
Weight, height, temperature, BP, pulse[4]	X		X		X		X		X
ECOG performance status[5]	X		X		X		X		X
12-Lead electrocardiogram (ECG)[6]	X		X	X	X				
Registration/Hematology[7]	X		(X)	X	X		X		X
Chemistry[8]	X		(X)	X	X	X	X		X
Coagulation tests[9]	X		(X)	X	X				
Urinalysis[10]	X		(X)		X		X		
Ophthalmology Examination[32]	X *[X]*			*[X]*			*[Cycle 3, one year and yearly thereafter]*		*[X]*
Safety assessment (adverse events)[11]	X		X	X	X	X	X		X
Tumor assessment *,***[12]	X							X	X

Protocol Activity	**Screening***	**Lead-in PK Period[31]**	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks******	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day -7**	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Survival[13]	Until at least 1 year after the patient's final dose (except for MET-amplified NSCLC Cohort, ROS1 marker positive NSCLC Cohort and NSCLC patients with tumors harboring MET Exon 14 alterations enrolled into the Enriched Other Cohort)								
Concomitant medications[14]	X		X	X	X	X	X		
Contraceptive Check (as applicable)[34]	X		X		X		X		X
Female patients: Pregnancy test[15]	X		X		X		X		X
Special Laboratory Studies									
Plasma sampling for full PF-02341066 PK in patients not participating in the MDZ study[16]		*X*	*X*	*X*	*X*				
Plasma sampling for full PF-02341066 PK in patients participating in the MDZ study[17]			*X*	*X*	*X*				
Two plasma sampling points for PF-02341066 PK[18]						X	X (up to Cycle 5; also at disease progression if patient is still taking PF-02341066)		
Plasma sampling for full MDZ PK[19]		*X*			*X*				
Blood sample for PF-02341066 metabolite profiling[20]				*X*					
Blood sample for pharmacogenomics[21] (Optional for clinical sites in Japan)	X								
24-hour urine collection for PF-02341066[22]				*X*					
Urine Sample for 6 beta-hydroxycortisol/cortisol (6ß-OHC/C) ratio[23]			*X*	*X*	*X*				
CCI [redacted]									
Plasma sample for circulating free nucleic acid profiling[27] (As per the Protocol Administrative Clarification Letter dated 12 October 2015, applicable only to NSCLC patients with tumors harboring MET Exon 14 alterations and will be collected only at screening and End of Treatment)	X		*X*						X

Protocol Activity	**Screening***	**Lead-in PK Period**[31]	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks******	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day -7**	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
[18F]-FLT-PET and [18F]-FDT-PET[30]	*X*				*X*				
PF-02341066 treatment[28]		X	Once a day or twice a day continuously						
MDZ Treatment for patients participating in the MDZ study[29]		*X*			*X*				
Male patients: Hypogonadism Testing for MET-amplified NSCLC and Enriched Other cohorts[33] (Patients enrolled in Japan will not participate in hypogonadism testing)			X	X	X		Cycles 4, 6 and every 3 cycles thereafter		X

( ) If it has not been performed within 7 days.
* Allowable window for tumor assessment imaging is ±7 days; ±2 days for all other assessments.
* Allowable window for screening assessments is up to -7 days from Day -14 (ie, Day -21 to Day 0).
* End of Treatment (EOT) visit should be conducted 28 days postdose ±2 days. If a patient withdraws from study treatment and new anticancer is subsequently administered, the EOT visit should occur prior to the initiation of new anticancer therapy.
[ ] Special ophthalmology tests for all NSCLC patients enrolled following IRB/EC approval of Amendment #17 until written notification by Sponsor. As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. See Section 7.3 for additional details.
**Cycle length is 4 weeks (28 days) except for ALK marker negative NSCLC patients in which cycle length is 3 weeks (21 days).
***Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle. Once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle (every 12 weeks for the ALK marker negative NSCLC cohort based on 3-week calendar schedule). For patients on 4-week cycles, once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). However, for patients on 3-week cycles, once a patient has completed 35 cycles, tumor imaging may be performed every eighth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit.
****Every 6 weeks for ALK marker negative NSCLC patients.

1. Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.
2. Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.
3. Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.
4. Height need not be collected after the first measurement.
5. ECOG performance scale will be available in the Appendix 2 of the protocol.

6. 12-Lead ECG: Three consecutive 12-lead ECGs will be performed at least 2 minutes apart during the screening period; Cycle 1 Day 1 at pre-dose (0 hour), 6 hours post-dose (4 hours as of June 16, 2008) (~C_{max}), and 24 hours post-dose; Cycle 1 Day 15 and Cycle 2 Day 1 at pre-dose and 6 hours (4 hours as of June 16, 2008) (~C_{max}) post-dose. Once IRB/EC approval of Amendment #17, patients in the RP2D cohorts and ALK Marker Negative NSCLC RP2D Cohort #2 will have triplicate ECGs collected at least 2 minutes apart during the screening period; Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hour) and 2-6 hours post-dose which are corresponding to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.
7. Hematology: WBC with differential count, hemoglobin, and platelet count.
8. Blood Chemistry: Total and indirect bilirubin, alanine aminotransferase (ALT), asparatate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1. C2D15 chemistry required after approval of Amendment #20.
9. Coagulation: PT and PTT.
10. Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.
11. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.
12. Tumor Imaging: CT or MRI scan to be performed to assess disease status at screening, every 8 weeks, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end/withdrawal from study treatment. For patients in the ALK marker negative NSCLC cohort, tumor assessments will be performed every 6 weeks (based on a calendar schedule) starting after the first dose. If renal cysts are observed, active surveillance with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging.
13. Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the patient's final dose. For ROS1 marker positive NSCLC cohort, MET-amplified NSCLC cohort and MET Exon 14 alterations NSCLC patients (in the Enriched Other cohort, excluding patients enrolled in clinical sites in Japan): As of IRB/EC approval of Amendment #22, all patients enrolled into these cohorts should be followed for survival every 3 months after discontinuing study treatment until one year after the last patient in each of these cohorts has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. As of IRB/EC approval of Amendment #23, all patients enrolled into these cohorts should be followed for survival every 3 months after discontinuing study treatment until two years after the last patient in each of these cohorts has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. For NSCLC patients with tumors harboring MET exon 14 alterations enrolled in clinical sites in Japan: survival shall be followed every 3 months after discontinuing study treatment until two years after the last patient from Japan has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor.
14. Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from study treatment, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.
15. Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. As of June 16, 2008, this test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB)/Ethic Committee (EC) or if required by local regulations. As of IRB/EC approval of Protocol Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy; once at Screening and once at Cycle 1 Day 1 before PF-02341066 administration. Pregnancy tests will also be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2 for further detail.

16. *See Section 7.5.1.1 for detailed procedures.*

17. *See Section 7.5.1.1 for detailed procedures.*

18. Two PK sampling points (pre-dose and *4-8 hours* [2-8 hours *as of May 1, 2007]* post-dose) will be obtained on Day 15 of Cycle 2, Day 1 of Cycle 3 and Day 1 of subsequent cycles (up to Cycle 5) for all patients. Upon IRB/EC approval of Amendment #18, patients in the RP2D cohorts (ie, MET-amplified NSCLC and Enriched Other cohorts) *and ALK Marker Negative NSCLC Cohort #2* will have PK samples collected on Day 1 of Cycle 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. In addition, for patients in the MET-amplified NSCLC, ROS1 marker positive NSCLC and Enriched Other cohorts, a PK sample should be taken around the time that disease progression is confirmed as long as the patient is on PF-02341066.

19. *In the MDZ interaction sub-study, a pharmacokinetic profile of MDZ will be collected after a single oral MDZ dose on Day –7 (lead-in period) and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 9, and 24 hours post dose.*

20. *A 5-mL blood sample will be collected at 4-8 hours post dose on Cycle 1 Day 15 in the RP2D midazolam interaction cohort for metabolite profiling of PF-02341066.*

21. Blood sample for pharmacogenomics: A single whole blood biospecimen (4 mL) will be collected at baseline (within 2 weeks prior to the first dose) for possible analysis of DNA sequence variation in genes that may affect PK of the study drugs, may be associated with specific adverse events or toxicities, or may correlate with efficacy. (For patients enrolled in clinical sites in Japan: blood sample for pharmacogenomics is optional)

22. *Urine will be collected for 24 hours after PF-02341066 dosing on Cycle 1 Day 15 in the RP2D midazolam interaction cohort over the following intervals: 0 to 4 hours, 4 to 12 hours and 12 to 24 hours post-dose.*

23. *Morning spot urine sample will be collected on Day 1 of Cycle 1, Day 15 of Cycle 1 and Day 1 of Cycle 2. Once IRB/EC approval of Amendment #17, these samples will no longer be collected.*

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27. Plasma sample for circulating nucleic acid profiling (MET-amplified NSCLC and Enriched Other cohorts only): As of IRB/EC approval of Amendment #21, blood biospecimen (10 mL) for nucleic acid analysis (eg, circulating free DNA [cfDNA] or RNA [cfRNA]) will be collected. As of the Protocol Administrative Clarification Letter

dated 12 October 2015, plasma sample for circulating nucleic acid profiling is applicable only to NSCLC patients with tumors harboring MET Exon 14 alterations and only required at Screening and End of Treatment.

28. *A single dose of PF-02341066 will be given on Day –7 (lead-in period) for all patients except the patients who are scheduled for the MDZ interaction sub-study. After IRB/EC approval of Amendment #16, Day -7 dosing will only be required for dose escalation cohorts.*

29. *For patients who are scheduled for the MDZ interaction sub-study only. A 2-mg single oral dose of MDZ will be given on Day –7 and Cycle 2 Day 1. On Cycle 2 Day 1, MDZ will be given concurrently with PF-02341066.*

30. *If a biopsy is obtained, it should be performed no more than 3 days following completion of both [^{18}F]-FLT-PET and [^{18}F]-FDG-PET. [^{18}F]-FLT-PET and [^{18}F]-FDG-PET should be performed at least 24 hours apart. With the approval of Amendment #13 by the IRB/EC, no additional patients will undergo PET imaging.*

31. *Not required for additional patients who enter the study at a previous dose level when enrollment is closed for the current dose level or for patients enrolled in the RP2D enriched population cohort who are exempted for Day -7 dosing. Also, upon site IRB/EC approval of Amendment #12, Day -7 dosing is also not required for non-Asian patients in the enriched population or ALK marker negative NSCLC cohorts. Upon IRB/EC approval of Amendment #13, only patients enrolled in the QD dose escalation part of the study or Asian patients enrolled in any cohort will have the Day -7 lead-in dose.*

32. *Once Amendment #12 is approved by the IRB/EC, an ophthalmology examination will be performed at screening for all new patients.* The ophthalmology examination should be repeated during the study when visual disturbances have been observed and when there is an increase in grade for visual disturbances (includes all ongoing patients). The ophthalmology examination should include ocular characteristics, visual acuity, fundoscopy and slit lamp examination. *All NSCLC patients enrolled after Amendment #17 is approved by the IRB/EC will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor.* As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. All ophthalmology examinations should be performed by an ophthalmologist. *Time points of this special testing are designated by "[ ]" in the Schedule of Activities Table and are performed at Screening, Cycle 1 Day 15, Cycle 3 Day 1, one year, and yearly thereafter. For NSCLC patients on a 4-week cycle, the yearly ophthalmology examination will be done at Cycle 14 Day 1, and every 13 cycles thereafter. For NSCLC patients on a 3-week cycle, the yearly ophthalmology examination will be done at Cycle 18 Day 1 and every 17 cycles thereafter. These tests should also be done within 2-8 weeks after discontinuation of PF-02341066. There is a ±2 week window for the yearly ophthalmology examination.*

33. Hypogonadism Laboratory Tests (male patients only): All male patients enrolled into the MET-amplified NSCLC and Enriched Other cohorts after IRB/EC approval of Protocol Amendment #21 will have hypogonadism laboratory tests. Required tests include: total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone, dihydroepiandosterone sulfate, estradiol and prolactin. Blood draws **MUST** be taken before PF-02341066 dosing and between 07:00 and 10:00 a.m. and, for each individual patient, the time of the draw should be as consistent across visits as feasible. If either total testosterone or free testosterone decrease to a value that is both 25% lower than baseline and below the lower limit of normal, then a repeat laboratory test of both of these parameters must be performed at the next clinic visit to confirm hypogonadism. **Note**: Patients enrolled in clinical sites in Japan will not participate in hypogonadism testing. See Section 7.2, Appendix 9, Appendix 11, and Appendix 12 for further details.

34. Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/IC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

ITALICIZED TEXT IS OUTDATED INFORMATION AND SHOULD BE DISREGARDED

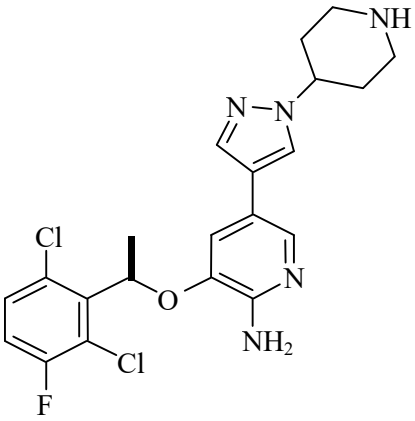
1. INTRODUCTION

1.1. Background

Human cancers comprise a diverse array of diseases that collectively are one of the leading causes of death in developed countries throughout the world (American Cancer Society, 2005).[1] The progression of cancers is caused by a complex series of multiple genetic and molecular events including gene mutations, chromosomal translocations, and karyotypic abnormalities (Hanahan & Weinberg, 2000).[3] Although the underlying genetic causes of cancer are both diverse and complex, each cancer type has been observed to exhibit common traits and acquired capabilities that facilitate its progression. These acquired capabilities include dysregulated cell growth, sustained ability to recruit blood vessels (ie, angiogenesis), and ability of tumor cells to spread locally as well as metastasize to secondary organ sites (Hanahan & Weinberg, 2000).[3] Therefore, the ability to identify novel therapeutic agents that 1) inhibit molecular targets that are altered during cancer progression or 2) target multiple processes that are common to cancer progression in a variety of tumors is predicted to yield improved therapeutic benefit.

PF-02341066

Chemical Structure:



Chemical Name:
(*R*)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1*H*-pyrazol-4-yl)-pyridin-2-ylamine

Molecular Formula: $C_{21}H_{22}Cl_2FN_5O$

PF-02341066 is a small-molecule inhibitor of the MET (mesenchymal-epithelial transition factor)/HGFR receptor tyrosine kinase. The rationale for use of this mechanism to treat cancer is supported by an emerging paradigm in oncology that robust clinical efficacy can be obtained with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification.

Recent examples include Gleevec® in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations, Tarceva® in non-small cell lung cancer with mutant EGFR, Herceptin® in breast cancers with amplified HER-2/neu, and SU11248 targeting the VHL-dependent VEGF pathway in renal cell carcinoma. An extensive body of literature indicates that MET/HGFR is one of the most frequently mutated or otherwise abnormally activated RTKs in various human cancers (Christensen et al, 2005).[2] Tumor types in which MET/HGFR was reported to be genetically altered by mutation or gene amplification include oncology indications with a strong unmet medical need such as renal, metastatic colorectal, glioma, non-small cell lung, gastric, and head and neck cancers (Christensen et al, 2005).[2] In addition, PF-02341066 demonstrated potent activity against NPM-ALK, an oncogenic fusion protein variant of the Anaplastic Lymphoma Kinase, which results from a chromosomal translocation which is implicated in the pathogenesis of human anaplastic large cell lymphoma (Pulford et al, 2004).[4] In addition to the rationale for PF-02341066 based on the genetic dysregulation of its tyrosine kinase targets, an additional rationale is based on its predicted ability to target multiple processes that are common to cancer progression in a variety of tumors. Inappropriate activation of MET/HGFR (including wild-type MET) is implicated in dysregulation of multiple tumor oncogenic processes such as mitogenesis, survival, angiogenesis, invasive growth, and especially in the metastatic process (Christensen et al, 2005).[2] Furthermore, the expression of MET and HGF, its sole, high-affinity ligand, were demonstrated to correlate with poor prognosis or metastatic progression in a number of major human cancers (Christensen et al, 2005).[2] The other molecular target of PF-02341066, NPM-ALK, is implicated in the dysregulation of cell proliferation and apoptosis in ALCL lymphoma cells (Pulford et al, 2004).[4] Consistent with its predicted mechanism of action, PF-02341066 inhibited target-dependent tumor cell proliferation or invasion, induced tumor cell apoptosis, and inhibited angiogenesis in nonclinical tumor models. Oral administration of PF-02341066 also demonstrated efficacy, including marked cytoreductive antitumor activity, in several tumor models that expressed activated MET/HGFR or NPM-ALK. The collective rationale for investigation of PF-02341066 in clinical studies is built on genetic alteration of its molecular targets, its predicted ability to target multiple processes that are common to cancer progression, and preclinical efficacy data.

Safety:

The primary PF-02341066 toxicities in nonclinical studies were observed in the gastrointestinal tract (rat, dog, monkey), hematopoietic system (rat, dog, monkey), kidneys (rat), reproductive organs (rat), and actively growing long bones (rat). Additional effects related to PF-02341066 administration involved the cardiovascular system based on safety pharmacology studies, and genetic toxicity findings. Other findings of uncertain risk to humans include the decreased cellularity in lymphoid organs, elevated liver enzymes, potential for phototoxicity, and effects on the salivary glands.

Gastrointestinal Effects: Clinical signs of diarrhea were observed in rats (500 mg/kg/day), dogs (≥6 mg/kg/day), and monkeys (50 mg/kg/day). Focal edema was observed in the gastric submucosa in rats given 500 mg/kg/day for 4 days, as well as focal ulceration, inflammation, and glandular hyperplasia in one female. Gastrointestinal effects were not observed in the 1-month study in rats, where doses were tolerated for the full term of the

study. Emesis and diarrhea were dose-limiting toxicities observed during the single-dose escalation range-finding study in dogs. Following single doses of 10, 25, and 40 mg/kg, severe gastrointestinal effects were observed, including bloody emesis and diarrhea, along with mucous membranes in the feces. Histopathological examination of the intestines revealed blood-filled dilated mucosal and submucosal vessels (congestion) and luminal contents of mucus admixed with low numbers of neutrophils. In the 1-month study in dogs, PF-02341066 at ≥6 mg/kg/day induced emesis, the incidence and frequency of which decreased as the study progressed, and occasional diarrhea. There was no effect on food consumption or body weight, and no histopathological correlate was identified at the end of the study. Diarrhea and soft feces were also observed in monkeys given 50 mg/kg/day of PF-02341066. A decrease in phosphorus observed in this study may have been related to decreased intestinal absorption. Marked cecal erosion and ulceration were observed in one monkey euthanized moribund on Day 21.

Kidney Effects: Microscopic evidence of minimal to mild renal cortical tubule vacuolation was observed following 28 days of dosing in male rats treated with ≥50 mg/kg/day of PF-02341066. Urinalysis revealed significant decreases in urine pH from 50 mg/kg/day in males and at 150 mg/kg/day in females. The mechanism for renal tubular vacuolation is not known, however HGF is highly expressed in the kidney tubular epithelium (Birchmeier, 2003)[5] with reported cytoprotective effects on renal tubular epithelium (Liu, 1998).[6]

Testes Effects: Microscopic evidence of minimal testicular pachytene spermatocyte degeneration was observed in rats given ≥50 mg/kg/day of PF-02341066 for 28 days. The mechanism responsible for the degenerative effects in the testes is not understood, however MET is known to be expressed on human seminiferous epithelium and on immature and mature spermatozoa (Depuydt, 1996).[7]

Hematopoietic Effects: Bone marrow hypocellularity was observed in toxicity studies in rats and monkeys with PF-02341066. Repeated administration of PF-02341066 for 28 days caused bone marrow hypocellularity at doses of 150 mg/kg/day (rats, males only) and 50 mg/kg/day (monkeys). Minimal bone marrow hypocellularity was also produced in rats of both sexes when PF-02341066 was administered for shorter time duration (2 days at 2000 mg/kg and 4 days at 500 mg/kg/day). Bone marrow hypocellularity was not observed in dogs, however a decrease in white blood cells was identified following 3 single doses up to 40 mg/kg and 7 days of PF-02341066 at 20 mg/kg/day. In monkeys, cytospin examination showed evidence of increased numbers of macrophages and debris consistent with bone marrow cytotoxicity, and correlated with the bone marrow hypocellularity observed histopathologically. Hematological analysis revealed decreased reticulocyte counts and suggested suppression of erythroid production within the bone marrow. In addition, WBC precursors lacked granulation characteristically present in these cells suggesting potential peroxidase deficiency in granulocytes. This change in granulation was also noted in dogs given 20 mg/kg/day for 28 days. Vacuolated lymphocytes were identified in male rats given 150 mg/kg/day, the significance of which is unclear.

Lymphoid Tissue Effects: Lymphoid depletion was observed in the thymus, spleen, lymph nodes, or GALT in rats and dogs given PF-02341066. Findings in rats given 500 mg/kg/day for 4 days were attributed to stress (stress leukogram and clinical signs of intolerance were

observed). Decreased cellularity was also observed in lymphoid organs in the 1-month study in rats at ≥50 mg/kg/day, however, these findings were considered of uncertain origin. Decreased thymus weight (≥6 mg/kg/day) correlated to thymic lymphoid depletion in male dogs given 20 mg/kg/day PF-02341066 for 28 days, and was also considered to be of uncertain relationship to treatment.

Cardiovascular Effects: In vivo cardiovascular effects were observed in the safety pharmacology study in anesthetized dogs. PF-02341066 administration was associated with decreases in heart rate and increases in LVEDP at 84 and 164 ng/mL free plasma concentration. There were also statistically significant differences compared with vehicle-treated animals in myocardial contractility (LV+dP/dt) at 164 ng/mL free plasma concentration. Although there was a statistically significant decrease in myocardial contractility, it should be noted that the actual myocardial contractility values in the treated animals were similar to the pre-dose values. The main effects of PF-02341066 on ECG parameters were statistically significant increases in PR interval, QRS, and QT interval at 84 and 164 ng/mL free plasma concentration. The prolongation of PR-interval, QRS and QT-interval is probably due to the reduction in heart rate observed at these doses. Monophasic action potential duration during cardiac pacing is a heart rate-independent index of cardiac repolarization. There were statistically significant increases in $MAPD_{100}$ at sinus rhythm at 84 and 164 ng/mL free plasma concentration. The increases in $MAPD_{100}$ at sinus rhythm were consistent with the decreases observed in heart rate. The plasma concentrations of PF-02341066 achieved in this study were up to 44 times the free efficacious plasma level predicted in humans (8.1 nM or 3.7 ng/mL). In vitro, PF-02341066 blocked potassium currents or human ether-a-go-go-related gene (hERG) channel conduction with IC_{50} and IC_{20} values of 1.1 μM (495 ng/mL) and 0.3 μM (135 ng/mL), respectively. In the rat aortic tension model, in vitro dog isolated Purkinje fibers, and in freshly isolated Guinea pig ventricular myocytes, PF-02341066 produced effects consistent with calcium channel antagonism. The hERG assay, rat aortic model, Guinea pig myocyte assay, and Purkinje fiber data suggest that PF-02341066 is mixed-channel blocker and this may explain the lack of effect on $MAPD_{100}$ during pacing in this study. The decrease in diastolic blood pressure observed at a free plasma concentration of 164 ng/mL may reflect the calcium channel antagonist effects observed in the rat isolated aorta model. The nonclinical data suggest that free plasma concentrations greater than or equal to 84 ng/mL may produce changes in the heart rate and at higher free plasma concentrations (164 ng/mL) changes in diastolic blood pressure.

Bone Effects: Repeated administration of PF-02341066 for 28 days caused minimal decreased bone formation at the primary spongiosa of growing long bones at a dose of 150 mg/kg/day in male rats. Though an off-target relationship cannot be ruled out, reports of in vitro data describe possible autocrine regulation of osteoclasts, paracrine regulation of osteoblasts (Grano, 1996),[8] and modulation of bone resorptive activity of osteoclasts in response to HGF (Fuller, 1995),[9] that may be suggestive of a pharmacological effect on bone. This toxicity is not expected in the adult patient population, whose growth plates are inactive.

Liver Effects: An elevation in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) was observed in rats and monkeys given PF-02341066. Rats given 2000 mg/kg/day for 2 days, 500 mg/kg/day for 4 days, or ≥50 mg/kg/day for 28 days showed

an elevation in liver enzymes without a microscopic correlate. Monkeys given 50 mg/kg/day of PF-02341066 also had elevated ALT and AST without histological correlate. The elevation of liver enzymes is of uncertain relevance.

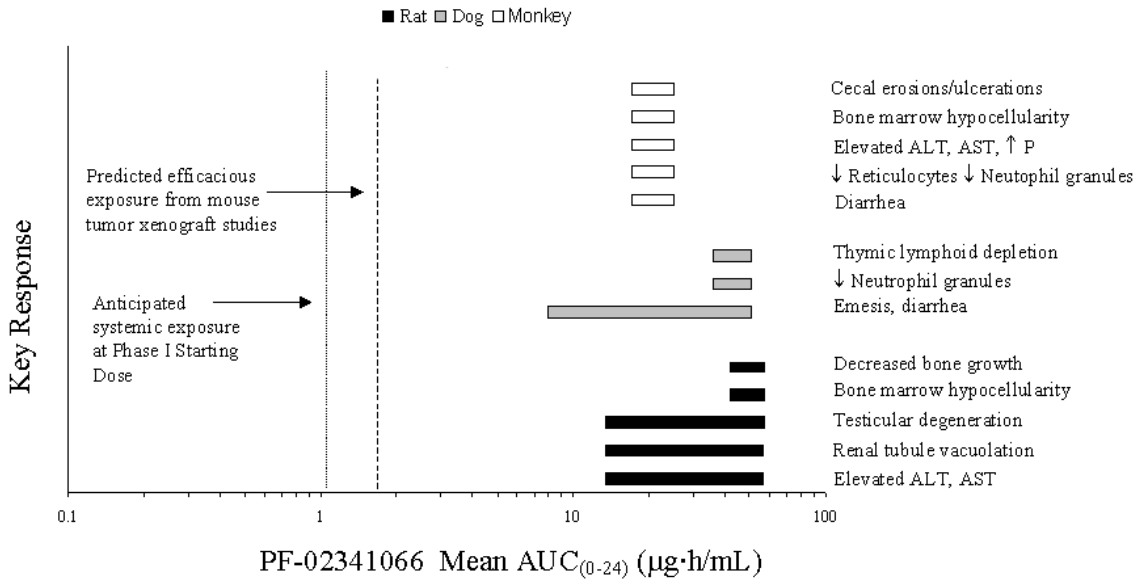
Genotoxic Effects: PF-02341066 was associated with an increased frequency of structural chromosomal aberrations in the in vitro cytogenetics assay with and without metabolic activation under the 3-hour test condition. In addition to the clastogenic response, the kinetochore staining results from the in vitro micronucleus evaluation and the observation of polyploidy in the cytogenetics assay were consistent with an aneugenic response to PF-02341066. Increased incidences in micronucleated polychromatic erythrocytes (and micronucleated normochromatic erythrocytes) were observed at all doses evaluated in vivo (rat) in males only. The increases in micronuclei were associated with changes in other bone marrow parameters consistent with bone marrow toxicity.

Phototoxic Effects: PF-02341066 potential for phototoxicity was evaluated due to significant absorbance in the UVA-UVB/visible range from 290 to 700 nm with a molar extinction coefficient of ≥1000 L/Mol/cm, and its photodegradative property. PF-02341066 was evaluated in the 3T3 fibroblast NRU assay with probable phototoxicity results. Distribution of PF-02341066 to tissues with likely sun exposure is not known. Patients will be advised to avoid excessive sun exposure while on trial, eg by wearing long sleeve clothing and sunglasses and applying sunscreen when outdoors.

Other Effects: Single-cell necrosis was observed in the ovaries and salivary glands of rats given 500 mg/kg/day that were euthanized on Day 4 due to moribundity. Mild depletion of secretory material was also observed in the salivary glands. Effects in the ovaries and salivary glands were not observed in the subsequent 1-month study. Increases in WBC counts were observed in the rat and monkey, consistent with an inflammatory response.

Complete information on PF-02341066 may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure.

Figure 2. Summary of 1-Month Repeat-Dose Toxicodynamics for PF-02341066



1.2. Rationale

MET/HGFR has been well characterized for its role in regulation of cell growth, migration, and invasion of both tumor cells and endothelial cells. An extensive body of literature indicates that MET/HGFR is one of the receptor tyrosine kinases (RTKs) most frequently mutated or otherwise abnormally activated in late-stage human cancer. When activated, MET/HGFR plays a critical role in regulation of tumor oncogenic processes such as mitogenesis, survival, and invasive growth, and especially in the metastatic process. Additionally, the emerging role of MET/HGFR in the regulation of tumor angiogenesis indicates potential for dual anti-tumor and anti-angiogenic mechanisms. Activating mutations in MET/HGFR have been identified in multiple patient populations, including NSCLC (Non Small Cell Lung Cancer), SCLC (Small Cell Lung Cancer), renal cancers, head and neck cancers, and hepatocellular cancer. In addition to activation driven by mutation, MET/HGFR gene amplification/ overexpression resulting in increased kinase activity has been frequently observed in gastric and colorectal cancer patients. Furthermore, MET/HGFR is also activated in human tumors by other mechanisms (eg, autocrine loops, paracrine activation from tumor-associated stroma). Collectively, the dysregulation of MET/HGFR in tumors by multiple mechanisms along with the potential role of MET/HGFR in tumor angiogenesis comprises a large potential patient population. Most importantly, in preclinical proof of concept studies, both neutralizing monoclonal antibody and RTK inhibitor exhibit convincing antitumor activity in several xenograft models, which supports the concepts that MET is a valid target for treatment of cancer.

Mutations in MET Exon 14 were previously reported to be oncogenic drivers in preclinical models of lung cancer (Ma et al, 2003; Ma et al, 2006; Kong-Beltran et al, 2006).[22,23,24] Given the role of MET/HGFR in regulation of cell growth, migration, and invasion of both tumor cells and endothelial cells, there is increasing interest in understanding the potential effectiveness of tyrosine kinase inhibitors as a treatment in NSCLC patients with tumors

harboring MET Exon 14 alterations. Paik et al (2015) reported on 3 crizotinib-treated patients with NSCLC harboring alterations leading to MET Exon 14 skipping. All 3 crizotinib-treated patients were shown to have a partial response.[21]

In conclusion, MET has been shown to be a valid target, and PF-02341066 is a potent and selective inhibitor of MET. PF-02341066 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window, providing increased confidence that mechanism-based toxicity will not be limiting in the clinic.

1.2.1. Rationale for Selection of Starting Dose

The starting dose for PF-02341066 in the first in human (FIH) trial in cancer patients has been determined to be 50 mg daily, based on information derived from the 1-month repeat dose toxicology studies in rats and dogs (see current IB).

The doses tested in the 1-month toxicology rat study were 10, 50, and 150 mg/kg/day orally and the doses in the 1-month dog study were 1, 6, and 20 mg/kg/day orally. In the rat study, there were no deaths at any dose levels. The NOAEL identified in the rat study was 10 mg/kg/day. Only mild to moderate toxicities were observed at the highest dose (150 mg/kg), indicating that the STD_{10} in rats was greater than 150 mg/kg (900 mg/m^2). There was a significant gender difference suggesting that the male rat was more sensitive than the female, associated with increased plasma exposure of PF-02341066 in male rats. In the dog study, no serious, irreversible toxicities were observed at any dose level. Hence, the NOAEL was determined to be 20 mg/kg/day in the dog study.

According to DeGeorge et al. (1998),[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 (STD_{10}) 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. Since one-tenth of the highest dose tested in rats (90 mg/m^2, equivalent to 4.5 mg/kg in dogs) did not cause any serious, irreversible toxicity in dogs, the starting dose in humans can be estimated as 90 mg/m^2, ie, 150 mg daily dose, assuming body surface area of 1.7 m^2 for humans.

However, the 150 mg starting dose in humans would project a PF-02341066 plasma exposure (steady-state plasma AUC of 3.26 μg·hr/mL) exceeding the NOAEL (AUC of 2.16 μg·hr/mL at 10 mg/kg) in male rats, the most sensitive species. Furthermore, since the plasma protein binding for PF-02341066 is lower in humans (90.7%) than in rats (94.3%), the unbound AUC (AUC_u) in humans (0.303 μg·hr/mL) at the 150 mg starting dose will be higher than that at the NOAEL in rats (0.123 μg·hr/mL). In humans, a dose of 61 mg is expected to yield an unbound drug plasma AUC approximately equal to that observed in rats at the NOAEL. Since the exposure-based human dose projection provides a lower estimate for the clinical starting dose (61 mg) than that based on 1/10 of the STD_{10} in rats (150 mg), this dose

rounded to 50 mg (the highest available strength for a single capsule) once daily will be used as the starting dose for the FIH study.

1.2.2. Rationale for Evaluation of Midazolam (MDZ) Interaction

PF-02341066 is predominantly metabolized via the CYP3A isozymes in human liver microsomes and hepatocytes. PF-02341066 also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes with a k_{inact} of 0.11 min^{-1} and K_I of 3.0 μM. Based on these values, the projected PF-02341066 therapeutic dose of 100 mg ($C_{max, free}$ 19 nM) is predicted to increase the systemic exposure (AUC) of co-administered drugs that are CYP3A substrates by approximately 80% due to CYP3A 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-02341066 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 Human (FIH) study to assess the potential PF-02341066 related CYP3A inhibition.

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 pharmacokinetics (PK) following a single oral 2-mg dose will be evaluated before and after repeated daily administration of PF-02341066 at 3 dose levels (the next higher dose after the initial dose, the efficacious dose, and the RP2D), in order to assess the effects of PF-02341066 on CYP3A activity in the GI 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.

2. TRIAL OBJECTIVES

1. Determine the safety profile of PF-*02341066 including identification of dose limiting toxicity (DLT) and maximum tolerated dose (MTD).*

2. *Determine the recommended Phase 2 doses (RP2D) and regimens of PF-02341066.*

3. Determine pharmacokinetic profile of PF-02341066 following oral administration *including the effect of food.*

4. *Perform initial evaluation of PF-02341066 related CYP3A4 inhibition using midazolam (MDZ) as a probe.*

5. *Determine the effect of the co-administration of rifampin on the multiple-dose plasma pharmacokinetics of PF-02341066.*

6. *Determine the effect of the co-administration of itraconazole on the plasma pharmacokinetics of PF-02341066.*

CCI

8. Document any evidence of anti-tumor activity of PF-02341066.

CCI [redacted]

10. Evaluate the effect of PF-02341066 on parameters related to hypogonadism in males.

2.1. Trial Endpoints

1. *To determine the MTD and potential phase 2 dose(s) of PF-02341066.*

2. To characterize the plasma pharmacokinetic (PK) profile following oral administration of PF-02341066*, including the effect of food and a midazolam study to evaluate the potential for time-dependent inhibition (TDI) of CYP3A4 at different PF-02341066 dose levels.*

3. To determine the safety, tolerability *and the DLT* of PF-02341066.

4. *Plasma PK parameters of PF-02341066 and its metabolite(s) following multiple oral doses of PF-02341066 alone and when co-administered with rifampin.*

5. *Plasma PK parameters of PF-02341066 and its metabolite(s) following single (if possible) and multiple oral doses of PF-02341066 alone and when co-administered with itraconazole. As of Protocol Amendment #22, the Single and Multiple-Dose Design will no longer be performed.*

CCI [redacted]

7. To document evidence of anti-tumor activity, including tumor response rate (by RECIST for solid tumors and response criteria for lymphomas and multiple myelomas), duration of response, time to response, progression free survival, overall survival, probabilities of survival at 6 and 12 months and others as appropriate.

CCI [redacted]

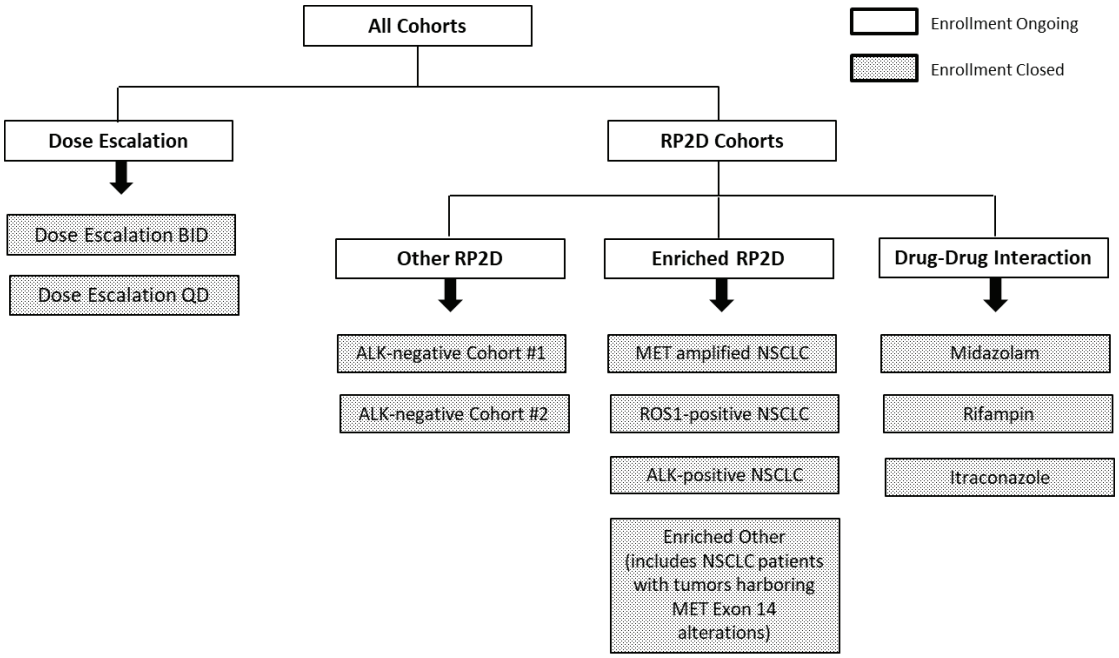
9. Blood testosterone and other blood parameters associated with detecting hypogonadism in males [*Appendix 12*].

3. TRIAL DESIGN

Open label, multi-center Phase 1 dose escalation, safety, pharmacokinetic [redacted] study.

Figure 3 provides the status of each of the RP2D cohorts of this study, based on Protocol Amendment #24.

Figure 3. Summary of RP2D Cohorts Based on Protocol Amendment #24



4. PATIENT SELECTION

This clinical trial 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.

Rifampin interaction sub-study: Refer to Appendix 6 for details on patient selection.

Itraconazole interaction sub-study: Refer to Appendix 7 for details on patient selection.

ALK-negative NSCLC Cohort #2: Refer to Appendix 8 for details on patient selection.

Patients with MET-amplified NSCLC: Refer to Appendix 9 for details on patient selection.

ROS1 marker positive NSCLC patients: Refer to Appendix 10 for details on patient selection.

Enriched Other cohort: Refer to Appendix 11 for details on patient selection.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. Tumor eligibility:

    - All cohorts except RP2D enriched population cohort: Histologically confirmed advanced malignancies (except for leukemias) refractory to standard of care therapy, or for whom no standard of care therapy is available.

    - RP2D enriched population cohort: Histologically confirmed advanced malignancies that meet one of the following criteria:

        - Positive for MET amplification by FISH (excluding polysomy). After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

        - Positive for ALK chromosomal translocations or gene amplification including but not limited to NPM-ALK positive anaplastic large cell lymphoma, inflammatory myofibroblastic tumors, echinoderm microtubule-associated protein-like 4 (EML4)-ALK positive non-small cell lung cancer or ALK-positive melanoma. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor. After IRB/EC approval of Amendment #18 patients with NSCLC that is positive for ALK chromosomal translocations or gene amplifications will not be allowed to enter the enriched RP2D cohort.

        - Positive for known MET kinase domain activating mutations including but not limited to V1110L, H1112L, H1112Y, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, M1268T, P1009S, T1010I, R988C, V941L but excluding Y1248C, Y1248H, Y1248D, Y1253D; mutations in the intron/exon splice site regions flanking exon 14 resulting in exon 14 deletion and Y1003X mutations in exon 14 affecting binding of the E3 ubiqitin ligase, CBL (casitas B-lineage lymphoma). After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

        - Chromosomal translocations/fusions that lead to altered transcriptional regulation of MET and/or HGF including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma. Patients with these tumors may enter the study without prior confirmation of MET and/or HGF alterations. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

- Positive for chromosomal translocations at *ROS1* gene including but not limited to CD74-ROS1 and SLC34A2-ROS1 fusion events in NSCLC *and FIG-ROS1 in glioblastoma.*

- Other molecular changes for which there are data to suggest a biologic rationale for PF-02341066 treatment, eg, TRK1 fusions.

- *ALK marker negative NSCLC Cohort #1: Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adenosquamous histology). Patients must have received only one prior chemotherapy and this regimen must have been platinum-based. Patients who have also been treated with an EGFR tyrosine kinase inhibitor may enter the trial. However, on a case-by-case basis and in agreement between the Sponsor and Investigator, patients who have had at least one prior chemotherapy treatment may be allowed to enter the trial. All patients must either be non-smokers, ex-smokers or light smokers (≤10 pack-years).*

- *ALK marker negative NSCLC Cohort #2: Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adenosquamous histology). Patients must have received at least one prior chemotherapy regimen. Patients must have been determined to be ALK-negative by the central laboratory but may have been pre-screened and shown to have ALK negative NSCLC by a local test. All patients must either be non-smokers, ex-smokers or light smokers (≤10 pack-years).*

2. Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.0). However, for the enriched population RP2D cohort, patients whose tumors are not measurable, may enter the study upon approval by the Sponsor. Target lesions that have been previously irradiated will not be considered measurable (lesion) unless increase in size is observed following completion of radiation therapy. RECIST v 1.1 will be used to evaluate tumors for patients in the ALK marker negative NSCLC cohorts.

3. Able, in the investigator's opinion, to receive at least 2 cycles of treatment.

4. Female or male, 18 years of age or older. For patients enrolled at clinical sites in Japan as part of the Enriched Other Cohort: Female or male, 20 years of age or older.

5. ECOG performance status 0 or 1. However, patients in the RP2D enriched population cohort or ALK marker negative NSCLC cohorts with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.

6. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).

7. Adequate organ function as defined by the following criteria:

    - Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.
    - Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).
    - Absolute neutrophil count (ANC) ≥1500/μL.
    - Platelets ≥100,000/μL (≥30,000/μL for the enriched RP2D population cohort and the ALK marker negative NSCLC cohorts).
    - Hemoglobin ≥9.0 g/dL (≥8.0 g/dL after IRB/EC approval of Amendment #21).
    - Serum creatinine ≤2.0 x ULN.

8. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment. For investigational sites using the Western Institutional Review Board (WIRB), patients who lack the capacity to consent for themselves will not be able to enroll into this study.

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

4.2. Exclusion Criteria

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

1. Major surgery, radiation therapy, or systemic anti-cancer therapy within 4 weeks of starting study treatment; within 2 weeks of starting study treatment for patients in the RP2D enriched population or ALK marker negative cohorts.

2. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue except for patients with neuroblastoma, lymphoma or myeloma.

3. For MET dependent tumors, prior therapy specifically directed against MET or HGF; for ALK dependent tumors, prior therapy specifically directed against ALK; for ROS1 dependent tumors, prior therapy specifically directed against ROS1.

4. Current treatment on another clinical trial.

5. Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 4 weeks (2 weeks for the RP2D enriched population cohort and the ALK marker negative NSCLC cohorts) and not taking medications contraindicated to Exclusion Criteria #11-13.

6. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 3 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted. [Implement 3 month guidance upon IRB/EC approval of Amendment #20].

7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc >470 msec. Upon agreement between the Investigator and Sponsor, patients with QTc >470 msec but <490 msec in the presence of a right bundle branch block or with an implanted cardiac pacemaker may enroll into the study [Implement upon IRB/EC approval of Amendment #20].

8. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

9. Pregnant female patients, breastfeeding female patients (including patients who intend to interrupt breastfeeding), male patients with pregnant female partners who are unwilling or unable to use a condom for the duration of the pregnancy, female and male patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of study treatment and for 90 days after the last dose of investigational product.

10. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior, or end-stage renal disease on hemodialysis or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and would make the patient inappropriate for entry into this study.

11. Use of drugs that are known strong CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.

Itraconazole Interaction sub-study: Refer to Appendix 7 for further details.

12. Use of drugs that are known strong CYP3A4 inducers within 12 days prior to the first dose of PF-02341066, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. All concomitant medication must be approved by the Sponsor.

Rifampin interaction sub-study: Refer to Appendix 6 for further details.

13. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.

14. *Patients who will participate in the MDZ interaction sub-study must not: (1) have any contraindications to MDZ administration according to the current package insert for MDZ; (2) take any MDZ dose which is not specified in the protocol within 7 days of the first dose of MDZ; and (3) take any medications or herbal supplements known to be CYP3A inhibitors or inducers 7 days (for CYP3A inhibitors) or 12 days (for CYP3A inducers) prior to the first dose of MDZ. All concomitant medication must be approved by the Sponsor.*

15. Patients with known interstitial fibrosis or interstitial lung disease. However after IRB/EC approval of Amendment #20: History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis. As of IRB/EC approval of Protocol Amendment #24, this exclusion criterion is as follows: History of extensive disseminated/bilateral or known presence of any grade interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

16. Patients who are investigational site staff members directly involved in the conduct of the study 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 study [Implement upon IRB/EC approval of Amendment #20].

4.3. Withdrawal Criteria

Every effort within the bounds of safety and patient choice will be made to have each patient continue to receive study drug. Patients are to discontinue study treatment when any of the following occurs:

- Patient refusal of further therapy (withdrawal of consent);
- Intolerable Adverse Event (AE) that does not improve with dose adjustments;
- Objective tumor progression or clinical deterioration unless there is reasonable evidence of clinical benefit as agreed upon with the Sponsor to justify continuation of study treatment;

- Investigator conclusion that it is in the patient's best interest to discontinue therapy (eg, poor patient tolerance, poor compliance with either protocol monitoring or with taking the study drug, etc);

- Initiation of treatment with another anticancer therapy. Of note: localized anticancer therapy (eg, topical treatment of non-melanoma skin malignancy, intravesical Bacillus Calmette-Guerin [BCG] treatment) may be acceptable upon prior Sponsor and Investigator agreement and written Sponsor approval.

- Pregnancy;

- Complete response, at the investigator's and patient's discretion. Complete response must be confirmed no less than 1 month after the initial response was observed prior to discontinuing study treatment.

4.4. Randomization Criteria

This is an open-label, single-arm study.

4.5. Life Style Guidelines

4.5.1. Contraception

In this study, patients of childbearing potential will receive PF-02341066, which has been associated with teratogenic risk. As of IRB/EC approval of Amendment #21, all male patients who are able to father children and female patients who are of childbearing potential, and are sexually active and at risk for pregnancy must agree to use 2 methods of highly effective contraception throughout the study and continued for at least 90 days after the last dose. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient from the list of permitted contraception methods (see below), and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of two of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use 2 highly effective contraceptive methods consistently and correctly according to the Schedule of Activities and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if 1 or both of the selected contraceptive methods is discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

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, implanted or transdermal hormonal methods of contraception are allowed provided the patient plans to remain 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 or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

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

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets at least one of the criteria for non-childbearing potential as described below (as of IRB/EC approval of Amendment #21):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure; or

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; laboratory confirmation [e.g., a serum follicle stimulating hormone level] may be indicated.

All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

Female patients of childbearing potential must take precautions to prevent pregnancy since the effects on the fetus are unknown.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose.

Note for patients enrolled in the rifampin interaction sub-study (see Appendix 6): female patients using oral or other systemic hormonal contraceptives should additionally use nonhormonal methods of birth control during rifampin therapy. Refer to Appendix 6 for further details.

4.5.2. Sunlight Exposure

Patients treated with PF-02341066 should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study.

4.5.3. Dietary Restrictions

There is special requirement for patients who will participate in the MDZ interaction sub-study:

- *Patients should not eat or drink products containing grapefruit from 7 days prior to enrollment until 24 hours after completion of MDZ administration on C2D1.*

For patients enrolled in the rifampin interaction sub-study, refer to Appendix 6 for further details.

For patients enrolled in the itraconazole interaction sub-study, refer to Appendix 7 for further details.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigational Site Folder.

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 numbers, contact information for the investigational site, and contact details for a contact center 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 patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only 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 the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. TRIAL TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is PF-02341066.

PF-02341066 will be administered orally once or twice a day in continuous 28-day cycles except 21-day cycles for patients in the ALK marker negative NSCLC cohort (see Schedule of Activities and Appendix 8).

There will be a lead-in period in which single-dose pharmacokinetics of PF-02341066 or MDZ (for patients participating in the MDZ sub-study) will be characterized prior to initiation of continuous dosing in the first cycle of treatment. With the exception of cohorts in which the evaluation of a MDZ interaction is scheduled or patients who are exempted from the Day -7 lead-in dose (see below), all other patients will receive a single dose of

PF-02341066 seven days prior to the start of Cycle 1 (Day –7) in order to characterize the complete PK profile of PF-02341066 after a single dose. With the approval of Amendment #13, only patients enrolled in the QD dose escalation part of the study or Asian patients enrolled in any cohort will have the Day -7 lead-in dose. 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-02341066 on Cycle 2 Day 1. During the study, real-time pharmacokinetic monitoring will be conducted as much as possible.

The PF-02341066 dose regimen may be changed if the pharmacokinetics and safety data suggest that a discontinuous regimen or another dosing frequency may be preferable. If a BID dosing regimen is incorporated, all study assessments will be based on morning dosing (Day -7 dosing will still be a single PF-02341066 dose). Dosing of oral PF-02341066 will be based on flat milligram increments without adjustment for body size. The dose will be 50 mg QD in the initial cohort.

Patients will be successively assigned to the next available treatment slot within a dose level.

Each dose cohort will initially include a minimum of 3 evaluable patients for assessment of toxicity within the first cycle. Dose escalation will occur in 100% increments until either of the following occurrences: (1) drug related toxicity of Grade 2 severity occurs in 2 or more patients within a dose level; or (2) mean unbound $AUC_{0\text{-}24}$ exceeds 2.4 μg·h/mL (the highest unbound AUC tested in the one-month toxicology studies). Escalation increments will then become 40%. In any cohort, if 1 patient experiences a DLT, 3 additional patients will be enrolled to that dose level. If 2/3 or 2/6 patients experience a DLT, no further dose escalation will occur (see Figure 4). Patients will continue treatment at their assigned dose level for at least 2 cycles to observe for cumulative toxicity. They may then be treated at the next higher dose level provided it has been shown to be safe in a previously treated cohort.

If the highest cohort being evaluated is closed to new enrollment, additional patients who have a cytogenetic abnormality as described in Section 4.1 (Inclusion #1) may enter the study at the previous dose level. These patients *will not participate in the midazolam sub-study and* will not have *the Day -7 lead-in dose of PF-02341066 or any corresponding PK assessments. They will be evaluated for safety but will not contribute to the MTD assessments. These patients will enter the study on Day 1 of Cycle 1. Additionally, patients scheduled to enroll in the RP2D enriched population cohort (see RP2D Cohorts Section) may be exempted from the Day -7 lead-in dose depending on the their overall medical condition. This exemption will be granted on a case-by-case basis as agreed upon by the investigator and Sponsor. Upon IRB/EC approval of Amendment #12, non-Asian patients will also be exempt from the Day -7 lead-in dose. Amendment #13 extends the requirements as described in the second paragraph of this section. Upon IRB/EC approval of Amendment #16, Day -7 lead-in dose will only be required for the dose escalation cohort.*

Definition of MTD

The MTD will be defined as the dose level at which at most one of six patients experience DLT after 28 days of treatment have occurred (end of Cycle 1) with the next higher dose

having at least 2/3 or 2/6 patients experiencing DLT. The Sponsor with the agreement of the investigators may expand the cohort beyond six patients to better define the safety profile of this cohort in the search for the MTD. The MTD may be determined for both QD and BID dosing. As of Protocol Amendment #20, the MTD determined from the QD dose escalation cohort will not be expanded beyond 6 patients.

Definition of DLT

DLT will have occurred when the patient has one or more of the toxicities noted in the Table 1. To determine dose escalation between cohorts, a DLT must occur within the first 28 days of treatment (end of Cycle 1). Toxicities will be graded according to the NCI CTCAE Version 3.0 (see Table 1).

Table 1. Dose Limiting Toxicities

Toxicity Category	***Toxicity/Grade***
Hematologic	*Prolonged grade 4 neutropenia for >7 days*
	[a] Febrile neutropenia, defined here as grade 4 neutropenia with fever >38.5°C, both sustained over a 24 hour period.
	Neutropenic infection: ≥ Grade 3 neutropenia with Grade ≥3 infection
	Grade ≥3 thrombocytopenia with bleeding or grade 4 lasting ≥7 days *Lymphopenia is not considered a DLT unless accompanied by infection.*
Other non-hematologic toxicity	*Grade 3 or 4 toxicities (except for alopecia, Grade 3/4 hypophosphatemia, grade 3 hypertension with controlled blood pressure [<140/90], and Grade 3/4 hyperuricemia without signs and symptoms of gout). Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy.*

[a] *Febrile neutropenia qualifies as a DLT only if the fever and neutropenia are documented to be coincident in time and reconfirmed.*

Doses may not be modified until a DLT has been reached. The study investigator may implement dose suspension in order to ensure patient safety; this will be considered dose-limiting toxicity for the purpose of dose-escalation if PF-02341066 has to be suspended for more than 3 days. The occurrence of a DLT necessitates immediate interruption of the scheduled study treatment in that patient. Resumption of study treatment for patients experiencing DLTs is permitted, contingent on the return of the DLT to <Grade 1 severity and interruption or delay in treatment for no more than 4 weeks. Resumption of treatment after resolution of a DLT will be at the next lower dose level tested (or 50% lower if the DLT occurs with the first dose level). Patients who discontinue treatment before completing Cycle 1 (DLT evaluation period) for reasons other than treatment-related toxicity (ie, 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.

To contribute information to the assessment of safety for any dose level, a patient must receive at least 75% of the planned PF-02341066 doses or experience a treatment-related AE that prompts early treatment interruption or discontinuation.

One or more lower dose level(s) may be tested in search of the MTD, defined as the dose level immediately below that in which 2/3 or 2/6 patients experience DLTs. Dose escalation may be stopped if 1) MAD produces PF-02341066 concentrations that are at least 5-fold greater than the projected target concentration, 2) exposure plateaus as the dose is increased and 3) MTD cannot be reached within a reasonable dose range (up to 2000 mg).

Midazolam interaction sub-study

The potential for CYP3A inhibition due to PF-02341066 will be evaluated using MDZ as a CYP3A4 substrate probe at 3 dose levels of PF-02341066: the next higher dose after the initial dose, the efficacious dose, and the RP2D (see Figure 4). The MDZ interaction study will be conducted starting in the second dose cohort, and at a higher dose (ie, the predicted efficacious dose) in which the trough unbound plasma concentration of PF-02341066 at the steady state will equal or exceed the projected target unbound plasma concentrations (12.8 nM). If the target unbound plasma concentration of PF-02341066 is achieved in the second cohort, then the MDZ sub-study may not be performed with the higher dose cohort. In the second cohort or the efficacious dose cohort, at least 3 evaluable patients per cohort will be assessed for the effect of repeat PF-02341066 administration on the pharmacokinetics of midazolam. If a significant change in MDZ clearance (>3-fold increase in MDZ AUC in all 3 patients, or >5-fold increase in 2 or more patients) is observed at any PF-02341066 dose level, further dose escalation may be terminated.

The effect of PF-02341066 on CYP3A activity will be evaluated at the RP2D. Eight evaluable patients will be required for the MDZ interaction study in one of the RP2D cohorts (see RP2D Cohorts Section). The results of the MDZ interaction sub-study at the RP2D will be used to determine if there is any need for concomitant medication restrictions or dose modifications in future PF-02341066 studies.

Patients enrolled in the MDZ interaction sub-study 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-02341066 on Cycle 2 Day 1 (morning dose if the BID regimen is employed).

Rifampin interaction sub-study: Refer to *Appendix 6* for further details.

Itraconazole interaction sub-study: Refer to *Appendix 7* for further details.

RP2D cohorts

The RP2D will be determined as a dose below or equal to MTD, at which PF-02341066 is unlikely to cause an inhibition of CYP3A4 activity. There will be two RP2D cohorts:

1. The first RP2D cohort will evaluate drug-drug interactions. This includes the MDZ, rifampin and itraconazole interaction sub-studies noted above.

    a. *The MDZ interaction sub-study requires 8 evaluable patients. Enrollment is closed with a total of 15 patients treated.*

b. The Rifampin interaction sub---study requires 8 evaluable patients. Enrollment is closed with a total of 18 patients treated.

c. The Itraconazole interaction sub--study requires 8 evaluable patients. Enrollment is closed with a total of 18 patients treated.

2. The second RP2D cohort will be composed of an enriched population of approximately 484 patients:

a. A group of ALK marker positive NSCLC patients. Enrollment is closed with a total of 154 patients treated.

b. Three categories of NSCLC patients with MET amplification defined as:

1) *MET/CEP7 ratio of ≥5.0 (Group 1):* As per the Protocol Administrative Clarification Letter (PACL) dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to ≥4.0. As per the PACL dated 11 September 2018, this group was closed to further enrollment. The remaining 14 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

2) *MET/ CEP7 ratio >2.2 to <5.0 (Group 2):* As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to >2.2 to <4.0 and this group was closed to further enrollment. The remaining 13 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort;

3) *MET/CEP7 ratio ≥1.8 to ≤2.2 (Group 3):* As per the PACL dated 12 October 2015, this group was closed to further enrollment.

A total of 68 slots are planned for enrollment. As of IRB/EC approval of Protocol Amendment #24, enrollment is closed. Further details for the MET-amplified NSCLC cohort is provided in Appendix 9.

c. A group of 50 NSCLC patients positive for chromosomal translocations at ROS1 gene, including but not limited to CD74-ROS1 and SLC34A2-ROS1 fusion events, will be enrolled. Enrollment is closed with 50 patients treated. Further detail for the ROS1 marker positive NSCLC cohort is provided in Appendix 10.

d. Approximately 171 patients with disease with molecular markers (other than ALK marker positive NSCLC and ROS1 marker positive NSCLC) that may confer sensitivity to PF-02341066 will be enrolled into the 'Enriched Other' cohort. This cohort also includes NSCLC patients with tumors harboring MET Exon 14 alterations. Sponsor approval is required for enrollment into this cohort. Further details for the 'Enriched Other' cohort are provided in Appendix 11.

After IRB/EC approval of Amendment #18 patients with NSCLC that is positive for ALK chromosomal translocations or gene amplifications will not be allowed to enter the enriched cohort. As of the PACL dated 07 December 2017, the remaining 13 open enrollment slots in the Enriched Other cohort were assigned specifically to NSCLC patients with tumors harboring MET Exon 14 alterations rather than the broader Enriched Other cohort. Thus, the Enriched Other cohort will be open only for enrollment of NSCLC patients with MET Exon 14 alterations. As of the Investigator Communication Letter dated January 7, 2019, further enrollment of NSCLC patients with tumors harboring MET exon 14 alterations is closed.

ALK Marker Negative NSCLC Cohort #1:

e. *This cohort will consist of NSCLC patients who are negative for the ALK translocation as determined by the ALK break apart FISH assay used in Protocols A8081007 and A8081005. A minimum of 25 to a maximum of 50 evaluable patients will be enrolled into this cohort. Patients will be dosed at the RP2D, ie, 250 mg BID of PF-02341066, with a cycle length of 3 weeks. Every effort will be made to ensure that baseline characteristics for these patients are comparable to those of ALK marker positive patients enrolled in the A8081007 trial. In addition to encouraging ALK marker negative patients identified under the A8081007 study to consider enrollment in the Phase 1 trial, baseline characteristics for patients in the A8081007 study will be evaluated in a pooled fashion across treatment groups and enrollment of patients in the Phase 1 trial may be adjusted to reflect characteristics on specific variables (eg, gender, age, etc). However, upon agreement between the Sponsor and Investigator, patients who have similar baseline characteristics to the ALK positive NSCLC patients in this study may be allowed to enter this study. In order to increase comparability of response evaluation between ALK marker negative and ALK marker positive patients, tumor scans from ALK marker negative patients enrolled in this trial will be evaluated by an independent radiology group. As of the Note to File issued 25 October 2012, tumor scans from patients enrolled into ALK marker negative NSCLC Cohort #1 will no longer be collected for and submitted to an independent radiology laboratory for review. Enrollment is closed with 47 patients treated.*

f. *ALK Marker Negative NSCLC Cohort #2: This cohort will consist of NSCLC patients who are negative for the ALK translocation as determined by the ALK break apart FISH assay by the central laboratory selected by the Sponsor. At least 20 patients will be enrolled into this cohort. Patients will be dosed at the RP2D, ie, 250 mg BID of PF-02341066, with a cycle length of 3 weeks. Patients may have been pre-screened using a local ALK test. However, only patients whose pre-screening ALK test was negative and confirmed negative by the central laboratory selected by the Sponsor may be enrolled in this trial. No molecular testing for MET or ROS1 may be performed prior to patient enrollment. As of the Note to File dated 19 June 2012, the requirement that*

no molecular testing for MET or ROS1 to occur prior to patient enrollment was removed. Thus, MET or ROS1 testing may have been performed prior to patient entry into this cohort. However if the test result is either MET or ROS1 positive, then the patient cannot be enrolled into this cohort. Patients should, however, have sufficient tumor tissue, ie, 9 slides, if possible, each containing unstained tissue sections that are 5 microns thick, to be tested for ROS1 fusion, MET amplification CCI [redacted] *The Sponsor will provide tumor shipment instructions for ROS1 and MET testing under separate cover. Enrollment is closed with 21 patients treated. Further detail for the ALK marker negative NSCLC Cohort #2 is provided in Appendix 8.*

CCI [redacted]

In addition, if possible, up to 6 patients will undergo pre- and post-dose [^{18}F]-FLT-PET. Also, if possible, the same patients who have biopsies performed, will undergo [^{18}F]-FLT-PET. A separate sub-study with at least 6 evaluable patients with MET mutation or amplification will undergo pre- and post-dose [^{18}F]-FLT-PET and [^{18}F]-FDG-PET. With the approval of Amendment #13 by the IRB/EC, no additional patients will undergo PET imaging. Finally, 12 evaluable patients in this cohort will participate in a fed/fast sub-study (see below). Clinical sites in Korea will not participate in this sub-study. Depending upon the overall results from the RP2D cohorts, a different dose/schedule may be tested in additional cohorts.

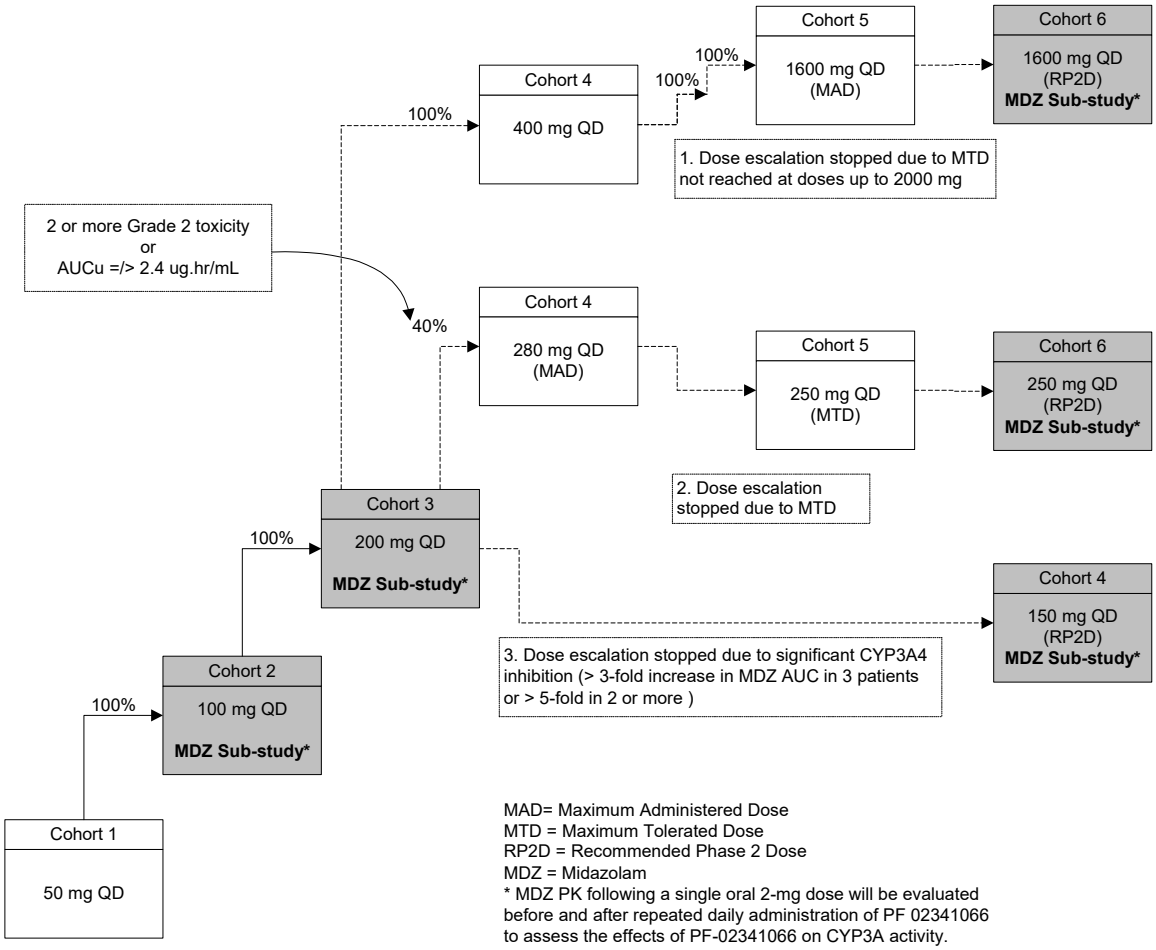
For patients who participate in the fed/fast sub-study, the effect of a high-fat, high-calorie breakfast on PF-02341066 pharmacokinetics will be studied. Each patient will serve as their own control in which PF-02341066 is administered under either "fed" or "fasted" conditions on Day -7 and Day 1 of Cycle 1 (morning dose if the BID regimen is employed). Pharmacokinetic sampling times are described in Section 7.5.1.1. The testing order for fed versus fasted conditions will be as follows: the first 6 patients to participate in this sub-study will be tested under fed followed by fasted conditions, the next 6 patients will be tested under fasted followed by fed conditions. If patients are receiving PF-02341066 on a BID dosing schedule, the evening dose of Day 1 of Cycle 1 will be cancelled. Patients who have had a gastrectomy or have dietary restrictions or adverse events that preclude a 10-hour overnight fast or cannot consume the high-fat, high-calorie meal will not be required to participate in this sub-study. See Section 5.2.3.1 for additional details on the high-fat, high-calorie meal.

All tumor scans from ALK marker positive NSCLC patients enrolled in the enriched population cohort (including ALK marker positive NSCLC patients in the dose escalation cohort) will be evaluated by an independent radiology group. As of the Note to File issued 25 October 2012, tumor scans from ALK marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review.

All tumor scans from ROS1 marker positive NSCLC patients enrolled will be collected and submitted to an independent radiology laboratory for review until notification is received

from the Sponsor. As of IRB/EC approval of Protocol Amendment #23, tumor scans from ROS1 marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review. As of IRB/EC approval of Protocol Amendment #23, all tumor scans from NSCLC patients with tumors harboring MET Exon 14 alterations will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. *All tumor scans from NSCLC patients with MET gene amplification will be collected and held at the investigative site until notification is received from the Sponsor. With Sponsor approval and IRB/EC notification, the Sponsor may request tumor scans from these patients to be submitted to an independent radiology laboratory for review at a later date.* As per PACL dated 9 March 2018, all tumor scans for patients enrolled in the MET-amplified NSCLC cohort will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Amendment #24, tumor scans from patients with MET-amplified NSCLC will no longer be collected and submitted to an independent radiology review laboratory.

Figure 4. Example of Dose Escalation Scenario



Dose Reductions

Intrapatient dose reduction after Cycle 1 (DLT evaluation period) will be permitted once a patient has experienced unexpected toxicity provided the criteria for patient withdrawal from study treatment have not been met. All intrapatient dose reductions are relative to the next lowest dose of the current cycle (dose level). Dose reduction of the regimen will be dependent on the attribution of toxicity as PF-02341066-related or possibly related to PF-02341066. The investigator (in discussion with the Sponsor) has discretion as to whether to discontinue or modify the dosages of the study drug, depending on the severity and timing of the event(s). A maximum of 2 dose reductions will be allowed per patient.

For patients enrolled in the RP2D cohorts, intrapatient dose reduction is permitted at any time. Following IRB/EC approval of Amendment #16, dose level -1 is 200 mg BID and dose level -2 is 250 mg QD. A maximum of 2 dose reductions will be allowed per patient.

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.

5.1. Management of Selected PF-02341066-Related Adverse Events

5.1.1. Nausea and Emesis

For nausea and emesis, treat with standard anti-emetics such as prochlorperazine or ondansetron. Taking the medication with food may reduce nausea. Prophylactic antiemetics should be considered.

5.1.2. Diarrhea

For CTCAE Grade 1 diarrhea, symptomatic care such as loperamide (Imodium®) or no intervention at investigator judgment.

For CTCAE Grade 2 diarrhea, loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). No dose modification unless patient is intolerant or symptom is recurrent.

For CTCAE Grade ≥3 (despite use of loperamide), treatment should be withheld until recovery to Grade ≤1.

5.1.3. Bradycardia

Concurrent use of PF-02341066 with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible, due to the increased risk of symptomatic bradycardia.

Heart rate and blood pressure should be monitored regularly. Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see Table 2b.

It is important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.

5.1.4. Pneumonitis

Investigators must evaluate thoroughly patients who demonstrate potential signs /symptoms of pneumonitis. If a patient has a potential diagnosis of pneumonitis or drug related lung injury, the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period in the absence of disease progression, other pulmonary disease, infection or radiation effects:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacterial pathogens;
- Blood culture should be performed in febrile patients. Consider appropriate serologies (mycoplasma, legionella, CMV, other viruses, etc.);
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology);
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture, microbiology and cytology;

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- A plasma sample for BNP (B-type Natriuretic peptide) to evaluate for evidence of CHF;
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis *jirovecii*).

If clinically appropriate, high dose corticosteroid treatment should be initiated.

Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis.

For any case of drug-related pneumonitis, discontinue PF-02341066 and contact the Sponsor (see Table 2b).

5.1.5. Renal Cyst

The development of complex renal cysts has been reported in some patients with NSCLC treated with PF-02341066. These cysts may be symptomatic or asymptomatic, and have usually developed within the first several months of starting PF-02341066. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended. Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be

performed at the time of the renal cyst diagnosis and thereafter following the same schedule as for tumor imaging. Contrast-enhanced CT scanning or magnetic resonance imaging should be performed assuring full visualization of the kidneys. Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts. Dipstick and urine microscopy should be performed on Day 1 of each cycle.

Table 2a and Table 2b describe the recommended dose modifications for study treatment-related toxicities prior to Amendment #12 and after Amendment #12, respectively (Note: Pneumonitis-related dose modification added with Amendment #15).

Table 2. Dose Modifications for PF-02341066 Associated Toxicity

Table 2a Dose Modifications for PF-02341066 Associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level. For recurrent subjectively intolerable toxicity (at least a week interruption on 2 occasions) that is not controlled by optimal supportive medication, reduce the dose to next lower dose level tested.*	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level, or reduce the dose to next lower dose level tested* at the discretion of the investigator.**	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose to next lower dose level tested* and resume treatment, or discontinue at the discretion of the investigator.**
Hematologic	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.***	Withhold dose until toxicity is Grade ≤2, then reduce the dose to next lower dose level tested* and resume treatment.***

* If the next lower level is below the first dose level tested in the study (dose level of the first cohort of patients), reduce the dose by 50%.
** 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.
*** Patients with recurrent Grade 3 neutropenia or thrombocytopenia for >7 days will dose reduce in the next cycle. Patients who develop Grade 3 or Grade 4 lymphopenia may continue study treatment without interruption.

Table 2b. Dose Modifications for PF-02341066 Associated Toxicity (after IRB/EC Approval of Amendment #12)

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 to next lower dose level tested at the discretion of the investigator.*	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose to next lower dose level tested and resume treatment, or discontinue at the discretion of the investigator.*
ALT or AST elevation possibly related to PF-02341066 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 AST and total bilirubin when symptomatic or within 7 days.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment by reducing by one dose level. If Grade 3 ALT or AST elevation recurs, reduce further (at most 2 dose levels from the initial dose level). If recurrence at dose level-2, then discuss with Sponsor whether or not to discontinue permanently. If 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.	See Grade 3.
ALT or AST elevation and total bilirubin elevation ≥2 x ULN (in 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 (particularly Ca+, K+ and Mg+) and concomitant medications. Correct any electrolyte or magnesium	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily.	Discontinue treatment and do not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		abnormalities Continue at the same dose level.	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.	
Pneumonitis (not attributable to disease progression, infection, other pulmonary disease 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. 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.	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 250 mg once daily upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring. Permanently discontinue for recurrence.
Vision Disorder	Continue at the same dose level. Repeat ophthalmologic examination.	Continue at the same dose level. Repeat ophthalmologic examination.	Interrupt PF-02341066 until recovery to Grade ≤1. Repeat ophthalmologic examination+. Resume treatment by reducing by one dose level upon recovery to Grade ≤1.	Discontinue treatment until recovery. Repeat ophthalmologic examination+.
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	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			the same dose level**/*** or reduce by 1 dose level after discussion with Sponsor.	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 clinical correlate (eg, opportunistic infection) may continue study treatment without interruption.
*** Patients enrolling with platelet counts >30,000/μL (to <50,000/μL) will be monitored for drug-related decreases at which point dose modifications will be discussed with the Sponsor.
+ Ophthalmologic examination includes ocular characteristics, visual acuity, fundoscopy and slit lamp examination and should be performed by an ophthalmologist. *After IRB/EC approval of Protocol Amendment #17, only NSCLC patients will be evaluated for additional specialized ophthalmological testing which includes: refractive error, pupil size, fundus photography, optical coherence tomography and intraocular pressure. These additional tests will be performed at screening, Cycle 1 Day 15, Cycle 3 Day 1, 1 year and yearly thereafter and then at 2 to 8 weeks after discontinuation of PF-02341066. For all other patients, applicable ophthalmologic examinations should be repeated during the study whenever a vision disorder AE is observed or when there is an increase in CTCAE grade from the previous visit.* As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. See Section 7.3.

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

In the event of significant toxicity, dosing may be interrupted and/or reduced as described below. 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 2 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Dose Interruption

The study investigator may implement dose suspension and/or reduction in order to ensure patient safety; however interruption in treatment should last for no more than 6 weeks. If a longer interruption is required, discussion with the Sponsor must occur and agreement must be reached between both the Sponsor and Investigator.

Dose Re-Escalation

Doses reduced for drug-related toxicity should generally not be re-escalated. However, intrapatient re-escalation back one or two dose levels after at least 4 weeks of treatment at the reduced dose level may be permitted on a case-by-case basis depending on the clinical setting and assessment of risk/benefit ratio after discussion with the Sponsor.

Overdose Instructions

In the event of an overdose, the Sponsor should be contacted to discuss the details of the overdose and formulate a clinical management plan.

No information regarding overdose of PF-02341066 in humans is available. No antidote exists for the treatment of PF-02341066 overdose. In the event of an accidental overdose, the patient should be monitored for possible signs of toxicity as mentioned above. As there is no specific antidote for overdose of PF-02341066, general supportive care should be provided.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

5.2.1.1. PF-02341066

Prior to IRB/EC approval of Amendment #12:

PF-02341066 is filled in two tone gray capsules containing 10, 50 or 100 mg of study medication for oral administration. The drug product consists of PF-02341066 in a hard gelatin capsule. The capsules are packaged in HDPE bottles and should be stored at room temperature (15 to 25 ℃) and handled with care.

Following IRB/EC approval of Amendment #12:

PF-02341066 will also be provided as tablets containing 50 or 100 mg of study drug for oral administration. The 50 mg tablets are round in shape whereas the 100 mg tablets are oval in shape. The tablets are packaged in HDPE bottles and should be stored at 15 to 30°C and handled with care. PF-02341066 may also be supplied as an oral solution (25 mg/mL) upon Sponsor agreement and availability of supplies. The oral solution is buffered, sweetened, and grape-flavored and is packaged in HDPE bottles. Dosing instructions and storage conditions for the oral solution will be provided under separate cover.

Following IRB/EC approval of Amendment #25 (Japan specific amendment):

PF-02341066 formulated capsules can also be administered. This capsule formulation has been shown to be bioequivalent to the tablets and a powder in capsule (PIC). Two capsule dosage strengths will be used: 200 mg and 250 mg of PF-02341066 for oral administration. The capsules are packaged in HDPE bottles, should be stored at 1 to 30°C and handled with care.

5.2.1.2. Midazolam (MDZ)

MDZ syrup (2 mg/mL) for oral administration will be used for patients who will participate in the MDZ interaction sub-study. The drug name and lot number for MDZ should be recorded in Case Report Forms (CRFs).

5.2.1.3. Rifampin

See Appendix 6 for details.

5.2.1.4. Itraconazole

See Appendix 7 for details.

5.2.2. Preparation and Dispensing

5.2.2.1. PF-02341066

The study medication should be dispensed according to the schedule of treatment administration (Section 5.2.3). Dispensing will be done by a qualified staff member in bottles provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

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 PF-02341066.

Medication will be provided in bulk containers. Investigational sites will also be provided with a supply of bottles and non-patient-specific labels. 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, ie, supplies for one cycle, however; for patients who visit the clinic every 2 cycles (after completing 10 cycles), enough supply for 2 cycles will be provided.

Once Amendment #12 is approved by the IRB/EC, all newly enrolled patients will receive tablet supplies. For ongoing patients, tablets will be supplied gradually and eventually completely replace the capsule.

PF-02341066 is a cytotoxic agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. *Due to possible unknown hazards associated with topical and environmental exposure to experimental cytotoxic agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion.* Capsules or tablets must be swallowed intact. However, PF-02341066 tablets may be dissolved according to specific dosing instructions which will be provided under separate cover after Sponsor approval is granted. Administration of PF-02341066 through any other means besides orally is not permitted.

Therefore, if a patient is unable to swallow the study drug intact, then 2 options exist:

- When available, PF-02341066 may be supplied as an oral solution (25 mg/mL) as described in Section 5.2.1.1, or

- PF-02341066 tablets may be dissolved according to specific dosing instructions as noted above.

In either circumstance, prior approval must be obtained from the Sponsor, and thereafter, dosing instructions will be provided under separate cover.

Note: For patients enrolled in rifampin and itraconazole interaction sub-studies, only the tablet formulation of PF-02341066 will be administered from the first dose of PF-02341066 until the last dose of PF-02341066 when co-administered with rifampin or itraconazole. Refer to Appendix 6 and Appendix 7 for further details.

5.2.2.2. MDZ

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.

5.2.3. Administration

5.2.3.1. PF-02341066

Administration will be performed on an outpatient basis. *PF-02341066 should be taken with at least 8 oz. of water on an empty stomach, ie, patient should refrain from food and beverages (except water) for at least 2 hours prior to dosing and for at least 2 hours after dosing. However, starting on Day 2 of Cycle 2, patients may take PF-02341066 without regard to meals.* With the approval of Amendment #14, patients may take PF-02341066 without regards to meals upon the initiation of treatment unless otherwise indicated. 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 for QD dosing and 6 hours for BID dosing either way is allowed for any given dose, rather than miss a day's dose. If a patient misses a day's dose entirely, 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-02341066. Patients should also be instructed to swallow the trial medication whole and not chew the capsule or tablet prior to swallowing. No capsule or tablet should be ingested if it is broken, cracked, or otherwise not intact. Doses may be modified according to Table 2. The study investigator may implement dose suspension and/or reduction in order to ensure patient safety.

For patients participating in the food effect study, PF-02341066 will be administered following an overnight fast of at least 10 hours. For those patients scheduled to receive the "fed" treatment, a high-fat, high-caloric breakfast will be provided and must be consumed over 30 minutes. PF-02341066 will be administered with approximately 8 oz of water 30 minutes after the start of the meal. No additional food will be allowed until at least 2 hours post-dose. For patients scheduled to receive the "fasted" treatment, PF-02341066 will be administered with 8 oz of water. No food will be allowed for an additional 2 hours post-dose. For either treatment day, water will be allowed ad libitum. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal is recommended as a test 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 two eggs fried in butter, two strips of bacon (may be replaced with ham or cheese of similar caloric content), two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole-fat milk. However, it

is understood that some patients may not be able to consume the entire meal. Study staff should record the % of the standard breakfast that is consumed.

5.2.3.2. MDZ

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-02341066 on Cycle 2 Day 1.

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. 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.

5.2.3.3. Rifampin

Please see Appendix 6 for details.

5.2.3.4. Itraconazole

Please see Appendix 7 for details.

5.2.4. Patient Compliance

Patients will be required to return all bottles of study drug at the beginning of each cycle. The number of capsules or tablets remaining will be documented and recorded. Patients who are considered non-compliant will be withdrawn from study (see Section 6.1).

As of the Note to File (NTF) dated 08 February 2018, the following guidance was issued to sites regarding dosing compliance:

Study Treatment (Crizotinib) Dosing	**Report as Protocol Deviation**	**Report as Medication Error**
Patient unintentionally misses a total of < 20% of his/her doses within a given cycle	No	No
Patient unintentionally misses a total of ≥ 20% of his/her doses within a given cycle	Yes	Yes
Patient unintentionally takes 1 extra dose within a given cycle	Yes	No
Patient unintentionally takes >1 extra dose with a given cycle	Yes	Yes

Please note, unintentional missed or extra doses should be investigated further with the patient to determine other potential reasons for the missed or extra doses (ie, whether due to a possible adverse event), as well as how to minimize their reoccurrence

5.3. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all study drugs, ie, PF-02341066, *rifampin and itraconazole,* are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

PF-02341066 should be stored in its original container and in accordance with the drug label. See the Investigator's Brochure for storage conditions of the product.

Storage conditions stated in the single reference safety document (Investigator's Brochure) will be superseded by the storage conditions stated in the labeling.

Returned medication for PF-02341066 should be stored separately from medication that needs to be dispensed.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to the Sponsor upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labelling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once an excursion is identified, PF-02341066 must be quarantined and not used until the Sponsor provides documentation of permission to use it. It will not be considered a protocol deviation if the Sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct patients on the proper storage requirements for take home medications.

If an excursion is identified for itraconazole, the Sponsor should be contacted.

The investigational product manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

The above requirements are to be implemented upon IRB/EC approval of Amendment #21 if not previously implemented.

Capsules: *PF-02341066 investigational medication should be stored at 15-25℃ (room temperature). 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 at 15-25℃ (room temperature). Returned medication should be stored separately from medication that needs to be dispensed.*

200 mg and 250 mg Formulated Capsules (Japan specific amendment): PF-02341066 investigational medication should be stored at 1-30°C. 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 at 1-30°C. Returned medication should be stored separately from medication that needs to be dispensed.

Tablets: PF-02341066 investigational medication should be stored at 15-30°C. 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 at 15-30°C. Returned medication should be stored separately from medication that needs to be dispensed.

Oral Solution: In those cases when an oral solution is approved for use by the Sponsor, detailed instructions on storage will be provided under separate cover.

To ensure adequate records, all study drug will be accounted for in the CRF and drug accountability inventory forms as instructed by the Sponsor. Unless otherwise authorized, at the end of the clinical trial all drug supplies unallocated or unused by the patients must be returned to the Sponsor or its designee. Patients must return all containers to a designated study center participant. All containers of PF-02341066 that were sent to the investigator throughout the study must be returned to the Sponsor or designee, whether they are used or unused, and whether they are empty or contain capsules.

5.4. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

To ensure adequate records, all study drugs will be accounted for in a drug accountability inventory form/record as instructed by the Sponsor. Unless otherwise authorized by the Sponsor, all PF-02341066 supplies unallocated or unused by the patients must be destroyed by procedures approved by the Sponsor or returned to the Sponsor or its designee. All containers must be returned to the Investigator by the patient.

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place 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 the Sponsor and all destruction must be adequately documented.

5.5. Concomitant Medication(s)

All concomitant treatments, blood products, as well as non drug interventions (eg, paracentesis) received by patients from screening (within 14 days of first dose) to 28 days after the last dose of study treatment will be recorded on the CRF.

5.5.1. PF-02341066

Concurrent anticancer therapy with agents other than PF-02341066 is not allowed. Upon IRB/EC approval of Amendment #24, localized anticancer therapy (eg, topical treatment of non-melanoma skin malignancy, intravesical Bacillus Calmette-Guerin [BCG] treatment) may be acceptable upon prior Sponsor anad Investigator agreement and written Sponsor approval. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

PF-02341066 is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A. In vitro studies in human liver microsomes demonstrated that PF-02341066 is a time-dependent inhibitor of CYP3A.

Co-administration of PF-02341066 with strong CYP3A inhibitors may increase PF-02341066 plasma concentrations. The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of PF-02341066 and should be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

Co-administration of PF-02341066 with strong CYP3A inducers may decrease PF-02341066 plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, should be avoided.

PF-02341066 has been identified as an inhibitor of CYP3A both in vitro and in vivo. Caution should be exercised in administering PF-02341066 in combination with drugs that are predominantly metabolized by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. Co-administration of PF-02341066 should be avoided with CYP3A substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias, including but not limited to dihydroergotamine, ergotamine, and pimozide.

Patients participating in the MDZ interaction sub-study must not take any midazolam dose which is not specified in the protocol 7 days prior to the first dose of MDZ until 24 hours

after the last dose of MDZ. These patients must not take medications including herbal supplements known to be CYP3A inhibitors or inducers for 7 days or 12 days, respectively, prior to the first dose of MDZ until 24 hours after the last treatment of MDZ.

Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended.

Rifampin interaction sub-study: Refer to Appendix 6 for further details.

Itraconazole Interaction sub-study: Refer to Appendix 7 for further details.

All concomitant medication must be approved by the Sponsor.

5.5.2. 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.

5.5.3. Hematopoietic Growth Factors

For patients enrolled into the Dose Escalation cohorts, prophylactic use of hematopoietic growth factors to support neutrophil or platelet counts may NOT be used before completion of Cycle 1 (DLT evaluation period). After Cycle 1, the use of hematopoietic growth factors is at the discretion of the treating physician. For patients enrolled into all other cohorts, prophylactic use of hematopoietic growth factors is permitted at any time. 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. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

5.5.4. 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.

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

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, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible during the study.

5.5.5. Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. PF-02341066 treatment should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after. Irradiated lesions will be considered not evaluable for response but still can be used to assess disease progression. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate CRFs.

The effect of PF-02341066 on wound healing is not known and has not been investigated; therefore, caution is still advised on theoretical grounds (potential antiangiogenic effect) for any surgical procedures during the study. The appropriate interval of time between surgery and PF-02341066 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, PF-02341066 dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery. Postoperatively, the decision to reinitiate PF-02341066 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. TRIAL PROCEDURES

For trial procedures, please see Schedule of Activities and Section 7 (Assessments). For rifampin interaction sub-study, itraconazole interaction sub-study, ALK-negative NSCLC Cohort #2, MET-amplified NSCLC Cohort, ROS1 marker positive NSCLC Cohort, and Enriched Other Cohort please refer to the Schedule of Activities in the corresponding appendices. Upon IRB/EC approval of Protocol Amendment #24, for ongoing patients in the ALK marker positive NSCLC cohort, the ROS1 marker positive NSCLC cohort, the MET-amplified NSCLC cohort, and the Enriched Other cohort (including NSCLC patients with MET Exon 14 alterations) please refer to the Reduced Schedule of Activities in Appendix 13.

6.1. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time 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 investigational site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. 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.

If the patient withdraws from study treatment and also withdraws consent for disclosure of future information, no further 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.

If a patient withdraws from study treatment and new anticancer therapy is subsequently administered, the End of Treatment (EOT) visit should occur prior to the initiation of new anticancer therapy.

7. ASSESSMENTS

Assessment of adverse events, laboratory safety (hematology, coagulation, urinalysis, chemistry and pregnancy tests), vital signs, physical examinations, ECGs, ophthalmology examinations, tumor assessment, PK sampling, CCI [redacted] will be done according to time points specified in the Schedule of Activities table.

For details on the rifampin interaction sub-study refer to the Schedule of Activities table in Appendix 6.

For details on the itraconazole interaction sub-study refer to the Schedule of Activities table in Appendix 7.

For details on ALK-negative NSCLC Cohort #2, refer to the Schedule of Activities table in Appendix 8.

For details on patients with MET-amplified NSCLC, refer to the Schedule of Activities table in Appendix 9.

For details on the ROS1 marker positive NSCLC patients, refer to the Schedule of Activities table in Appendix 10.

For details on the Enriched Other cohort, refer to the Schedule of Activities table in Appendix 11.

Upon IRB/EC approval of Protocol Amendment #24, for ongoing patients in the ALK marker positive NSCLC cohort, the ROS1 marker positive NSCLC cohort, the MET-amplified NSCLC cohort, and the Enriched Other cohort (including NSCLC patients with MET Exon 14 alterations) refer to the Reduced Schedule of Activities table in Appendix 13.

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 cannot 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.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Adverse Events

Adverse Events: type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0), timing, seriousness, and relatedness; laboratory abnormalities.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2. Laboratory Safety Assessments

Where possible, laboratory tests 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; process depends on local medical practice. The copy of the laboratory test results must be retained in the patient's file at the clinical site for documentation purposes.

Hematology: hemoglobin, platelet count, white blood cell count, and differential count. Upon IRB/EC approval of Amendment #24, hematology will be collected for ongoing patients on the reduced schedule of activities (Appendix 13), as per local clinical practice.

Chemistry: total and indirect bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, sodium, potassium, chloride**,** CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. Upon IRB/EC approval of Amendment #24, LDH and uric acid will no longer be collected for ongoing patients on the Reduced Schedule of Activities (Appendix 13).

Coagulation: PT (Prothrombin Time) and PTT (Partial Thromboplastin Time). Upon IRB/EC approval of Amendment #24, coagulation will no longer be collected for ongoing patients on the Reduced Schedule of Activities (Appendix 13).

Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrites. Upon IRB/EC approval of Amendment #24, urinalysis will no longer be collected for ongoing patients on the Reduced Schedule of Activities (Appendix 13).

In cases of suspected drug-induced liver injury (DILI) as described in Section 8.6.2 the following laboratory tests should be obtained in addition to repeating measurements of AST, ALT and total bilirubin: albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels.

Pregnancy Test: Upon IRB/EC approval of Amendment #21 for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment; once at Screening and once at the Cycle 1 Day 1 visit before starting PF-02341066. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at Cycle 1 Day 1 before the patient may receive PF-02341066.

Pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study therapy, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected.

In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. (See Section 4.3).

Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations.

Hypogonadism Tests: All male patients enrolled into the MET-amplified NSCLC and Enriched Other cohorts, after IRB/EC approval of Protocol Amendment #21, will have the following laboratory tests done: total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone, dihydroepiandrosterone sulfate, estradiol and prolactin. Blood samples must be taken before PF-02341066 dosing and between 7:00 and 10:00 a.m. and, for each individual patient, the time of the draw should be as consistent across visits as feasible. Blood samples will be submitted to the central laboratory (See Laboratory Manual). Patients enrolled in clinical sites in Japan as part of the Enriched Other Cohort will not participate in hypogonadism testing.

- *Pre-dose blood samples will be taken at the following times: Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, every 3 cycles thereafter and at the End of Treatment visit.*

- *Repeat testing of total testosterone and free testosterone levels must be performed at the next clinic visit if a decrease of ≥25% from baseline to a value below the age-specific lower limit of normal is observed in either parameter.*

Upon IRB/EC approval of Protocol Amendment #24, sample collection for hypogonadism tests is no longer required.

Refer to Appendix 9 (MET-amplified NSCLC Cohort), Appendix 11 (Enriched Other Cohort), Appendix 12 (Hypogonadism Testing) for further details.

7.3. Other Safety Assessments

Physical Examination.

ECOG Performance Status.

Vital signs: body temperature, blood pressure, and heart rate (as of Protocol Amendment 22, "respiratory rate" was deleted as this assessment was incorrectly required by the protocol and has not been collected during this study).

ECG: A 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. Triplicate ECG measurements will be obtained at all time points. Three consecutive 12-lead ECGS will be collected approximately 2 minutes apart. Additional ECGs should be performed as clinically indicated. Upon IRB/EC approval of Protocol Amendment #24, ECG is no longer required.

Ophthalmology examination: includes ocular characteristics, visual acuity, fundoscopy and slit lamp examination. This ophthalmology examination should be performed for all patients at screening and repeated during the study when a visual change occurred or when there is an increase in grade for a visual change. *Once Amendment #17 is IRB/EC approved, all NSCLC patients enrolled after Amendment #17 approval will also undergo the following ophthalmology tests:*

- *Best correct distance visual acuity;*
- *Refractive error associated with best corrected distance visual acuity;*
- *Pupil size under standardized lighting conditions;*
- *Slit lamp biomicroscopy of the anterior segment including cell count and flare grading;*
- *Fundoscopy of the posterior segment;*
- *Intraocular pressure must be done twice for each eye. If test results deviate by more than 2 mmHg of each other, a third reading must be obtained;*
- *Ocular coherence tomography of the macula;*
- *Dilated fundus photography of the retina.*

These tests will be performed at screening, Cycle 1 Day 15, Cycle 3 Day 1, 1 year, yearly thereafter, and then 2-8 weeks after the last dose of PF-02341066. A total of 30 NSCLC patients are required to complete all time points. All NSCLC patients enrolled after IRB/EC approval of Amendment #17 will continue to undergo these special tests until written notification from the Sponsor. As of the Note To File dated 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. Findings from the ophthalmology examinations should be reported as an adverse event if a finding is considered to be an adverse event by the investigator or Sponsor.

7.4. Disease Imaging Studies

Screening/baseline imaging assessments will include CT or MRI scans of the chest, abdomen, and pelvis. Brain scans and bone scans will be performed at baseline if disease is suspected. Scans should be repeated every other cycle (ie, every 8 weeks for patients on 28 day cycle and every 6 weeks for patients on 21 day cycle) if disease is identified.

Assessment of tumor response and progression will be performed using CT or MRI scans of disease documented at baseline or suspected to have arisen since baseline and bone scans as appropriate. Disease response for solid tumors will be categorized using RECIST v. 1.0 (Appendix 3). For patients in the ALK marker negative NSCLC cohorts, disease response will be categorized using RECIST v. 1.1 (Appendix 5).

For patients in the ALK marker negative NSCLC Cohort #1 only and ALK marker positive NSCLC enriched population cohort, their scans will be reviewed by an independent radiology laboratory. As of the Note to File issued 25 October 2012, tumor scans from the ALK marker negative NSCLC Cohort #1 will no longer be collected for and submitted to an independent radiology laboratory for review. As of Amendment #20, tumor scans from ALK marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review.

Tumor scans from ROS1 marker positive NSCLC patients enrolled will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Protocol Amendment #23, tumor scans from ROS1 marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review.

As of IRB/EC approval of Protocol Amendment #23, all tumor scans from NSCLC patients with tumors harboring MET Exon 14 alterations will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor.

All tumor scans from NSCLC patients with- MET gene amplification will be collected and held at the investigative site until notification is received from the Sponsor. With Sponsor approval and IRB/EC notification, the Sponsor may request tumor scans from these patients to be submitted to an independent radiology laboratory for review at a later date. As per Protocol Administrative Clarification Letter dated 9 March 2018, all tumor scans for patients enrolled in the MET-amplified NSCLC cohort will be collected and submitted to an radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Amendment #24, tumor scans from patients with MET-amplified patients will no longer be collected and submitted to an independent radiology review laboratory.. However, response and progressive disease will still be based on the clinical site's-review of the scans. Disease response for lymphomas and multiple myelomas will be categorized using specific response criteria for each disease.

7.5. Pharmacokinetics

7.5.1. Plasma Pharmacokinetic Assessment

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). During the trial, actual collection times may change but the number of samples will remain the same.

As part of understanding the pharmacokinetics of the PF-02341066, plasma samples may be used for metabolite identification and/or evaluation of the bioanalytical method once Amendment #12 has been IRB/EC approved. These data will be used for internal exploratory purposes and will not be included in the clinical report. PK samples will be assayed for PF-02341066 (including its active moieties, if appropriate), MDZ or itraconazole (if appropriate) using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the storage and shipping of plasma samples will be provided in the Study Manual.

7.5.1.1. Plasma Pharmacokinetic Assessment for PF-02341066

In all dose escalation cohorts, blood samples for PF-02341066 (including its active moieties, if appropriate) will be collected as follows:

1. *For patients who do not participate in the MDZ interaction study, a full pharmacokinetic profile of PF-02341066 will be obtained after administration of a single dose on Day -7 (lead-in period) at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, 24, and 48 hours post dose. In addition, blood samples will be obtained at any two time points of the following: 72, 96, 120 and 144 hours post-dose. Blood samples for PF-02341066 pharmacokinetics will be also obtained on Day 1 of Cycle 1 at predose and 6 (2 hours as of May 1, 2007; 4 hours as of February 1, 2008) hours post-dose only, and Day 15 of Cycle 1 and Day 1 of Cycle 2 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose.*

2. *For patients who participate in the MDZ interaction sub-study* or patients *who are exempted from the Day -7* lead-in dose (see *Section 5*)*, blood samples for PF-02341066 pharmacokinetics will be collected on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 at 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose.*

For patients in the RP2D midazolam interaction cohort, blood collections will be as described in #2 above.

For patients in the rifampin interaction sub-study refer to Appendix 6 for details on blood collections.

For patients in the itraconazole interaction sub-study refer to Appendix 7 for details on blood collections.

For patients in the MET-amplified NSCLC cohort refer to Appendix 9 for details on blood collection.

For patients in the Enriched Other cohort refer to Appendix 11 for details on blood collection.

Blood samples for PF-02341066 (including its active moieties, if appropriate) will be collected as follows (when Amendment #10 is activated, clinical sites in Korea [or when amendment #13 is activated for Asian patients from all other sites] should only follow instruction # 4 below):

1. *For patients who participate in the food effect sub-study, a full pharmacokinetic profile of PF-02341066 will be obtained after dosing on Day -7 and Cycle 1 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, and 24 hours post-dose. Additional PK samples will be obtained pre-dose and 2-8 hours post-dose on Day 15 of Cycle 1 and Day 1 of Cycle 2. Note: Clinical sites in Korea will not participate in this sub-study.*

2. *For patients who do not participate in the food effect sub-study, a full pharmacokinetic profile of PF-02341066 will be obtained after dosing on Day -7 at the following times: 0 (pre-dose), 1, 2, 4, 6, 8, 9, 24 and 48 hours post-dose. In addition, blood samples will be obtained at any two time points of the following: 72, 96, 120 and 144 hours post-dose. Additional PK samples will be obtained pre-dose and 2-8 hours post-dose on Days 1 and 15 of Cycle 1 and Day 1 of Cycle 2. Once Amendment #13 is activated, the Day-7 blood collections will be eliminated. This change is only for non-Asian patients. Asian patients will follow Instruction #4. After Amendment #16 is IRB/EC approved, this change will apply to all patients.*

3. *For patients who are exempted from the Day -7 lead-in dose, blood samples for PF-02341066 PK will be collected on Cycle 1 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, and 24 hours post-dose. Additional PK samples will be obtained pre-dose and 2-8 hours post-dose on Day 15 of Cycle 1 and Day 1 of Cycle 2. Once Amendment #13 is activated, only a 0 (pre-dose) and 2-8 hour post morning dose sample will be collected on Cycle 1 Day 1. Once Amendment #13 is activated, the Day-7 blood collections will be eliminated. This change is only for non-Asian patients. Asian patients will follow Instruction #4. After Amendment #16 is IRB/EC approved, the Day -7 blood draws will be eliminated for all patients.*

4. *For patients who are enrolled in clinical sites in Korea, a full pharmacokinetic profile of PF-02341066 will be obtained after dosing on Day -7 at the following times: 0 (pre-dose), 1, 2, 4, 6, 8, 9, 24 and 48 hours post-dose. In addition, blood samples will be obtained at any two time points of the following: 72, 96, 120 and 144 hours post-dose. Blood samples for PF-02341066 pharmacokinetics will be also obtained on Day 1 of Cycle 1 at predose and 2-8 hours post-dose, and Day 15 of Cycle 1 and Day 1 of Cycle 2 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose. If the patient is exempted from the Day -7 lead-in dose, blood samples for PF-02341066 PK will be collected on Cycle 1 Day 1, Cycle 1 Day*

15 and Cycle 2 Day 1 at the following times points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, and 24 hours post-dose. Once Amendment #16 is IRB/EC approved, all patients enrolled in clinical sites in Korea will follow the updated Instruction #3.

For all cohorts except for the ALK marker negative NSCLC cohorts, in order to assess pharmacokinetics in patients receiving long-term treatment with PF-02341066, two PK sampling points (pre-dose and 4-8 hours [2-8 hours as of May 1, 2007] post-dose) will be obtained on Day 15 of Cycle 2, Day 1 of Cycle 3 and Day 1 of subsequent cycles (up to Cycle 5) for all patients.

For the ALK marker negative NSCLC cohort, plasma PK samples will be collected prior to morning dosing on Day 1 of Cycles 1, 2, 3 and 5 and 2-6 hours following dosing on Day 1 of Cycles 1, 3 and 5. Following IRB/EC approval of Amendment #18, patients in the RP2D MET-amplified NSCLC and Enriched Other cohorts and ALK marker negative NSCLC RP2D Cohort #2 will have PK samples collected on Day 1 of Cycles 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. In addition, for patients in the MET-amplified NSCLC, ROS1 marker positive NSCLC and Enriched Other cohorts, a PK sample should be taken around the time that disease progression is confirmed as long as the patient is still on PF-02341066 treatment.

Further details for the ALK marker negative NSCLC cohort #2 are provided in Appendix 8.

Further details for the MET-amplified NSCLC Cohort are provided in Appendix 9.

Further details for the ROS1 marker positive NSCLC cohort are provided in Appendix 10.

Further details for the Enriched Other cohort are provided in Appendix 11.

In addition to samples mentioned above, additional blood samples for PK evaluation may be requested from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and Sponsor). More than one PK sample per patient may be collected throughout the study; however the total blood volume of additional PK samples collected per patient should not exceed 15 mL (ie, no more than 5, 3 mL samples). As of IRB/EC approval of Protocol Amendment #23, the total blood volume of additional PK samples collected per patient should not exceed 20 mL (ie, no more than 5, 4 mL samples).

Blood samples (4 mL) for PF-02341066 pharmacokinetic analysis will be collected into appropriately labeled collection tubes containing KEDTA at protocol-specified times. Once collected, samples should be processed immediately and kept out of direct sunlight due to the light sensitive nature of PF-02341066. Blood samples will be placed immediately on ice-bath and centrifuged at approximately 1700 g for 10 minutes at 4°C. Plasma samples will be stored in appropriately labeled tubes at approximately -20°C within 1 hour of collection. Details regarding the sample preparation will be provided in the Laboratory Manual.

Upon IRB/EC approval of Protocol Amendment #24, blood samples for PK analysis will no longer be collected.

7.5.1.2. Plasma Pharmacokinetic Assessment for MDZ

In the MDZ interaction sub-study, a pharmacokinetic profile of MDZ will be collected after a single oral MDZ dose on Day –7 (lead-in period) and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 9, and 24 hours post dose.

Blood samples (2 mL) for MDZ pharmacokinetic analysis will be collected into appropriately labeled collection tubes containing sodium heparin at protocol-specified times. Blood samples must be placed immediately into an ice-water bath and centrifuged at approximately 1700 g for 10 minutes at 4 ℃ prior to storage. The plasma (approximately 1 mL) will be stored in appropriately labeled screw-capped polypropylene tubes at ≤-20 ℃ within 1 hour of sample collection. Details regarding the sample preparation will be provided in the Study Manual. Note: Clinical sites in Korea and Australia will not participate in the MDZ interaction sub-study.

7.5.2. Urine for Analysis of PF-02341066

In the RP2D midazolam interaction cohort, urine samples will be collected for 24 hours after PF-02341066 dosing on Cycle 1 Day 15 to measure PF-02341066 concentrations, and thereby determine the renal elimination of PF-02341066 from the body. Metabolites of PF-02341066 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 postdose. 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 from 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.

7.5.3. Plasma for PF-02341066 Metabolite Profiling

Additional 5-mL blood samples will be collected at 4-8 hours post dose on Cycle 1 Day 15 in the RP2D midazolam interaction cohort for metabolite profiling.

Detail collection procedure will be provided in the study manual.

7.5.4. Blood Sample for Pharmacogenomics

Blood samples for genotyping will be examined to assess the impact of allelic variants of drug-metabolizing enzymes and transporters. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in pharmacokinetics (PKs) or to explore the relationship with AEs. Samples will be retained for a period of up to 3 years following the submission of the final clinical study report (CSR).

A 4-mL blood sample will be collected from each subject into a plastic dipotassium ethylenediaminetetraacetic acid (K_2EDTA) tube at times specified in the SCHEDULE OF ACTIVITIES section of the protocol.

CCI [redacted]

The pharmacogenomic (PGx) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PGx processing steps, including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

For patients enrolled in clinical sites in Japan as part of the Enriched Other Cohort, blood sample collection for pharmacogenomics is optional.

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

A midstream morning spot urine sample (10 mL) will be collected into an appropriately labelled plastic screw topped collection container prior to dosing of any drug on Day 1 of Cycle 1, Day 15 of Cycle 1 and Day 1 of Cycle 2. Urine samples should be frozen immediately and stored at -20℃. The urinary 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio will be determined to evaluate the potential of CYP3A4 induction. These samples will no longer be collected once IRB/EC approval of Amendment #17.

Sample analysis will be performed using a validated bioanalytical method in accordance with Pfizer standard operating procedures.

CCI [redacted]

CCI

[redacted]

7.5.8. [^{18}F]-FLT-PET and [^{18}F]-FDG-PET Imaging (RP2D enriched population cohort only)

If possible, at least 6 evaluable patients with MET mutations/amplification will be enrolled into the imaging portion of the RP2D enriched population cohort. These patients will undergo [^{18}F]-FLT-PET and [^{18}F]-FDG-PET imaging. Also, if possible, the same patients that have pre- and post-dose biopsies will undergo PET imaging. The screening [^{18}F]-FLT-PET and [^{18}F]-FDG-PET 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. A patient will be considered evaluable if they have 2 or more baseline target lesions each identified by both [^{18}F]-FLT-PET and [^{18}F]-FDG-PET imaging. All evaluable lesions must have a baseline [^{18}F]-FLT-PET SUV of at least 2, and a baseline [^{18}F]-FDG-PET SUV ≥3.5 (liver) or ≥5 (non-liver). Results of the PET sub-study will be scored according to the methods developed by the American College of Radiology Imaging Network (ACRIN; http://www.acrin.org/petcorelab.html). These assessments will be performed as per the Schedule of Activities. With the approval of Amendment #13 by the IRB/EC, no additional patients will undergo PET imaging.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (SAE) (see Section 8.6) requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. 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 an 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 begin from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the clinical trial, ie, prior to undergoing any trial-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.

Adverse events (serious and non-serious) should be recorded on the Case Report Form (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 anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event 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 adverse events 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;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under trial should be reported as adverse events 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 adverse events.

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 AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 trial dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or Sponsor.

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

8.6. Serious Adverse Events

A serious adverse event 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 serious adverse events unless the outcome is

fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. 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 adverse event and as a serious adverse event with Common Terminology Criteria for Adverse Events (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 adverse event 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 Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (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 ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 x ULN or not available.

- For patients with pre-existing AST **OR** ALT **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 preexisting AST or ALT baseline values above the normal range; AST or ALT values ≥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 1 x ULN **or** if the value reaches ≥3 x ULN (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, a 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 and total bilirubin, laboratory tests should also include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen and/or protein adduct levels. 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 serious adverse events.

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 adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event 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 clinical trial (eg, for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (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 adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.8. Severity Assessment

If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 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 3.0 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 adverse event. A severe event is not necessarily a serious adverse event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (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 adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not 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 trial records.

In addition, if the investigator determines a serious adverse event is associated with trial 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 serious adverse event 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 woman (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 any trial patient or trial patient's partner becomes or is found to be pregnant during the trial patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) 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 EDP supplemental form. This must be done irrespective of whether an adverse event 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 EDP 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 EDP supplemental 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 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 a serious adverse event (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 serious adverse events.

Additional information about pregnancy outcomes that are reported as serious adverse events 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 serious adverse events. In addition, infant deaths after 1 month should be reported as serious adverse events 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 Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

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

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

When a patient withdraws because of an SAE, the serious adverse event 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 adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events.

8.14. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event 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 a serious adverse event immediately (eg, if an outpatient trial 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 adverse event.

For all serious adverse events, 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 serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event 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 adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

Up to approximately 600 patients will be enrolled in the study including patients in the dose escalation and RP2D cohorts see Figure 1. *With Sponsor written approval and IRB/EC notification, 10 to 15 additional patients may be enrolled (for a total overall enrollment of approximately 580 patients) to reach the target enrollment of approximately 40 to 50 NSCLC patients with tumor harboring MET Exon 14 alterations and approximately 20 to 25 male patients for hypogonadism evaluation in the event that overall enrollment is achieved prior to reaching these targets.*

9.1.1. Dose Escalation Phase

The number of patients to be enrolled in the dose escalation phase of this study will depend upon the observed safety profile and study objectives, which will determine the number of patients per dose level, the number of dose escalations and the number of cohorts.

It is anticipated that a total of approximately 70 patients will be enrolled in the dose escalation phase of this study to determine both the QD MTD and the BID MTD.

The operating characteristics for the dose escalation part of this study design are shown in Table 3, which provides the probability of escalation to the next higher dose for each underlying true DLT rate. For example, for a toxicity that occurs in 5% of patients, there is a greater than 95% probability of escalating. Conversely, for a common toxicity that occurs with a rate of 70%, the probability of escalating is <5%.

Table 3. Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	*5%*	*10%*	*20%*	*30%*	*40%*	*50%*	*60%*	*70%*	*80%*	*90%*
Probability of Escalating Dose	*0.97*	*0.91*	*0.71*	*0.49*	*0.31*	*0.17*	*0.08*	*0.03*	*0.01*	*0.001*

Table 4 shows the probability of failing to observe toxicity in a sample size of 3 or 6 patients given various true underlying toxicity rates. For example, with 6 patients, the probability of failing to observe toxicity occurring at least 40% of the time is less than 5%.

Table 4. Probability of Failing to Observe Toxicity (at Least One DLT Given the True Underlying DLT Rate) at a Dose Level

True Underlying DLT Rate	*5%*	*10%*	*20%*	*30%*	*40%*	*50%*	*60%*	*70%*	*80%*	*90%*
Probability of Failing to Observe Toxicity, N=3	*0.86*	*0.73*	*0.51*	*0.34*	*0.22*	*0.13*	*0.064*	*0.027*	*0.008*	*0.001*
Probability of Failing to Observe Toxicity, N=6	*0.74*	*0.53*	*0.26*	*0.12*	*0.047*	*0.016*	*0.0041*	*<0.001*	*<0.001*	*<0.001*

9.1.2. RP2D Midazolam Interaction Cohort

*Eight evaluable patients will be required for the MDZ interaction study in the RP2D cohort. The effect of multiple doses of PF-02341066 on MDZ will be evaluated by estimating the $AUC_{0\text{-}last}$ ratio of MDZ in presence of PF-02341066 and MDZ alone. Based on data from previous single dose MDZ studies conducted at Pfizer, it is estimated that the within-patient coefficient of variation (CV) for the $AUC_{0\text{-}\infty}$ data is 25%. The standard deviation of the difference in log-transformed data is then estimated to be 0.348 [(sqrt 2) *(sqrt(ln(1+CV^2)))]. If PF-02341066 increases MDZ $AUC_{0\text{-}\infty}$ by 2 fold (a 100% increase), then 8 patients will ensure that the width of the 90% confidence interval for the ratio will be no longer than 1.12, with 80% probability (see Table 5). A probable 90% confidence interval is calculated to be: (1.52, 2.64). The sample size is calculated using a paired t-test (nQuery, Version 4.0).*

Table 5. Expected Precision for Effect of PF-02341066 on MDZ (90% CI, 80% coverage probability, 25% CV)

Sample Size	*Estimated Ratio*	*Probable CI, Lower Limit*	*Probable CI, Upper Limit*	*Probable CI Width*
8	*1.3*	*0.987*	*1.713*	*0.726*
	1.5	*1.138*	*1.976*	*0.838*
	2.0	*1.518*	*2.635*	*1.117*

9.1.3. RP2D Enriched Population Cohort

It is anticipated that approximately 484 patients will be enrolled into the RP2D enriched population cohort. Inclusion in this cohort is based on the inclusion criteria described in Section 4.1 and in Appendix 8 for ALK marker negative NSCLC patients, Appendix 9 for patients with MET-amplified NSCLC, Appendix 10 for ROS1 marker positive NSCLC patients and Appendix 11 for the Enriched Other cohort which includes patients with disease with molecular markers (other than ALK marker positive NSCLC, ROS1 marker positive NSCLC and MET-amplified NSCLC) that may confer sensitivity to PF-02341066. *Two sub-studies will also be included in this cohort: (1) [^{18}F]-FLT-PET and (2) food effect. First, approximately 6 patients will participate in a [^{18}F]FLT-PET sub-study which should be sufficient to identify at least a 15% decline in standardized uptake value (SUV) compared to baseline.* CCI [redacted] *Second,*

for the food effect sub-study, twelve patients will provide at least 80% power to detect at least a 2-fold in the AUC or C_{max} between fed and fasting drug administration (assumes an intrapatient CV of 10% for AUC and C_{max}).

9.1.3.1. ALK Marker Negative NSCLC Cohorts

9.1.3.1.1. ALK Marker Negative NSCLC Cohort #1

The main objective of this ALK marker negative NSCLC cohort is to evaluate the objective response in this group of patients and to compare with the objective response observed from ALK marker positive NSCLC patients enrolled in Study A8081007 and/or Study A8081005, as appropriate. Depending on the recruitment for the ALK marker negative NSCLC cohort, patients with more than one previous treatment may be enrolled. Response to PF-02341066 among ALK marker negative patients is expected to be low (to date no objective responses were observed in the unselected population in this study). Therefore, the subset of ALK marker negative patients in this cohort will be first limited to a total of 25 patients.

If ≤3 objective responses (CR or PR) are observed in the first 25 ALK marker negative patients, no additional ALK marker negative NSCLC patients will be enrolled into this trial. With 25 patients and exactly 3 objective responses, the 90% exact confidence interval (CI) (3%, 28%) around the observed response rate (12%) will not overlap with the 90% CI around the assumed estimate of 40% for ALK marker positive patients (assuming that 159 ALK marker positive patients are enrolled in the PF-02341066 arm of Study A8081007). Of note, the patient population in the current trial has been heavily pre-treated with a median number of 3 previous systemic therapies and the observed objective response rate (ORR) for the ALK marker positive NSCLC group is ~60%.

If >3 objective responses are observed among the 25 ALK marker negative patients, additional patients may be enrolled in this trial as noted in Table 6.

Table 6. Power Calculation for ALK Marker Negative NSCLC Cohort #1

Responses in First 25 ALK - Patients	***Additional ALK - Patients to be Enrolled***	***Total ALK - Patients in this Trial***	***Exact 90% CI * Around ORR (column 1/ column 3 x 100)***	***Exact 90% CI Around 40% ORR Assumed for 160 ALK + Patients (Protocol A8081007)***
4	*5*	*30*	*(5%, 28%)*	*(34%, 47%)*
5	*10*	*35*	*(6%, 28%)*	*(34%, 47%)*
6	*15*	*40*	*(7%, 27%)*	*(34%, 47%)*

**Assumes that no responses are observed after additional ALK marker negative patients are enrolled in this trial*

If ≥7 responses are observed among the first 25 ALK marker negative patients, then no additional patients will be enrolled beyond 40 until read out of study A8081007 study results.

9.1.3.1.2. *ALK Marker Negative NSCLC Cohort #2*

In order to further characterize the anti-tumor activity of PF-02341066 in ALK marker negative NSCLC patients, at least 20 patients will be enrolled into this cohort. These patients may have been pre-screened by a local ALK test but only those who were determined to have ALK-negative NSCLC may be eligible for enrollment. The results of the negative

local test must be confirmed by the central laboratory before entry into the study. No testing for ROS1 or MET may be performed prior to patient enrollment. As of the Note to File dated 19 June 2012, the requirement that no molecular testing for MET or ROS1 to occur prior to enrollment was removed. However, if MET or ROS1 testing was performed prior to patient enrollment and the test result for either MET or ROS1 was positive, then the patient could not be enrolled onto this cohort.

Further details for the ALK marker negative NSCLC Cohort #2 are provided in Appendix 8.

9.1.3.2. *MET-Amplified NSCLC Cohort*

In order to further evaluate the anti-tumor activity of PF-02341066 associated with MET amplification, patients with MET-amplified NSCLC will be enrolled into one of the following categories:

- *High Level MET Gene Amplified Category (MET/CEP7 ratio ≥5.0; Group 1):* As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to ≥4.0). As per the PACL dated 11 September 2018, this group was closed to further enrollment. The remaining 14 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

- *Medium Level MET Gene Amplified Category (MET/CEP7 ratio >2.2 to <5; Group 2):* As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to >2.2 to <4.0 and this group was closed to further enrollment. The remaining 13 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort;

- *Low Level MET Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2; Group 3):* As per the PACL dated 12 October 2015, this group was closed to further enrollment.

For each category, an ORR of 10% was considered to be uninteresting for further study for this category with 30% considered interesting for further exploration. Using a Simon optimal two-stage design with alpha=0.05 and 80% power, a test of the null hypothesis that p ≤10% versus the alternative p ≥30% requires 10 evaluable patients in the first stage. If ≤1 objective response (CR or PR) is observed in the first 10 patients for any category, no additional patients in that category will be enrolled. If 2 or more objective responses are observed in the first stage for any category, the first stage may be expanded by enrolling 19 additional patients in that category. However, upon completion and evaluation of the first stage, a decision will be made whether or not to expand to the second stage in any of the 3 categories investigated. Within a category, if >5 objectives responses are observed, the null hypothesis will be rejected.

As of a PACL issued June 27, 2014, 4 objective responses were observed in the High Level MET Gene Amplification category and the cohort was expanded to an additional 19 patients, for a total of 29-31 patients. As of a PACL issued October 28, 2014, 2 objective responses were observed in the Medium Level MET Gene Amplified category and the cohort was expanded to an additional 19 patients, for a total of 29-31 patients.

Further details for the MET-amplified NSCLC cohort are provided in Appendix 9.

To increase the likelihood of achieving the target enrollment of approximately 20 to 25 evaluable male patients with hypogonadism testing in a timely manner, the Sponsor decided to close enrollment of patients into the MET low amplification NSCLC category (MET/CEP7 ratio ≥1.8 to ≤2.2) due to slow enrollment, effective as of the Protocol Administrative Clarification Letter dated 12 October 2015. Thus, the remaining unused enrollment slots (estimated to be approximately 28: 9 from Simon first-stage and 19 from Simon second-stage) was transferred to the Enriched Other cohort. With Sponsor approval and IRB/EC notification, other conditions including, but not limited to, slow enrollment in the medium and/or high level MET amplification categories, may trigger transfer of additional enrollment slots from these MET gene amplification categories to the Enriched Other cohort. As per the PACL dated 15 May 2017, further enrollment of NSCLC patients into the MET intermediate amplification group was closed and the remaining 13 enrollment slots were transferred to the Enriched Other cohort to facilitate further enrollment of patients with MET Exon 14-positive NSCLC. As per the PACL dated 11 September 2018, further enrollment of NSCLC patients into the MET high amplification group was closed and the remaining 14 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

9.1.3.3. ROS1 Marker Positive NSCLC Cohort

To further evaluate the anti-tumor activity of PF-02341066 in patients with NSCLC positive for a chromosomal translocation in the ROS1 gene, approximately 30 patients will be enrolled. An ORR of 10% was considered to be uninteresting for further study for this cohort with 30% considered interesting for further exploration. With 27 evaluable patients, there is at least 85% power to test the null hypothesis that the ORR is less than or equal to 0.10 vs. the alternative hypothesis that it is greater than 0.10 assuming an alternative target rate of 0.30 with a one-sided alpha=0.05 using a single stage design. The null hypothesis will be rejected if greater than or equal to 6 objective responses are observed among the 27 evaluable patients. A total of approximately 30 patients will be enrolled into this cohort to adjust for 10% loss of patients who are not evaluable for response.

As of a database snapshot date of 19 April 2012, 8 confirmed objective responses (CR, partial response [PR]) were observed in a total of 14 response evaluable patients enrolled in the ROS1 marker-positive NSCLC cohort. Based on the number of confirmed objective responses observed (CR, PR), the null hypothesis was rejected. As recorded in the Note to File dated 12 November 2012, and in Protocol Amendment 20, the sample size of the ROS1 marker-positive NSCLC cohort was increased to a total of 50 patients in order to provide a more robust estimation of antitumor activity in this patient population.

Further details for the ROS1 marker positive NSCLC cohort are provided in Appendix 10.

9.1.3.4. Enriched Other Cohort

To evaluate the anti-tumor activity of PF-02341066 in patients with other tumor types that have a molecular marker that confers sensitivity to PF-02341066 (eg, other tumor types besides NSCLC), the sample size of the Enriched Other cohort will be dependent upon the

number of enrolled patients meeting the criteria for this cohort; however it is anticipated that approximately 171 patients will be enrolled.

Further details for the Enriched Other cohort are provided in Appendix 11.

In the Enriched Other cohort, approximately 50 NSCLC patients with tumors harboring MET Exon 14 alterations will be enrolled. In addition, a separate group of approximately 5 NSCLC patients with tumors harboring MET Exon 14 alterations will be enrolled in clinical sites in Japan. With Sponsor written approval and IRB/EC notification, additional patients may be enrolled as described earlier in this section (Section 9.1) to reach this target enrollment in the event that overall enrollment is achieved prior to reaching this target.

In NSCLC patients with tumors harboring MET Exon 14 alterations, an ORR of 10% will be considered uninteresting for further study for this group, with 30% considered interesting for further exploration. With 33 evaluable patients, there is at least 90% power to test the null hypothesis that the ORR is less than or equal to 0.10 versus the alternative hypothesis that it is greater than 0.10 assuming an alternative target rate of 0.30 with a one-sided α=0.05 based on a single stage design using exact test. The null hypothesis will be rejected if ≥7 objective responses are observed among the first 33 evaluable patients. As of data cutoff date 01 August 2016, 11 confirmed objective responses (CR, PR) were observed in a total of 28 response-evaluable patients with MET Exon 14-positive NSCLC. Based on the number of confirmed objective responses observed, the null hypothesis was rejected. The proportion of responders will be estimated with better precision if the number of evaluable patients exceeds 33 patients.

1. As of Amendment 23 (21 February 2017), the sample size in the Enriched Other cohort was further increased to a total of 130 patients, including approximately 50 patients with MET Exon 14-positive NSCLC. In addition, a separate group of approximately 5 patients with MET Exon 14-positive NSCLC was planned to be enrolled in clinical sites in Japan.

2. As of the PACL issued 15 May 2017 further enrollment of NSCLC patients into the MET intermediate amplification group was closed and the remaining 13 enrollment slots were transferred to the Enriched Other cohort to facilitate further enrollment of patients with MET Exon 14-positive NSCLC. As a result, the total enrollment for patients with MET Exon 14-positive NSCLC was increased to 68 patients (50 original patients + 13 transferred slots + 5 Japanese patients).

3. As of the PACL issued 07 December 2017, sites were allowed to enroll additional 13 patients with MET Exon 14-positive NSCLC into the Enriched Other cohort, which were originally slotted for the broader Enriched Other cohort and were now assigned specifically to patients with MET Exon 14-positive NSCLC. As a result, the total enrollment of the Enriched Other cohort subset of patients with MET Exon 14-positive NSCLC increased to 81 patients (68 + 13 patients).

4. As of the PACL issued 11 September 2018, further enrollment of NSCLC patients into the MET high amplification group was closed and the remaining 14 enrollment

slots were transferred to the MET Exon 14-positive NSCLC subgroup within the Enriched Other cohort. As a result, the total enrollment for patients with MET Exon 14-positive NSCLC was increased to 103 patients (81+14+8 additional slots were permitted without exceeding the total overall study enrollment of approximately 600 patients).

5. As of the Investigator Communication Letter dated January 7, 2019, further enrollment of NSCLC patients with tumors harboring MET Exon 14 alterations was closed.

9.1.4. RP2D Rifampin Interaction Sub-study

At least 8 evaluable patients, who complete full PK sampling for PF-02341066 on Cycle 1 Day 15 and Cycle 2 Day 1, will be required for the rifampin interaction study in the RP2D cohort. A total of approximately 25 patients will be enrolled into this cohort to obtain the 8 evaluable patients (eg, adjust for loss of patients due to early discontinuations, etc). Eight evaluable patients will provide 90% confidence intervals for the difference between treatments of ±0. 276 on the natural log scale for steady state AUC (AUC_{ss}), with 80% coverage probability. An approximately 36% decrease in PF-02341066 AUC_{ss} is anticipated when co-administered with rifampin.[11] (See Table 7).

Table 7. Expected Precision for Effect of Rifampin on PF-02341066 (90% CI, 80% Coverage Probability, 25% CV)

Sample Size	*Estimated Ratio*	*Probable CI, Lower Limit*	*Probable CI, Upper Limit*	*Probable CI Width*
8	*0.3*	*0.228*	*0.395*	*0.167*
	0.5	*0.379*	*0.659*	*0.280*
	0.8	*0.607*	*1.054*	*0.447*
	1.0	*0.759*	*1.318*	*0.559*

Table 7 presents the width of 90% confidence intervals for the AUC ratio for different estimated effects assuming a within-patient coefficient of variation (CV) of 25%. Sample size calculations are based on a 2-sided paired t-test with 80% tolerance probability (nQuery, Version 7.0).

For additional details on the rifampin sub-study, refer to Appendix 6.

9.1.5. *RP2D Itraconazole Interaction Sub-study*

At least 8 evaluable patients, who complete full PK sampling for PF-02341066 on Cycle 1 Day 15 and Cycle 2 Day 1, will be required for the itraconazole interaction study in the RP2D cohort. As of Protocol Amendment #22, the Single and Multiple-Dose PK Design will no longer be required. Approximately 25 patients will be enrolled to obtain at least 8 evaluable patients for multiple-dose PK (eg, adjust for loss of patients due to early discontinuations, etc). Eight evaluable patients will provide 90% confidence intervals for the difference between treatments of ±0.276 on the natural log scale for AUC_{ss}, with 80% coverage probability. An approximately 2-fold increase in PF-02341066 AUC_{ss} is anticipated when co-administered with itraconazole.[12] (See Table 8).

Table 8. Expected Precision for Effect of Itraconazole on PF-02341066 (90% CI, 80% Coverage Probability, 25% CV

Sample Size	*Estimated Ratio*	*Probable CI, Lower Limit*	*Probable CI, Upper Limit*	*Probable CI Width*
8	*1.0*	*0.759*	*1.318*	*0.559*
	2.0	*1.517*	*2.635*	*1.118*
	3.0	*2.277*	*3.955*	*1.678*

Table 8 presents the width of 90% confidence intervals for the AUC ratio for different estimated effects assuming a within-patient coefficient of variation (CV) of 25%. Sample size calculations are based on a 2-sided paired t-test with 80% tolerance probability (nQuery, Version 7.0).

For additional details on the itraconazole sub-study, refer to Appendix 7. See the Statistical Analysis Plan for further details regarding complete evaluability criteria.

9.1.6. Hypogonadism

The sample size for laboratory testing will be determined by the number of eligible male patients who enroll in the MET-amplified NSCLC and the Enriched Other cohorts. Accordingly, assuming 50% of patients enrolled will be male, projected sample sizes are as follows:

- It is anticipated that up to 25 males (approximately 19 from the MET-amplified Cohort and approximately 6 from the Enriched Other Cohort) may be available for hypogonadism testing. Testing will be performed at Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, every 3 cycles and End of Treatment. As few as 10 male patients may achieve the Cycle 6 Day 1 testing.

9.2. Analysis

Unless otherwise specified, the study population for all safety analyses will include all patients enrolled in the study who receive at least one dose of PF-02341066. The study population for efficacy analyses depends on the parameter; the analysis of some endpoints (eg, ORR, disease control rate [DCR]) will be based on a response evaluable population while the analysis of other endpoints (eg, progression free survival [PFS] and overall survival [OS]) will be based on the safety population.

Due to the exploratory nature of this study, no confirmatory inferential analyses are planned, and no imputation for missing data will be done. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and pharmacokinetic parameters. Data will also be displayed graphically, where appropriate.

9.2.1. Efficacy Analysis

For each cohort and tumor type, the best overall response (confirmed CR, confirmed PR, SD or PD according to RECIST criteria) for each patient evaluable for response will be listed. Other endpoints including overall response rate, duration of response, time to response,

progression free survival, probabilities of survival at 6 and 12 months and others as appropriate, may be summarized to further evaluate anti-tumor activity. Details regarding endpoint definitions and methods of analysis are presented in the Statistical Analysis Plan.

For ORR summaries, patients enrolled into a specific cohort (eg, ALK marker negative NSCLC cohort) at the time of study entry but subsequently determined through molecular testing to be positive for a marker relevant to another cohort (eg, ROS1 marker positive or MET-amplified NSCLC) may be summarized together as a subgroup within their initial cohort and also pooled with patients in the other cohort as appropriate.

9.2.1.1. *Analysis of ALK Marker Negative NSCLC Cohorts*

The best response (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) per RECIST version 1.1 will be summarized. ORR calculated as the number of evaluable patients with a best response of confirmed CR or PR divided by the total number of evaluable patients in the ALK marker negative cohort will be provided, along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Further details for the ALK marker negative NSCLC Cohort #2 are provided in Appendix 8.

9.2.1.2. Analysis of MET-Amplified NSCLC Categories

For each of the 3 MET-amplified NSCLC categories, the null hypothesis that the ORR is less than or equal to 0.10 vs. the alternative hypothesis that it is greater than 0.10 will be tested as described in Section 9.1.3.2.

The best overall response (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) per RECIST version 1.0 will be summarized or listed, as appropriate. The ORR, calculated as the number of evaluable patients with a best overall response of CR or PR divided by the total number of evaluable patients, will be provided along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Further details for the MET-amplified NSCLC cohort are provided in Appendix 9.

9.2.1.3. *Analysis of ROS1 Marker Positive NSCLC Cohort*

The null hypothesis that the ORR is less than or equal to 0.10 vs. the alternative hypothesis that the ORR is greater than 0.10 will be tested as described in Section 9.1.3.3.

The best response per RECIST version 1.0 will be summarized. ORR, calculated as the number of evaluable patients with a best overall response of CR or PR divided by the total number of evaluable patients, will be provided along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Further details for the ROS1 marker positive NSCLC cohort are provided in Appendix 10.

9.2.1.4. Analysis of Enriched Other Cohort

All data for the Enriched Other cohort will be listed, including the best overall response per RECIST version 1.0. However, summaries of ORR will be presented by tumor type/molecular marker, as appropriate depending on the number of patients who have the same tumor type and molecular marker.

Specifically, all safety and antitumor activity data of NSCLC patients with tumors harboring MET Exon 14 alterations will be summarized separately from the Enriched Other Cohort. *Data from patients with tumors harboring MET Exon 14 alterations who are enrolled outside of Japan will be summarized separately and may be combined, for specific reporting, as described in the Statistical Analysis Plan, with the data from patients enrolled in clinical sites in Japan.*

ORR, calculated as the number of evaluable patients with a best overall response of CR or PR divided by the total number of evaluable patients, will be provided along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Further details for the Enriched Other cohort- are provided in Appendix 11.

9.2.1.5. Hypogonadism Testing

The statistical analysis of hypogonadism parameters (total and free testosterone levels, SHBG, luteinizing hormone, follicle stimulating hormone, dihydroepiandrosterone sulfate, estradiol and prolactin) will be exploratory. The laboratory parameter of primary interest is free testosterone, with secondary interest in total testosterone, SHBG, luteinizing hormone and follicle stimulating hormone. Details regarding hypogonadism parameters, endpoint definitions and methods of analysis are decribed in the Statistical Analysis Plan..

9.2.2. Analysis of Pharmacokinetics

9.2.2.1. Single- and Multiple-Dose PF-02341066 PK Analysis

All patients who complete at least one day of PK blood sampling will be included in the PK analyses. Standard plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve from zero time to the time of the last measurable concentration ($AUC_{0\text{-}last}$) and/or area under the plasma concentration versus time curve from zero time to the dosing interval time τ (AUC_{τ}) for PF-02341066 (including its active moieties, if appropriate) will be estimated using non-compartmental analysis. If data permit, area under the plasma concentration versus time curve to infinity ($AUC_{0\text{-}\infty}$), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F) and apparent volume of distribution (Vd/F) will be also estimated. Descriptive statistics of these PK parameters, including mean, standard deviation, coefficient of variation, and median, will be provided by dose and day of assessment in tabular form.

9.2.2.2. Effect of PF-02341066 on MDZ PK

Plasma concentration-time data of MDZ after each dose 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 Vd/F. Descriptive statistics will be provided for these PK parameters in tabular form.

The primary pharmacokinetic parameter $AUC_{0\text{-}last}$ will be utilized to estimate the effect of multiple doses of PF-02341066 on a single dose of MDZ. In the RP2D cohort, the parameter will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect and subject as the random effect. Ninety-percent confidence intervals for the ratio of geometric means of MDZ $AUC_{0\text{-}last}$ in presence of PF-02341066 and MDZ alone will be computed to assess the interaction.

9.2.2.3. Effect of Food on PF-02341066 PK

The effect food will be assessed based on $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, and C_{max} by determining the ratios (fed/fast) of geometric means of these PK parameters and the 90% confidence intervals for the ratios.

9.2.2.4. Effect of Rifampin on PF-02341066 PK

For the rifampin sub-study, plasma concentration-time data of PF-02341066 and its metabolite(s) before and after multiple doses of rifampin will be analyzed using non compartmental methods to estimate individual PK parameters including, but not limited to, C_{max}, T_{max}, C_{trough}, AUC_{tau}, CL/F (PF-02341066 only), and metabolite-to-parent ratio. Descriptive statistics will be provided for these PK parameters in tabular form.

The primary pharmacokinetic parameters AUC_{tau} and C_{max} will be utilized to estimate the effect of rifampin on multiple-dose PK of PF-02341066. The parameters will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect and patient as the random effect. The ratios (Test/Reference) of adjusted geometric means and 90% confidence intervals for the ratios will be computed for PF-02341066 AUC_{tau} and C_{max} to assess the interaction. PF-02341066 alone will be the Reference and PF-02341066 in the presence of rifampin will be the Test.

For more details on the rifampin interaction study refer to Appendix 6.

9.2.2.5. *Effect of Itraconazole on Single- and Multiple-Dose PF-02341066 PK*

As of Protocol Amendment #22, blood samples for single-dose PK parameters for PF-02341006 and its metabolite(s) will no longer be required. For the itraconazole sub-study, plasma concentration-time data of PF-02341066 and its metabolite(s) following single (if possible) and multiple doses of PF-02341066 before and after itraconazole treatment will be analyzed using non compartmental methods to estimate individual PK parameters including, but not limited to, C_{max}, T_{max}, Ctrough, $AUC_{0\text{-}t}$, AUC_{tau}, CL/F (PF-02341066 only), and metabolite-to-parent ratio. Descriptive statistics will be provided for these PK parameters in tabular form.

Plasma concentration data of itraconazole (if available) will be summarized and descriptive statistics will be provided in tabular form.

Pharmacokinetic parameters AUC_{tau} and C_{max} will be utilized to estimate the effect of itraconazole on multiple-dose PK of PF-02341066. The parameters will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect and patient as the random effect. The ratios (Test/Reference) of adjusted geometric means and 90% confidence intervals for the ratios will be computed for PF-02341066 AUC_{tau} and C_{max} to assess the interaction. PF-02341066 alone will be the Reference and PF-02341066 in the presence of itraconazole will be the Test. For exploratory purposes, the effect of itraconazole on the PK of PF-06260182 (metabolite of PF-02341066) will be analyzed according to the above description.

Multiple-Dose PK Design: Each patient is scheduled to receive treatment for two treatment periods (A followed by B) as described below:

> *Treatment Period A (Test): PF-02341066 250 mg QD will be administered from Cycle 1 Day 1 to Cycle 1 Day 15 and itraconazole 200 mg QD from Cycle 1 Day 1 to Cycle 1 Day 16 (before Cycle 1 Day 16 PF-02341066 dosing).*
>
> *Treatment Period B (Reference): PF-02341066 250 mg QD will be administered from Cycle 1 Day 16 to Cycle 2 Day 1.*

If possible, pharmacokinetic parameters AUC_{0-t} and C_{max} will be utilized to estimate the effect of itraconazole on the single-dose PK of PF-02341066. The parameters will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect and patient as the random effect. The ratios (Test/Reference) of adjusted geometric means and 90% confidence intervals for the ratios will be computed for PF-02341066 AUC_{0-t} and C_{max} to assess the interaction. PF-02341066 alone will be the Reference and PF-02341066 in the presence of itraconazole will be the Test.

For more details on the itraconazole interaction sub-study refer to Appendix 7.

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[redacted]

9.2.4. Pharmacogenomics Analysis

Data from pharmacogenomic assays will be summarized as applicable.

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[redacted]

9.2.6. Urinary 6 beta-Hydroxycortisol/Cortisol Ratio

Data from urine assays for 6 beta-Hydroxycortisol/Cortisol (6β-OHC/C) Ratio will be summarized as applicable.

9.2.7. PK/PD Modeling

Population pharmacokinetic analysis of samples collected in this study will be performed in accordance with the FDA guidance on Population Pharmacokinetics (February 1999).[18] The plasma concentration data set from this study may be pooled with data sets from other PF-02341066 clinical studies. Population pharmacokinetic analysis will involve mixed effects modeling performed using appropriate software (eg, NONlinear Mixed-Effect Modeling (NONMEM)). The data from the analysis will describe the PK following single and multiple dose administration of PF-02341066 and describe covariates that are important determinants of PF-02341066 disposition including, but not limited to, demographic data, concomitant medications, pharmacogenomics.

In addition, population PK/PD modeling will be attempted to investigate any causal relationship between PF-02341066 exposure (including its active moieties, if appropriate) and biomarker, safety, anti-tumor activity, and/or laboratory data.

These modeling analyses may be reported separately from the final Clinical Study Report.

9.2.8. Safety Analysis

For each dose escalation cohort (BID and QD), DLT's will be summarized by category (hematologic and non-hematologic) and by MedDRA preferred term.

Adverse Events (AEs) will be coded by system organ class (SOC) and preferred term according to MedDRA terminology. AE severity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

A listing of all AEs including detailed information collected for each AE (description of event, onset date/time, duration, seriousness, severity, relationship to study drug, action taken, clinical outcome) will be presented.

The number and percentage of patients who experienced any: AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized. The denominator used to calculate incidence percentages consists of patients receiving at least 1 dose of PF-02341066. AE data will be presented by dosing schedule across cycles and for each cycle. The denominator for each cycle is defined as those patients available at the start of the cycle who received at least 1 dose of PF-02341066 for that cycle. Emphasis in the analyses will be placed on AEs classified as treatment emergent.

Additional summaries of adverse events (AE) and of other safety data will be presented in tabular and/or graphical format and summarized descriptively, as appropriate.

Analysis of Clinical Labs: Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment.

Summary tables, graphic displays and shift tables, as appropriate, will be prepared to illustrate the results over time on study.

9.2.9. [^{18}F]-FLT-PET Analysis

For [^{18}F]-FLT-PET, SUV will be calculated for each evaluable lesion at baseline and then average baseline SUV will be determined. The mean change in the SUV from baseline for each lesion within a patient and overall for each patient will be determined and the overall mean change will be calculated. Descriptive statistics in tabular form will be used to summarize the results.

9.3. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the Sponsor may conduct unblinded reviews/reporting of the data during the course of the study for the purpose of safety and efficacy assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.4. Data Monitoring Committee

An external Data Monitoring Committee (DMC) will not be established for the study. The PF-02341066 Clinical Team will monitor safety throughout the project through the following efforts:

- Surveillance for serious adverse experiences (SAEs) according to regulatory guidelines.
- Routine monitoring of non-serious adverse experiences as they are recorded in the case report forms or appear in the source documents at the study sites.
- Periodic teleconferences with the principal investigators on individual studies to share experiences and ensure communication.

Findings having immediate implication for the management of patients on study will be communicated to all Principal Investigators in the timeframe associated with unexpected and drug-related SAEs.

Safety surveillance studies will include routine monitoring of clinical laboratory parameters, physical examination, adverse event (AE) reporting, electrocardiogram (ECG) monitoring, and cardiac function studies. Increased monitoring of certain serum biochemistry, blood count, imaging studies/cardiac studies and physical examination will be dependent on animal toxicology findings and consultation with The Food and Drug Administration (FDA).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during the study conduct 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 are 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. This verification may also occur after study completion.

During study conduct and/or after study completion, the trial site may be subject to review by the institutional review board (IRB)/ ethics committee (EC), 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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 case report form (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 trial.

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 or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF, or part of the CRF, may also serve as the 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) guidelines, according to local regulations, or as specified in the Clinical Study Agreement, 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 trial records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to and 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)/Ethics Committee (EC)

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

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

12.2. Ethical Conduct of the Trial

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

12.3. Patient Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, 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 study patients. The study site will maintain a confidential list of patients who participated in the study linking each patient's numerical code to his or her actual identity.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

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

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his/her own consent, the source documents must record why the patient did not provide consent (eg, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse) and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

Note: For investigational sites using WIRB, patients who lack the capacity to consent for themselves will not be able to enroll into this study.

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

End of Trial in all participating sites is defined as the time at which it is deemed that sufficient patients have been recruited and completed the trial as specified in the protocol and the clinical study report (CSR) has been finalized.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-02341066 at any time.

If a trial 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 period set by Pfizer. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF TRIAL RESULTS

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 all 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.

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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.

16. REFERENCES

1. American Cancer Society, Cancer Facts and Figures 2005. Atlanta: American Cancer Society; 2005.

2. Christensen JG, Burrows J, Salgia R. c-Met as a target in human cancer and characterization of inhibitors for therapeutic intervention. Cancer Letters 2005;225:1-26.

3. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.

4. Pulford K, Morris SW, Turturro F. Anaplastic lymphoma kinase proteins in growth control and cancer. J Cell Physiol 2004;199:330-58.

5. Birchmeier C, Birchmeier W, Gherardi E, et al. Met, metastasis, motility, and more: Nat Rev Mol Biol 2003;4:915-25.

6. Liu Y, Sun AM, Dworkin LD. Hepatocyte Growth Factor protects renal epithelial cells from apoptotic cell death. Biochem Biophys Res Comm 1998;246:821-6.

7. Depuydt CE, Zalata A, dePotter PR, et al. The receptor encoded by human c-Met oncogene is expressed in testicular tissue and on spermatozoa. Mol Hum Reprod 1996;2(1):2-8.

8. Grano M, Galimi F, Zambonin G, et al. Hepatocyte Growth Factor is a coupling factor for osteoclasts and osteoblasts. Proc Nat Acad Sci 1996;93:7644-8.

9. Fuller K, Owens J, Chambers TJ. The effect of Hepatocyte Growth Factor on the behaviour of osteoclasts. Biochem Biophys Res Comm 1995;211(2):334-40.

10. DeGeorge J, Ahn C-H, Andres P, Brower M, Giorgio D, Goheer M, Lee-Ham D, McGinn W, Schmidt W, Sun J, and Tripathi S. Regulatory considerations for preclinical development of anticancer drugs, Cancer Chemotherapy and Pharmacology 1998; 41, 173-185.

11. Fahmi OA, Maurer TS, Kish M, Cardenas E, Boldt S, and Nettleton D. A Combined Model for Predicting CYP3A4 Clinical Net Drug-Drug Interaction Based on CYP3A4 Inhibition, Inactivation, and Induction Determined in Vitro. Drug Metab Dispos 2008; 36, 1698-1708.

12. Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: A tale of 'bottom-up' vs 'top-down' recognition of covariates. Drug Metab Pharmacokinet. 2009; 1, 53-75.

13. Huiping Xu, Melissa O'Gorman, Weiwei Tan, Cathie Leister, Maryam Monajati, Nicoletta Brega, Grace Ni, Suzanne Phillips, Patricia Pardo, and Akintunde Bello. Effect of a Strong CYP3A Inducer Rifampin on the Pharmacokinetics of Crizotinib, a Dual ALK/MET Inhibitor, in Healthy Subjects. Poster #: 5392. AAPS Annual Meeting, Washington DC, USA.

14. Huiping Xu, Melissa O'Gorman, Weiwei Tan, Cathie Leister, Maryam Monajati, Nicoletta Brega, Grace Ni, Suzanne Phillips, Patricia Pardo, and Akintunde Bello. The Effect of a Potent CYP3A Inhibitor Ketoconazole on the Pharmacokinetics of Crizotinib, a Dual ALK/MET Inhibitor, in Healthy Subjects. Poster #: 5393. AAPS Annual Meeting, Washington DC, USA.

15. http://www.fda.gov/Drugs/DrugSafety/ucm371017.htm.

16. Drug Interaction Database, University of Washington, www.druginteractioninfo.org.

17. Therasse P, Arbuck, SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-216.

18. EA Eisenhauer et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-27, 2009.

19. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry, Population Pharmacokinetics. February 1999.

20. Weickhardt AJ, et al. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic non-small cell lung cancer. Cancer: Article published online 4 April 2012, DOI:10.1002/cncr. 27450.

21. Paik PK, et al. Response to MET Inhibitors in Patients with Stage IV Lung AdenocarcinomasHarboring MET Mutations Causing Exon 14 Skipping. Cancer Discov 2015;5:842-9.

22. Ma PC , Kijima T , Maulik G , et al. c- MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions . Cancer Res 2003; 63: 6272–81 .

23. Ma PC , Jagadeeswaran R , Jagadeesh S , et al. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non–small cell lung cancer . Cancer Res 2005 ;65:1479–88 .

24. Kong-Beltran M , Seshagiri S , Zha J , Zhu W , et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res 2006;66:283–9 .

Appendix 1. Serious Adverse Event Reporting

All serious adverse events regardless of suspected relationship to study drug must be faxed within 24 hours to the Pfizer Drug Safety Unit. If you have any questions please contact us at the numbers listed below.

U.S.:

FAX: Toll-Free (local) 1 866 997-8322

Korea:

FAX: Toll-Free (local) 079814206-4512

Alternate 1: +82 2 317-2135

Alternate 2: +1 973-660-8938

Australia:

FAX: Toll-Free (local): 1 800-034-314

Alternate 1: +1 973-660-8913

Japan:

FAX: Toll-Free (local): 120 44-2370

Alt. 1: +1 973-660-8963

Appendix 2. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance 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, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Onc 5:649-655, 1982.

Appendix 3. RECIST version 1.0 Tumor Assessment Criteria[17]

At baseline, tumor lesions will be categorized as measurable or non-measurable (defined below).

All baseline evaluations should be performed as close as possible to the first day of study treatment and never more than 4 weeks before starting therapy.

Measurable Lesions

- Lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques or ≥1.0 cm with spiral CT scan.

- A tumor lesion that is situated in a previously irradiated area is eligible for measurable disease provided: 1) there has been documented disease progression in this site; 2) the criteria for measurability as outlined above are met; 3) this is not the only site of measurable disease.

- All measurements should be determined using a ruler, calipers or digital technology, and recorded on the CRF in metric notation.

Nonmeasurable Lesions

All other lesions, including small lesions (longest diameter <2.0 cm with conventional techniques or <1.0 cm with spiral CT) and truly nonmeasurable lesions. Truly nonmeasurable lesions include bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis or pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Documentation of Target and Nontarget Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and measured and recorded at baseline. Target lesions (measurable) should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as present or absent.

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Accepted methods of tumor assessment include:

Clinical examination: clinically detected lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest x-ray: lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI: CT and MRI are the best currently available and most reproducible methods of measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Ultrasound: should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and non-small cell lung nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy and Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully or widely validated. Utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers.

CCI [redacted]

Tumor markers: tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered a complete clinical response.

Cytology and histology: the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

The following RECIST criteria will be the primary method utilized in this study for the assessment and reporting of tumor response data.

Complete Response (CR): Disappearance of all target and nontarget lesions, normalization of tumor marker levels, and no appearance of new lesions indicates complete response. Each of these must be documented on 2 occasions separated by at least 4 weeks.

Partial Response (PR): At least a 30% decrease in the sum of the LDs of target lesions (taking as reference the baseline sum), without progression of nontarget lesions and no appearance of new lesions indicates partial response. Each of these must be documented on 2 occasions separated by at least 4 weeks.

Stable Disease (SD): Neither CR, PR or PD criteria are met. Patients who have stable disease (SD) as their only response will be categorized as SD.

Progressive Disease (PD): ≥20% increase in the sum of the LD of target lesions taking as references the smallest sum LD recorded since the treatment started, unequivocal progression of existing nontarget lesions, or the appearance of 1 or more new lesions. The occurrence of a pleural effusion or ascites is also considered PD if substantiated by cytologic investigation and not previously documented. Pathologic fracture or collapse of bone is not necessarily evidence of disease progression; however, new bone lesions not previously documented are considered PD.

In cases where procedures used to assess tumor size suggest tumor necrosis or intratumor bleeding coincident with an increase in size, a PET scan or ultrasound should be considered because it is important to be sure that increasing lesions are due to increased tumor growth and not necrosis or bleeding.

Determination of Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. For PD, taking as reference the smallest measurements recorded since treatment started. For CR and PR the best response assignment will depend on the achievement of both measurement and confirmation (at the minimum of 28 days) criteria. Stable disease rate will be defined as the percentage of patients with stable disease based on the total number of patients evaluable for response.

Determination of best overall response is summarized in Table 9 with more details provided in the Supplemental SAP.

Table 9. Determination of Best Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR[a]	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR[b]	Non-PD	No	PR
SD[c]	Non-PD	No	SD
PD[d]	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] Complete response.
[b] Partial response.
[c] Stable disease.
[d] Progressive disease.

Appendix 4. Common Terminology Criteria for Adverse Events v3.0

Please use the link below to access the most recent CTCAE information:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Appendix 5. RECIST version 1.1 Tumor Assessment Criteria[18]

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

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 lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 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. 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 is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by the RECIST version 1.1

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 10.

Table 10. 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.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 11.

Table 11. Best Overall Response When Confirmation of CR and PR Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.		
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.		

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 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration 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/CCI 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 6. Rifampin Drug-Drug Interaction Sub-Study

Patients will be enrolled into the rifampin interaction sub-study prior to the enrollment of patients in the itraconazole interaction sub-study.

Background:

The aim of this sub-study is to determine the effect of the co-administration of rifampin on the multiple-dose plasma pharmacokinetics profile of PF-02341066. The starting dose of PF-02341066 will be 250 mg BID and approximately 25 patients will be enrolled to obtain 8 evaluable patients. See Section 9.1.4 for further details.

In vitro studies demonstrated that CYP3A4/5 are the major enzymes involved in the metabolic clearance of PF-02341066. Co-administration of a single 250 mg PF-02341066 dose with rifampin (600 mg QD), a strong CYP3A inducer, resulted in 81.8% and 68.5% decreases in PF-02341066 AUC_{inf} and C_{max}, respectively, compared to when PF-02341066 was given alone.[13] As PF-02341066 is also a CYP3A inhibitor, the magnitude of the effects of CYP3A inducers on steady state PF-02341066 exposures may differ from those seen after single doses. A mathematical modeling approach[11] based on preclinical and clinical data indicate that rifampin co-administration is likely to result in an approximately 36% decrease in the PF-02341066 AUC. Based on these findings no safety issues in using a 250 mg BID PF-02341066 dose in combination with rifampin are anticipated.

Note: Clinical sites in Korea will not participate in the rifampin interaction sub-study.

Patient Population:

This clinical trial 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.

Inclusion Criteria:

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. *Histologically confirmed advanced malignancies (except for leukemias) refractory to standard of care therapy, or for whom no standard of care therapy is available.*
2. *Not applicable; included to ensure consistent numbering.*
3. *Able, in the investigator's opinion, to receive at least 2 cycles of treatment.*
4. *Female or male, 18 years of age or older.*

5. *ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.*

6. *Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).*

7. *Adequate organ function as defined by the following criteria:*

   - *Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.*

   - *Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).*

   - *Absolute neutrophil count (ANC) ≥1500/μL.*

   - *Platelets ≥100,000/μL.*

   - *Hemoglobin ≥9.0 g/dL.*

   - *Serum creatinine ≤2.0 x ULN.*

8. *Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.*

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

Exclusion Criteria:

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

1. *Major surgery, radiation therapy, or systemic anti-cancer therapy within 4 weeks of starting study treatment; within 2 weeks of starting study treatment for anti-systemic therapy upon approval by the Sponsor.*

2. *Prior high-dose chemotherapy requiring hematopoietic stem cell rescue except for patients with neuroblastoma, lymphoma or myeloma.*

3. *Current treatment on another clinical trial.*

4. *Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 4 weeks and not taking medications contraindicated to Exclusion Criteria #10-13.*

5. *Any of the following within the 6 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 6 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted however care must be taken during the co-administration of rifampin and PF-02341066.*

6. *Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc interval >470 msec.*

7. *Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).*

8. *Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to the use of effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.* ***Female patients using oral or other systemic hormonal contraceptives should additionally use nonhormonal methods of birth control during rifampin therapy.***

9. *Other severe acute or chronic medical or psychiatric conditions or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, which would make the patient inappropriate for entry into this study.*

10. *Use of drugs or herbal supplements that are known CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066 until the completion of full PK sample collection on Cycle 2 Day 1. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.*

    Note: After the completion of PK blood sample collection on Cycle 2 Day 1, drugs that are known strong CYP3A4 inhibitors including (but not limited to) atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole should be avoided. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

11. *Use of drugs or herbal supplements that are known CYP3A4 inducers (with exception of rifampin doses as required in the protocol) within 12 days prior to the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 1. All concomitant medication must be approved by the Sponsor.*

    Note: After the completion of full PK blood sample collection on Cycle 2 Day 1, drugs that are known strong CYP3A4 inducers including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort should be avoided.

12. *Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.*

13. *Concurrent use of histamine H_2 antagonists (eg, cimetidine, famotidine, nizatidine and ranitidine) or proton-pump inhibitors (eg, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) from the start of the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 1. All concomitant medication must be approved by the Sponsor.*

14. *Patients with known interstitial fibrosis or interstitial lung disease.*

15. *Patients with a history of hypersensitivity to any of the rifamycins.*

16. *Patients having any contraindications to rifampin administration according to the current package insert (or regulatory equivalent) for rifampin.*

Sample Size:

A total of 25 patients with advanced malignancies refractory to standard of care therapy, or for whom no standard of care therapy is available will be enrolled in this interaction sub-study to obtain 8 evaluable patients. See Section 9.1.4 for further details.

Concomitant Medication:

Patients using oral or other systemic hormonal contraceptives should be advised to additionally use nonhormonal methods of birth control during rifampin therapy.

Rifampin has been observed to increase the requirements for coumarin-like anticoagulant drugs. It is therefore recommended that the prothrombin time be performed as frequently as necessary to establish and maintain the required anticoagulant dose.

The concurrent use of halothane or isoniazid is not permitted during the rifampin dosing period as the potential for hepatotoxicity is increased when these drugs are co-administered.

Probenecid and cotrimoxazole have been reported to increase rifampin blood levels and should be avoided during rifampin treatment.

Patients must not: (1) take any medications, herbal supplements or food known to be CYP3A inhibitors 7 days prior to the first dose of PF-02341066 until the completion of the full PK blood sample collection on Cycle 2 Day 1; (2) take any medications, herbal supplements or food known to be CYP3A inducers 12 days prior to the first dose of PF-02341066 until the completion of the full PK blood sample collection on Cycle 2 Day 1; and (3) take histamine H_2 antagonists (eg, cimetidine, famotidine, nizatidine and ranitidine) or proton-pump inhibitors (eg, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) from the start of the first dose of PF-02341066 until the completion of the full PK blood sample collection on Cycle 2 Day 1. All concomitant medications for patients enrolling in this sub-study must be approved by the Sponsor.

For further information please refer to the Rifampin Package Insert (or regulatory equivalent).

Administration:

PF-02341066

PF-02341066 (tablets) will be administered at a dose of 250 mg BID. PF-02341066 should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study except for at the time of co-administration of rifampin from Cycle 1 Day 16 until Cycle 2 Day 1. During this period, patients should fast for at least 2 hours before and 1 hour after dosing. On days of PK sampling, patients must take their daily dose of rifampin and morning dose of PF-02341066 at the clinic.

Refer to Section 5 Trial Treatments for details on PF-02341066 Formulation and Packaging (Section 5.2.1), Preparation and Dispensing (Section 5.2.2), Administration (Section 5.2.3) and Compliance (Section 5.2.4).

Rifampin

Commercially available rifampin will be administered at a dose of 600 mg QD starting on Cycle 1 Day 16. Dosing will continue until Cycle 2 Day 1 (total of 14 days). Rifampin should be administered at the same time of the morning dose of PF-02341066 either one hour before or 2 hours after a meal with a full glass of water (approximately 240 mL).

Plasma Pharmacokinetic Assessment for PF-02341066:

Blood samples for PF-02341066 and metabolite PF-06260182 will be collected as follows:

A full PK profile will be obtained on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 2, 4, 6, 8 and 10 hours following the morning dose of PF-02341066. In addition sparse sampling will be done on Cycle 1 Day 25, Cycle 1 Day 27, Cycle 2 Day 15 and Day 1 of Cycles 3 and 5 at the following time points: 0 (pre-dose) and 2-6 hours following the morning dose of PF-02341066.

Note: PK samples collected from Cycle 1 Day 15 to Cycle 2 Day 1 (rifampin co-administration period) will be analyzed for both PF-02341066 and its metabolite PF-06260182.

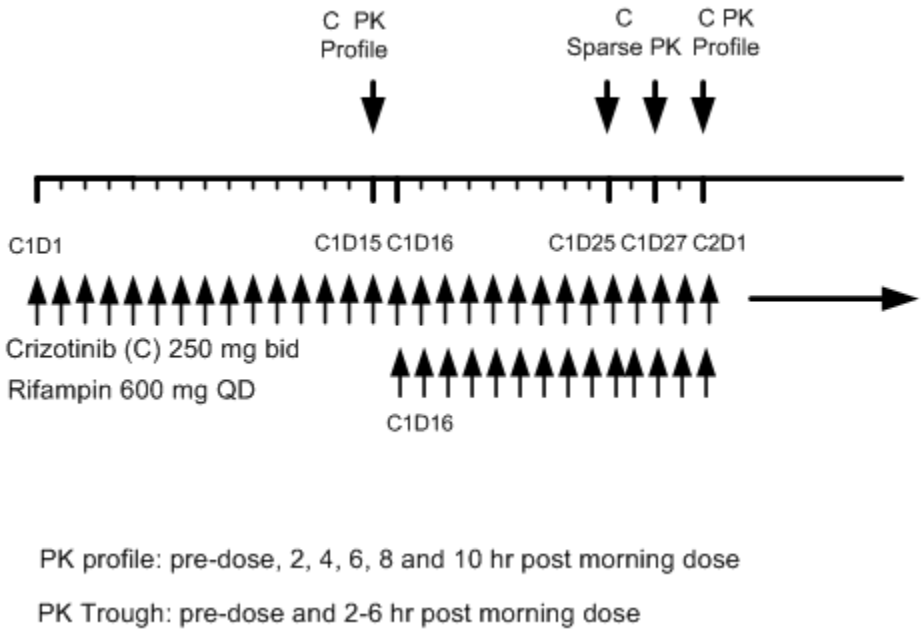
In addition to samples mentioned above, additional blood samples for PK evaluation may be requested from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and Sponsor). More than one PK sample per patient may be collected throughout the study; however the total blood volume of additional PK samples collected per patient should not exceed 15 mL (ie, no more than 5, 3 mL samples).

Refer to Section 7.5.1.1 for details regarding sample collection for PF-02341066 PK.

Note: No blood samples will be collected for the determination of rifampin concentrations.

Please see below for further details on dosing and PK sampling schedule (Figure 5).

Figure 5. Schema for Design of PF-02341066 and Rifampin Interaction Sub-Study



Schedule of Activities: Rifampin Drug-Drug Interaction Sub-study

Protocol Activity	***Screening****	***Cycle 1= 28 days****			***Cycle 2 = 28 days****		***Every 4 weeks** (after Cycle 2-Cycle 5)***	***Every 8 Weeks*****	***End of Treatment*** (28 Days Post Dose)
	Day -14 to Day 0	***Day 1 (pre-dose)***	***Day 15***	***Days 16, 25 & 27***	***Day 1***	***Day 15***	***Day 1***		
Informed consent[1]	*X*								
Medical history[2]	*X*								
Physical examination[3]	*X*	*X*			*X*		*X*		*X*
Weight, height, temperature, BP, pulse[4]	*X*	*X*			*X*		*X*		*X*
ECOG performance status[5]	*X*	*X*			*X*		*X*		*X*
12-Lead electrocardiogram (ECG)[6]	*X*	*X*	*X*		*X*	*Repeat as clinically indicated.*			
Registration/Hematology[7]	*X*	*(X)*	*X*		*X*		*X*		*X*
Chemistry[8]	*X*	*(X)*	*X*		*X*		*X*		*X*
Coagulation tests[9]	*X*	*(X)*	*X*		*X*				
Urinalysis[10]	*X*	*(X)*			*X*		*X*		
Ophthalmology Examination[20]	*X [X]*		*[X]*				*[Cycle 3 only]*		*[X]*
Safety assessment (adverse events)[11]	*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*
*Imaging only if renal cysts are identified**[12]								*X*	
Concomitant medications[13]	*X*	*X*	*X*	*X*	*X*	*X*	*X*		
Pregnancy test[14]	*X*					*X*			*X*
Special Laboratory Studies									
Plasma sampling for full PF-02341066 PK[15]			*X*		*X*				
Sparse plasma sampling points for PF-02341066 PK[16]				*X (D25 & D27)*		*X*	*X (Cycles 3 & 5)*		
Blood sample for pharmacogenomics[17]	*X*								
PF-02341066 treatment[18]		*X*	*X*	*X*	*X*	*X*	*X*	*X*	
Rifampin treatment[19]				*X (D16)*	*X*				

( ) If it has not been performed within 7 days.

** Allowable window for imaging is ±7 day; ±2 days for all other assessments with the exception of Days 16, 25 and 27. There is a ±1 day window for Days 25 and 27 (but these visits should be 2 days apart).*

** Allowable window for screening assessments is up to -7 days from Day -14 (ie, Day -21 to Day 0).*
[ ] Special ophthalmology tests for all NSCLC patients enrolled until written notification by Sponsor. See Section 7.3 for additional details.
***Cycle length is 4 weeks (28 days).*
****Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle.*

1. *Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.*

2. *Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.*

3. *Physical Examination: During Screening and on Day 1 of each cycle: examination of major body systems.*

4. *Height need not be collected after the first measurement.*

5. *ECOG performance scale will be available in the Appendix 2 of the protocol.*

6. *12- Lead ECG: Three consecutive 12-lead ECGs will be performed at least 2 minutes apart during the screening period; Cycle 1 Day 1 at pre-dose (0 hour); Cycle 1 Day 15 at pre-dose (0 hour) and 4 hours post-dose (~C_{max}); and Cycle 2 Day 1 at pre-dose, and 4 hours post-dose. These time points correspond to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.*

7. *Hematology: WBC with differential count, hemoglobin, and platelet count.*

8. *Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2, calcium, phosphorus, BUN, creatinine, uric acid, glucose. If ALT ≥ Grade 3 and total bilirubin ≥ Grade 2, then liver function tests should be repeated every 48 hours until ALT ≤ Grade 2.*

9. *Coagulation: PT and PTT. Rifampin has been observed to increase the requirements for coumarin-like anticoagulant drugs. It is therefore recommended that the prothrombin time be performed as frequently as necessary to establish and maintain the required anticoagulant dose if the patient is on a coumarin-like anti-coagulant.*

10. *Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.*

11. *Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.*

12. *If renal cysts are observed, monitoring with appropriate imaging should be performed every 8 weeks following diagnosis.*

13. *Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.*

14. *Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated at Cycle 2 Day 15 and whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected.*

15. *A full pharmacokinetic profile of PF-02341066 and metabolite(s) will be obtained on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 2, 4, 6, 8 and 10 hours.*

16. *Sparse PK sampling will be done on Cycle 1 Day 25 and Cycle 1 Day 27, Cycle 2 Day 15, and Day 1 of Cycles 3 and 5 at the following time points: 0 (pre-dose) and 2-6 hours*

17. *A single blood sample will be collected at baseline (within 2 weeks prior to the first dose) to genotype the alleles of cytochrome P450 enzymes and drug transport proteins.*

18. *PF-02341066 will be dosed at 250 mg BID.*

19. *Commercially available rifampin will be dosed at 600 mg QD starting Cycle 1 Day 16 and finishing on Cycle 2 Day 1 (14 days).*

20. *An ophthalmology examination will be performed at screening for all patients. The ophthalmology examination should be repeated during the study when visual disturbances have been observed and when there is an increase in grade for visual disturbances. The ophthalmology examination should include ocular characteristics, visual acuity, fundoscopy and slit lamp examination. All NSCLC patients enrolled will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor. All ophthalmology examinations should be performed by an ophthalmologist. The time points of this special testing is designated by "[ ]" in the Schedule of Activities Table.*

Appendix 7. *Itraconazole Drug-Drug Interaction Sub-Study*

The aim of this sub-study is to determine the effect of itraconazole on the multiple-dose plasma pharmacokinetics of PF-02341066 when itraconazole is co-administered. If multiple-dosing of PF-02341066 in combination with itraconazole is tolerable (as defined in the Study Design Section), a cohort of patients may be also enrolled to determine the effect of itraconazole on single and multiple-dose plasma pharmacokinetic profiles of PF-02341066. As of Protocol Amendment #22, the Single and Multiple-Dose Design will no longer be performed. The starting dose of PF-02341066 will be 250 mg QD and approximately 25 patients will be enrolled to obtain at least 8 evaluable patients for multiple-dose PK. See Section 9.1.5 for more details. Patients who are enrolled in the study but not treated may be replaced to obtain at least 8 evaluable patients for multiple-dose PK.

The magnitude of the effects of CYP3A inhibitors on steady state PF-02341066 exposures may differ from those seen after a single dose of PF-02341066 as PF-02341066 is also a CYP3A inhibitor. An autoinhibition-mediated change in apparent clearance of PF-02341066 was observed during chronic PF-02341066 treatment. There are limited data with single doses of PF-02341066 administered with ketoconazole (200 mg BID), a strong CYP3A inhibitor. Co-administration of a single 150 mg oral dose of PF-02341066 in the presence of ketoconazole, resulted in increases in PF-02341066 systemic exposure, with PF-02341066 AUC_{inf} and C_{max} values that were approximately 3.2 fold and 1.4 fold higher, respectively, than those seen when PF-02341066 was administered alone.[14] SIMCYP (a population based pharmacokinetics modeling simulator) modeling[12] based on preclinical and clinical data, predict a 2-fold increase in PF-02341066 AUC when PF-02341066, at steady state, is co-administered with ketoconazole. The effect of itraconazole on PF-02341066 exposure cannot be properly predicted due to the lack of a validated physiologically based pharmacokinetic model. Based upon recent FDA guidance[15] on the use of ketoconazole, ketoconazole was replaced with another CYP3A strong inhibitor, itraconazole. However, it is expected that the magnitude of the effect of itraconazole would be no greater than that of ketoconazole given that itraconazole had a smaller inhibitory effect on the exposure of midazolam, a CYP3A probe, than ketoconazole.[16] Therefore, the PF-02341066 exposure at 250 mg QD when administered with itraconazole is expected to be similar to or lower than the PF-02341066 exposure at the maximum tolerated dose of 250 mg BID when administered alone. For these reasons, the same starting dose of PF-02341066 proposed for the ketoconazole drug-drug interaction, will be used for the itraconazole drug-drug interaction, ie, 250 mg QD. However, should additional data arise impacting this assumption, the Sponsor will adjust the starting dose of PF-02341066 accordingly.

Note: Clinical sites in South Korea will not participate in the itraconazole drug-drug interaction sub-study.

Patient Population:

This clinical trial 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.

***Inclusion Criteria**:*

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. *Histologically confirmed advanced malignancies (except for leukemias) refractory to standard of care therapy, or for whom no standard of care therapy is available.*

2. *Not applicable; included to ensure consistent numbering.*

3. *Able, in the investigator's opinion, to receive at least 2 cycles of treatment.*

4. *Female or male, 18 years of age or older.*

5. *ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.*

6. *Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).*

7. *Adequate organ function as defined by the following criteria:*

    - *Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.*

    - *Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).*

    - *Absolute neutrophil count (ANC) ≥1500/μL.*

    - *Platelets ≥100,000/μL.*

    - *Hemoglobin ≥9.0 g/dL (≥8.0 g/dL after IRB/EC approval of Amendment #21).*

    - *Serum creatinine ≤2.0 x ULN.*

8. *Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment. For investigational sites using WIRB, patients who lack the capacity to consent for themselves will not be enrolled into this study.*

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

***Exclusion Criteria**:*

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

1. *Major surgery, radiation therapy, or systemic anti-cancer therapy within 4 weeks of starting study treatment; within 2 weeks of starting study treatment for anti-systemic therapy upon approval by the Sponsor.*

2. *Prior high-dose chemotherapy requiring hematopoietic stem cell rescue except for patients with neuroblastoma, lymphoma or myeloma.*

3. *Current treatment on another clinical trial.*

4. *Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 4 weeks and not taking medications contraindicated to Exclusion Criteria #10 - 12 & 16.*

5. *History of or current evidence of congestive heart failure, or any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident including transient ischemic attack or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 3 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted.*

6. *Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc >470 msec. Upon agreement between the Investigator and Sponsor, patients with a QTc >470 msec but <490 msec in the presence of a right bundle branch block or with an implanted cardiac pacemaker may enter the study.*

7. *Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).*

8. *Pregnant female patients, breastfeeding patients, male patients with pregnant female partners who are unwilling or unable to use a condom for the duration of the pregnancy, female and male patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of study treatment and for 90 days after the last dose of investigational product.*

9. *Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior) or end-stage renal disease on hemodialysis or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, which would make the patient inappropriate for entry into this study.*

10. *Use of drugs or herbal supplements that are known CYP3A4 inhibitors (with exception of itraconazole doses as required in the protocol) within 7 days prior to the first dose of PF-02341066 until the completion of full PK sample collection on Cycle 2 Day 2. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.*

    Note: After the completion of PK blood sample collection on Cycle 2 Day 2, drugs that are known strong CYP3A4 inhibitors including (but not limited to) atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole should be avoided. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

11. *Use of drugs or herbal supplements that are known CYP3A4 inducers within 12 days prior to the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 2. All concomitant medication must be approved by the Sponsor.*

    Note: After the completion of full PK blood sample collection on Cycle 2 Day 2, drugs that are known strong CYP3A4 inducers including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort should be avoided.

12. *Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.*

13. *Concurrent use of oral ergot alkaloids, dofetilide, felodipine, levacetylmethadol, lovastatin, methadone, midazolam (oral), nisoldipine, quinidine, simvastatin, or triazolam from the start of the first dose of itraconazole until the completion of full PK blood sample collection on Cycle 2 Day 2. These drugs are also contraindicated with itraconazole use.*

14. *Concurrent use of histamine H_2 antagonists (eg, cimetidine, famotidine, nizatidine and ranitidine) or proton-pump inhibitors (eg, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) from the start of the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 2. All concomitant medication must be approved by the Sponsor.*

15. *History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.*

16. *Patients with a history of hypersensitivity to itraconazole or its excipients or to other azole antifungals.*

17. *Patient having any contraindications to itraconazole administration according to the current package insert (or regulatory equivalent) for itraconazole.*

18. *Concurrent use of nevirapine until the completion of full PK blood sample collection on Cycle 2 Day 2. Nevirapine will decrease plasma concentrations of itraconazole.*

19. *Patients who are investigational site staff members directly involved in the conduct of the study 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 study.*

Sample Size:

Approximately 25 patients with advanced malignancies refractory to standard of care therapy, or for whom no standard of care therapy is available will be enrolled in this interaction study to obtain at least 8 evaluable patients for multiple-dose PK. See Section 9.1.5 for further details.

Concomitant Medication:

Patients must not: (1) take any medications, herbal supplements or food known to be CYP3A inhibitors 7 days prior to the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 2; (2) take any medications, herbal supplements or food known to be CYP3A inducers 12 days prior to the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 2; and (3) take histamine H_2 antagonists (eg, cimetidine, famotidine, nizatidine and ranitidine) or proton-pump inhibitors (eg, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) from

the start of the first dose of PF-02341066 until the completion of full PK blood sample collection on Cycle 2 Day 2.

Itraconazole may decrease the elimination of drugs metabolized CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with itraconazole (Table 12). These elevated plasma concentrations may increase or prolong therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant itraconazole therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Please refer to the Itraconazole Package Insert (or regulatory equivalent) for complete information on drug interactions, contraindications, warnings and precautions.

Table 12. Drugs Whose Plasma Concentrations May Be Increased By Itraconazole[1]

Antiarrhythmics	*digoxin, dofetilide,[2] quinidine,[2] disopyramide*
Anticonvulsants	*carbamazepine*
Antimycobacterials	*rifabutin*
Antipsychotics	*pimozide[2]*
Benzodiazepines	*alprazolam, diazepam, midazolam,[2,3] triazolam[2]*
Calcium Channel Blockers	*dihydropyridines (including amlodipine, felodipine[2] and nisoldipine[2]), verapamil, diltiazem*
Gastrointestinal Motility Agents	*cisapride[2]*
HMG CoA-Reductase Inhibitors	*atorvastatin, cerivastatin, lovastatin,[2] simvastatin[2]*
Immunosuppressants	*cyclosporine, tacrolimus, sirolimus*
Oral Hypoglycemics	*oral hypoglycemics*
Protease Inhibitors	*indinavir, ritonavir, saquinavir*

[1] This list is not all-inclusive. From Sporanox® (itraconazole capsules) Package Insert April 2012.
[2] Contraindicated with itraconazole based on clinical and/or pharmacokinetics studies. Patients must not take these drugs from the first dose of itraconazole until the completion of full PK blood sample collection on Cycle 2 Day 2.
[3] Concomitant administration of itraconazole and oral midazolam is contraindicated. If midazolam is administered parenterally, special precaution and patient monitoring are required since the sedative effect may be prolonged.

All concomitant medications for patients enrolling in this sub-study must be approved by the Sponsor.

Hepatic Effects:

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. Some of these cases developed within the first week of treatment. If clinical signs and symptoms of liver disease develop, itraconazole treatment should be discontinued and liver function testing be performed.

Neurotoxicity:

If neurotoxicity occurs that may be attributable to itraconazole, itraconazole should be discontinued.

Study Design:

The study design will evaluate the effect of itraconazole on the multiple-dose PK of PF-02341066 (Figure 6). If multiple-dosing of PF-02341066 in combination with itraconazole is tolerable, PK testing may be expanded to evaluate the effect of itraconazole on the single and multiple-dose plasma pharmacokinetic profiles of PF-02341066 (Figure 7). As of Protocol Amendment #22, the Single and Multiple-Dose Design will no longer be performed. Approximately 25 patients will be enrolled to obtain at least 8 patients evaluable for multiple-dose PK. Patients who are enrolled in the study but not treated may be replaced to obtain at least 8 patients evaluable for multiple-dose PK.

Multiple-Dose Pharmacokinetic Design: Each patient is scheduled to receive treatment for two treatment periods (A followed by B) as described below:

> *Treatment Period A (Test): PF-02341066 250 mg QD will be administered from Cycle 1 Day 1 to Cycle 1 Day 15 and itraconazole 200 mg QD from Cycle 1 Day 1 to Cycle 1 Day 16 (before Cycle 1 Day 16 PF-02341066 dosing).*
>
> *Treatment Period B (Reference): PF-02341066 250 mg QD will be administered from Cycle 1 Day 16 to Cycle 2 Day 1.*

Tolerability will be considered established if the first 3 patients enrolled have no treatment-related adverse events requiring dose interruption or reduction from the first dose until Cycle 2 Day 2.

If the single and multiple-dose design is implemented, the ability of patients to complete the required PK evaluations of this design will be assessed. If ≤2 of the first 6 patients enrolled under this design are able to complete the serial PK samplings for the full PK profile of PF-02341066 required on Day -5 (Lead-in period), Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1, then the original multiple-dose PK design will be re-implemented.

Administration:

Multiple-Dose Pharmacokinetic Design

Itraconazole

Commercially available itraconazole will be administered at a dose of 200 mg QD starting on Cycle 1 Day 1. Dosing will continue through Cycle 1 Day 16 (total dosing of 16 days). On full PK profile days (Cycle 1 Day 15 and Cycle 1 Day 16) when itraconazole and PF-02341066 are to be co-administered, PF-02341066 should be dosed approximately 3 hours after itraconazole dosing. In addition, on Cycle 1 Days 15 and Cycle 1 Day 16 the dose of itraconazole will be administered in the clinic and must be taken with a standard meal defined as one that provides 15%, 35%, and 50% of calories from protein, fat, and carbohydrate, respectively, with a total of 500-700 calories provided or as instructed by the investigative site.

PF-02341066

PF-02341066 (tablets) will be administered at a dose of 250 mg QD starting on Cycle 1 Day 1 and dosing will continue through Cycle 2 Day 1. Starting on Cycle 2 Day 2, PF-02341066 will be administered at a dose of 250 mg BID. PF-02341066 BID doses should be administered approximately 12 hours apart.

On full PK profile days when itraconazole and PF-02341066 are co-administered, PF-02341066 should be dosed approximately 3 hours after itraconazole dosing (ie, Cycle 1 Day 15 and Cycle 1 Day 16). PF-02341066 may be given with or without food throughout the study except on the following PF-02341066 PK collection days: Cycle 1 Day 15, Cycle 1 Day 16 and Cycle 2 Day 1, when the dose of PF-02341066 should be taken without food. Patients should begin fasting after their itraconazole dose and for 1 hour after PF-02341066 administration on these PK collection days.

On days of PK sampling, patients must take their daily dose of itraconazole and PF-02341066 at the clinic.

See Figure 6 for a schematic regarding dosing and PK sample collection times.

See the Schedule of Activities PF-02341066 and Itraconazole Interaction Sub-Study Schema: Multiple Dose.

Single and Multiple-Dose Pharmacokinetic Design

Itraconazole

Commercially available itraconazole will be administered at a dose of 200 mg QD starting on Day -3. Dosing will continue through Cycle 1 Day 16 (total dosing of 19 days). On full PK profile days when itraconazole and PF-02341066 are to be co-administered, PF-02341066 should be dosed approximately 3 hours after itraconazole dosing (ie, Cycle 1 Days 1, 3, 15 and 16). In addition, on Cycle 1 Days 1, 3, 15 and 16, itraconazole will be administered in the clinic and must be taken with a standard meal defined as one that provides 15%, 35%, and 50% of calories from protein, fat, and carbohydrate, respectively, with a total of 500-700 calories provided or as instructed by the investigative site.

In addition, on Days -3, -2, (or -1) and Cycle 1 Day 2, itraconazole must be taken at the clinic with a standard meal provided or as instructed by the investigative site.

PF-02341066

PF-02341066 (tablets) will be administered. A single 250 mg dose of PF-02341066 will be given on Day -5. PF-02341066 dosing at 250 mg QD will start on Cycle 1 Day 1 through Cycle 2 Day 1. However, no PF-02341066 dose will be administered on Cycle 1 Day 2. Starting on Cycle 2 Day 2, PF-02341066 will be administered at a dose of 250 mg BID. PF-02341066 BID doses should be administered approximately 12 hours apart.

On full PK profile days when itraconazole and PF-02341066 are co-administered, PF-02341066 should be dosed approximately 3 hours after itraconazole dosing. PF-02341066 may be given with or without food throughout the study except on the following PF-02341066 PK collection days: Day -5, Cycle 1 Days 1, 15, 16 and Cycle 2 Day 1, when the dose of PF-02341066 should be taken without food. Patients should begin fasting after their itraconazole dose and for 1 hour after PF-02341066 administration on these PK collection days.

See Figure 7 for a schematic regarding dosing and PK sample collection times.

See Schedule of Activities for PF-02341066 and Itraconazole Interaction Sub-Study Schema: Single and Multiple-Dose.

Plasma Pharmacokinetic Assessment for PF-02341066 and its metabolite, PF-06260182:

Multiple-Dose Pharmacokinetic Design

Blood samples for PK of PF-02341066 and PF-06260182, will be collected as follows (Figure 6):

A full PK profile of PF-02341066 will be obtained after administration of multiple doses of itraconazole and PF-02341066 on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose. In addition, pre-dose PK samples will be collected on Cycle 1 Day 11, Cycle 1 Day 13, Cycle 1 Day 25 and Cycle 1 Day 27.

Note: PF-02341066 PK sampling is relative to the timing of PF-02341066 dosing.

PK samples collected for PF-02341066 will be analyzed for both PF-02341066 and PF-06260182. In addition to samples obtained as described above, additional blood samples for PK evaluation may be requested from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and Sponsor). More than one PK sample per patient may be collected throughout the study; however the total blood volume of additional PK samples collected per patient should not exceed 15 mL (ie, no more than 5, 3 mL samples). As of IRB/EC approval of Protocol Amendment #23, the total blood volume of additional PK samples collected per patient should not exceed 20 mL (ie, no more than 5, 4 mL samples).

Plasma Pharmacokinetic Assessment for Itraconazole and its metabolite(s)

Blood samples collected for itraconazole PK will only be analyzed upon the request of Sponsor based on the need of these data to more fully understand the sub-study findings.

Blood samples for itraconazole will be collected as follows:

Pre-dose PK samples (for itraconazole and its metabolites) will be taken prior to itraconazole dosing on Cycle 1 Day 15 and Cycle 1 Day 16 (Figure 6).

Note: Itraconazole PK sampling is relative to timing of Itraconazole dosing.

Please see below for further details on the multiple dose and pharmacokinetic sampling schedule (Figure 6).

Single and Multiple-Dose Pharmacokinetic Design

Blood samples for PF-02341066 and PF-06260182, will be collected as follows (Figure 7):

A full PK profile of PF-02341066 will be obtained after administration of a single dose on Day -5 (lead-in period) and Day 1 of Cycle 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, 24, 48 and either 72 or 96 hours post dose. Blood samples for the PF-02341066 PK profile will be also obtained on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose. In addition, pre-dose PK samples will be collected on Cycle 1 Day 11, Cycle 1 Day 13, Cycle 1 Day 25 and Cycle 1 Day 27.

Note: PF-02341066 PK sampling is relative to timing of PF-02341066 dosing.

PK samples collected for PF-02341066 will be analyzed for both PF-02341066 and PF-06260182.

In addition to samples obtained as described above, additional blood samples for PK evaluation may be requested from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and Sponsor). More than one PK sample per patient may be collected throughout the study; however the total blood volume of additional PK samples collected per patient should not exceed 15 mL (ie, no more than 5, 3 mL samples).

Refer Section 7.5.1.1 for details regarding sample collection for PF-02341066 PK.

Plasma Pharmacokinetic Assessment for Itraconazole and its metabolite(s):

Blood samples collected for itraconazole and its metabolite(s) PK will only be analyzed upon the request of Sponsor based on the need of these data to more fully understand the study findings.

Blood samples for itraconazole will be collected as follows:

Pre-dose PK samples (for itraconazole and its metabolites) will be taken prior to itraconazole dosing on Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 15 and Cycle 1 Day 16 (Figure 7).

Note: Itraconazole PK sampling is relative to timing of itraconazole dosing.

Details regarding the sample preparation will be provided in the Laboratory Manual.

Please see below for further details on the single and multiple dose and pharmacokinetic sampling schedule (Figure 7).

ECGs:

Multiple-Dose Pharmacokinetic Design

Three consecutive 12-lead ECGs will be performed at least 2 minutes apart at the following timepoints: Screening; Cycle 1 Day 1 and Cycle 1 Day 15 at pre-PF-02341066 dose (0 hour), 1 hour post-PF-02341066 dose (~T_{max} for itraconazole) and 4 hours post-PF-02341066 dose (~T_{max} for PF-02341066); and Cycle 2 Day 1 at pre-PF-02341066 dose (0 hour) and 4 hours post-PF-02341066 dose. These time points correspond to PK time points. ECGs should be performed within 15 minutes before PK blood draws at respective time points.

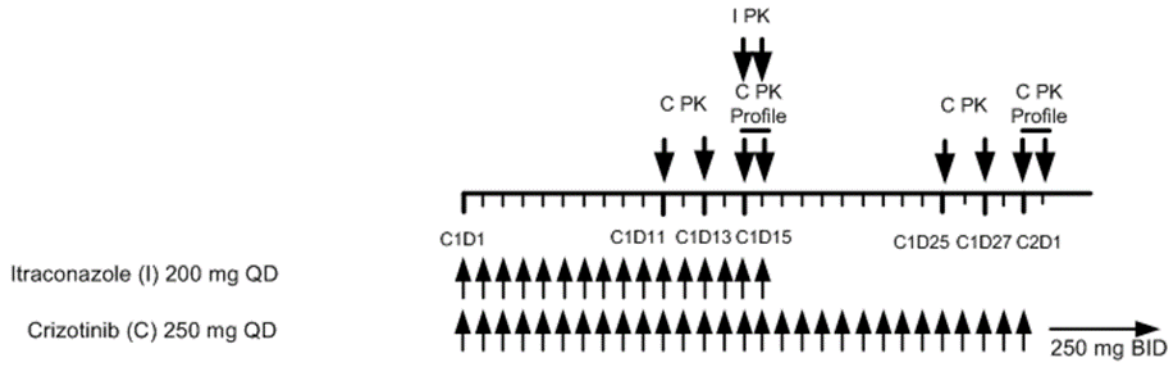
In addition to the time points noted, ECGs should be repeated as clinically indicated.

Single and Multiple-Dose Pharmacokinetic Design

Three consecutive 12-lead ECGs will be performed at least 2 minutes apart at the following timepoints: Screening; Day -5 lead-in dose at pre-PF-02341066 dose (0 hour); Cycle 1 Day 1 and Cycle 1 Day 15 at pre-PF-02341066 dose (0 hour), 1 hour post-PF-02341066 dose (~T_{max} for itraconazole) and 4 hours post-PF-02341066 dose (~T_{max} for PF-02341066); and Cycle 2 Day 1 at pre-PF-02341066 dose (0 hour) and 4 hours post-PF-02341006 dose. These time points correspond to PK time points. ECGs should be performed within 15 minutes before PK blood draws at respective time points.

In addition to the time points noted, ECGs should be repeated as clinically indicated.

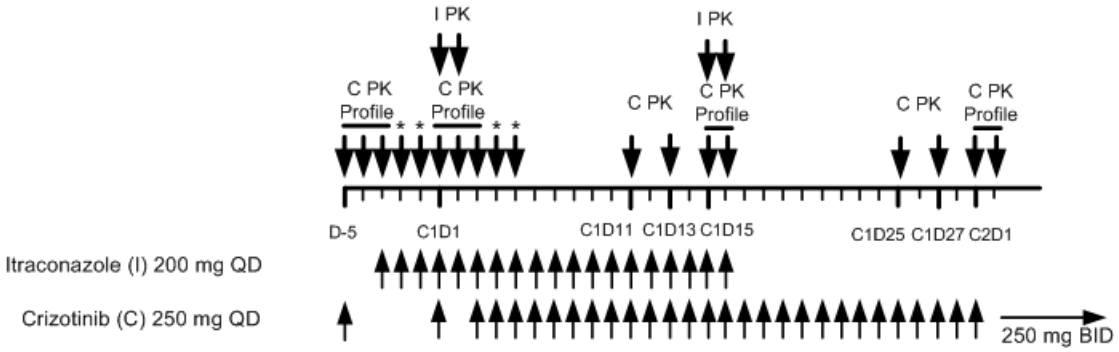
Figure 6. PF 02341066 and Itraconazole Schema: Multiple Dose-Design



Legend:

- C PK Profile = PF-02341066 full pharmacokinetic profile
- C PK = PF-02341066 pharmacokinetic collection
- I PK = Itraconazole pharmacokinetic collection
- CxDx = Cycle x Day x

Figure 7. PF-02341066 and Itraconazole Interaction Schema: Single and Multiple-Dose Design



Legend:

- C PK Profile = PF-02341066 full pharmacokinetic profile
- C PK = PF-02341066 pharmacokinetic collection
- I PK = Itraconazole pharmacokinetic collection
- D-5 = Day -5
- CxDx = Cycle x Day x

* Additional PK at D-2 or D-1 and C1D4 or C1D5 (i.e. 72 or 96 hours post-dose)

Schedule of Activities: PF-02341066 and Itraconazole Interaction Schema: Multiple-Dose Design

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	***Screening****	***Cycle 1= 28 days****				***Cycle 2 = 28 days****		***Every 4 weeks*** (Cycle ≥3)***	***Every 8 Weeks******	***End of Tx (28 Days Post Dose)****
	Day -14 to Day 0	***Day 1***	***Day 11, 13***	***Day 15***	***Days 25, 27***	***Day 1***	***Day 15***	***Day 1***		
Informed consent[1]	X									
Medical history[2]	X									
Physical examination[3]	X	X				X		X		X
Weight, height, temperature, BP, pulse[4]	X	X				X		X		X
ECOG performance status[5]	X	X				X		X		X
12-Lead electrocardiogram (ECG)[6]	X	X		X		X	*Repeat as clinically indicated.*			
Hematology[7]	X	(X)		X		X		X		X
Chemistry[8]	X	(X)		X		X	X	X		X
Coagulation tests[9]	X	(X)		X		X				
Urinalysis[10]	X	(X)				X		X		
Ophthalmology Examination[20]	X									
Safety assessment (adverse events)[11]	X	X	X	X	X	X	X	X		X
Imaging only if renal cysts are identified[12]									X	
Concomitant medications[13]	X	X	X	X	X	X	X	X		
Contraceptive Check (as applicable)[21]	X	X				X		X		X
Female patients: Pregnancy test[14]	X	X				X		X		X

Protocol Activity	*Screening**	*Cycle 1= 28 days***				*Cycle 2 = 28 days***		*Every 4 weeks**** *(Cycle ≥3)*	*Every 8 Weeks*****	*End of Tx (28 Days Post Dose)**
	Day -14 to Day 0	*Day 1*	*Day 11, 13*	*Day 15*	*Days 25, 27*	*Day 1*	*Day 15*	*Day 1*		
Special Laboratory Studies										
Plasma sampling for PF-02341066 and metabolite PK[15]			*X Sparse*	*X Full PK (Cycle 1 Days 15 & 16)*	*X Sparse*	*X Full PK (Cycle 2 Days 1 & 2*				
Plasma sampling for Itraconazole and metabolite(s) PK[16]				*X (Cycle 1 Days 15 & 16)*						
Blood sample for pharmacogenomics[17]	*X*									
PF-02341066 treatment[18]		*X ----------→X*								
Itraconazole treatment[19]		*X ----------→X (Starting Day 1) (Up to Day 16)*								

( ) If it has not been performed within 7 days.
** Allowable window for imaging is ±7 days; ±2 day window for all other assessments with the exception of PK collection days. There is a ±1 day window for Days 11, 13, 25 and 27 (but these visits should be 2 days apart). There is a ±2 day window for PK collection on Cycle 1 Day 15 and Cycle 2 Day 1.*
** Allowable window for screening activities is up to -7 days from Day -14 (ie, Day -21 to Day 0).*
** End of treatment visit should be conducted 28 days postdose ±2 days.*
***Cycle length is 4 weeks (28 days); Tx = Treatment.*
****Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle.*
*****If renal cysts are observed, imaging should be performed every 8 weeks.*

1. *Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.*
2. *Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.*
3. *Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.*
4. *Height need not be collected after the first measurement.*
5. *ECOG performance scale will be available in the Appendix 2 of the protocol.*
6. *12- Lead ECG: Three consecutive 12-lead ECGs will be performed at least 2 minutes apart at the following timepoints: Screening; Cycle 1 Day 1 and Cycle 1 Day 15 at pre-PF-02341066 dose (0 hour), 1 hour post-PF-02341066 dose and 4 hours post-PF-02341066 dose and Cycle 2 Day 1 at pre-PF-02341066 dose (0 hour) and 4 hours post- PF-02341066 dose. These time points correspond to PK time points. ECGs should be performed within 15 minutes before PK blood draws at respective time points.*
7. *Hematology: WBC with differential count, hemoglobin, and platelet count.*

8. *Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail.*
9. *Coagulation: PT and PTT. If a patient is on a coumarin-like drug, the anticoagulant effects should be carefully monitored and titrated as needed during itraconazole administration, since itraconazole may enhance the anticoagulant effects of coumarin-like drugs.*
10. *Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.*
11. *Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.*
12. *If renal cysts are observed, monitoring with appropriate imaging should be performed every 8 weeks following diagnosis.*
13. *Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.*
14. *Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. As of IRB/EC approval of Protocol Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy; once at Screening and once at Cycle 1 Day 1 before PF-02341066 administration. Pregnancy tests will also be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2 for further detail.*
15. *A full PK profile of PF-02341066 will be obtained after administration of multiple doses of itraconazole and PF-02341066 on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose. In addition, pre-dose PK samples will be collected on Cycle 1 Day 11, Cycle 1 Day 13, Cycle 1 Day 25 and Cycle 1 Day 27.*
16. *Pre-dose PK samples will be taken prior to itraconazole dosing on Cycle 1 Day 15 and Cycle 1 Day 16.*
17. *Blood sample for pharmacogenomics: A single whole blood biospecimen (4 mL) will be collected at baseline (within 2 weeks prior to the first dose) for possible analysis of DNA sequence variation in genes that may affect PK of the study drugs, may be associated with specific adverse events or toxicities, or may correlate with efficacy.*
18. *PF-02341066 dosing at 250 mg QD will start on Cycle 1 Day 1 through Cycle 2 Day 1. Starting on Cycle 2 Day 2, PF-02341066 will be administered at a dose of 250 mg BID.*
19. *Itraconazole will be dosed at 200 mg QD starting Cycle 1 Day 1 and finishing on Cycle 1 Day 16 (16 days).*
20. *An ophthalmology examination will be performed at screening for all patients. The ophthalmology examination should be repeated during the study when visual disturbances have been observed and when there is an increase in grade for visual disturbances. The ophthalmology examination should include ocular characteristics, visual acuity, fundoscopy and slit lamp examination.*

21. *Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.*

Schedule of Activities: PF-02341066 and Itraconazole Interaction Schema: Single and Multiple-Dose Design

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and If a patient withdraws from study treatment and new anticancer therapy is subsequently administered, the End of Treatment (EOT) visit should occur prior to the initiation of new anticancer therapy.

ASSESSMENTS *sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.*

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	***Screening****	***Lead-in PK Period***	***Cycle 1= 28 days****				***Cycle 2 = 28 days****		***Every 4 weeks ***** ***(Cycle ≥3)***	***Every 8 Weeks *******	***End of Tx (28 Days Post Dose)***
	Day -19 to Day -6	***Day -5, -4, -3***	***Day 1 (pre-dose)***	***Day 11, 13***	***Day 15***	***Days 25, 27***	***Day 1***	***Day 15***	***Day 1***		
Informed consent[1]	*X*										
Medical history[2]	*X*										
Physical examination[3]	*X*		*X*				*X*		*X*		*X*
Weight, height, temperature, BP, pulse[4]	*X*		*X*				*X*		*X*		*X*
ECOG performance status[5]	*X*		*X*				*X*		*X*		*X*
12-Lead electrocardiogram (ECG)[6]	*X*	*X (Day-5)*	*X*		*X*		*X*	*Repeat as clinically indicated.*			
Hematology[7]	*X*		*(X)*		*X*		*X*		*X*		*X*
Chemistry[8]	*X*		*(X)*		*X*		*X*	*X*	*X*		*X*
Coagulation tests[9]	*X*		*(X)*		*X*		*X*				
Urinalysis[10]	*X*		*(X)*				*X*		*X*		
Ophthalmology Examination[20]	*X*										
Safety assessment (adverse events)[11]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*		*X*
Imaging only if renal cysts are identified[12]										*X*	

Protocol Activity	***Screening****	***Lead-in PK Period***	***Cycle 1= 28 days****				***Cycle 2 = 28 days****		***Every 4 weeks ***** ***(Cycle ≥3)***	***Every 8 Weeks *****	***End of Tx (28 Days Post Dose)***
	Day -19 to Day -6	***Day -5, -4, -3***	***Day 1 (pre-dose)***	***Day 11, 13***	***Day 15***	***Days 25, 27***	***Day 1***	***Day 15***	***Day 1***		
Concomitant medications[13]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*		
Contraceptive Check (as applicable)[21]	*X*	*X (Day-5)*					*X*		*X*		*X*
Female patients: Pregnancy test[14]	*X*		*X*				*X*		*X*		*X*
Special Laboratory Studies											
Plasma sampling for PF-02341066 and metabolite PK[15]		*X Full PK (Days -5,-4,-3 & either -2 or -1)*	*X Full PK (Cycle 1 Days 1,2,3 and either Day 4 or 5)*	*X Sparse PK*	*X Full PK (Days 15 & 16)*	*X Sparse PK*	*X Full Pk (Cycle 2 Days 1 & 2*				
Plasma sampling for Itraconazole and metabolite(s) PK[16]			*X (Days 1,2)*		*X (Days 15,16)*						
Blood sample for pharmacogenomics[17]	*X*										
PF-02341066 treatment[18]		*X (Day -5 only)*	*X (no dose on C1D2)----------→X*								
Itraconazole treatment[19]		*X ----------→X (Starting Day -3) (up to Day 16)*									

( ) If it has not been performed within 7 days
** Allowable window for imaging is ±7 days, There is a + 7 day window for screening. There is a ±2 day window for all other assessments with the exception of PK collection days. There is a ±1 day window for Days 11, 13, 25 and 27 (but these visits should be 2 days apart). Once PF-02341066 is dosed on Day -5, PK collection on Cycle 1 Day 1 must be performed per schedule. There is a ±2 day window for PK collection on Cycle 1 Day 15 and Cycle 2 Day 1.*
***Cycle length is 4 weeks (28 days); Tx = Treatment.*
****Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle.*
*****If renal cysts are observed, imaging should be performed every 8 weeks.*

1. *Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.*
2. *Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.*
3. *Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.*

4. *Height need not be collected after the first measurement.*
5. *ECOG performance scale will be available in the Appendix 2 of the protocol.*
6. *12- Lead ECG: Three consecutive 12-lead ECGs will be performed at least 2 minutes apart at the following timepoints: Screening; Day -5 at pre-PF-02341066 dose (0 hour); Cycle 1 Day 1 and Cycle 1 Day 15 at pre-PF-02341066 dose (0 hour), 1 hour post-PF-02341066 dose and 4 hours post-PF-02341066 dose and Cycle 2 Day 1 at pre-PF-02341066 dose (0 hour) and 4 hours post- PF-02341066 dose. These time points correspond to PK time points. ECGs should be performed within 15 minutes before PK blood draws at respective time points.*
7. *Hematology: WBC with differential count, hemoglobin, and platelet count.*
8. *Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, glucose. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail.*
9. *Coagulation: PT and PTT. If a patient is on a coumarin-like drug, the anticoagulant effects should be carefully monitored and titrated as needed during itraconazole administration, since itraconazole may enhance the anticoagulant effects of coumarin-like drugs.*
10. *Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.*
11. *Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.*
12. *If renal cysts are observed, monitoring with appropriate imaging should be performed every 8 weeks following diagnosis.*
13. *Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.*
14. *Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations. As of IRB/EC approval of Protocol Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy; once at Screening and once at Cycle 1 Day 1 before PF-02341066 administration. Pregnancy tests will also be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/EC or if required by local regulations. See Section 7.2 for further detail.*
15. *A full PK profile of PF-02341066 will be obtained after administration of a single dose on Day -5 (lead-in period) and Day 1 of Cycle 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9, 24, 48 and either 72 or 96 hours post dose. Blood samples for PF-02341066 PK will be also obtained on Cycle 1 Day 15 and Cycle 2 Day 1 at the following time points: 0 (pre-dose), 1, 2, 4, 6, 8, 9 and 24 hours post dose. In addition, pre-dose PK samples will be collected on Cycle 1 Day 11, Cycle 1 Day 13, Cycle 1 Day 25 and Cycle 1 Day 27.*
16. *Pre-dose PK samples will be taken prior to itraconazole dosing on Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 15 and Cycle 1 Day 16.*
17. *Blood sample for pharmacogenomics: A single whole blood biospecimen (4 mL) will be collected at baseline (within 2 weeks prior to the first dose) for possible analysis of DNA sequence variation in genes that may affect PK of the study drugs, may be associated with specific adverse events or toxicities, or may correlate with efficacy.*

18. *A single 250 mg dose of PF-02341066 will be given on Day -5. PF-02341066 dosing at 250 mg QD will start on Cycle 1 Day 1 through Cycle 2 Day 1. However, no PF-02341066 dose will be given on Cycle 1 Day 2. Starting on Cycle 2 Day 2, PF-02341066 will be administered at a dose of 250 mg BID.*

19. *Itraconazole will be dosed at 200 mg QD starting Cycle 1 Day -3 and finishing on Cycle 1 Day 16 (19 days).*

20. *An ophthalmology examination will be performed at screening for all patients. The ophthalmology examination should be repeated during the study when visual disturbances have been observed and when there is an increase in grade for visual disturbances. The ophthalmology examination should include ocular characteristics, visual acuity, fundoscopy and slit lamp examination.*

21. *Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.*

Appendix 8. *ALK Marker Negative NSCLC RP2D Cohort #2*

This cohort will consist of NSCLC patients who are negative for the ALK translocation as determined by the ALK break apart fluorescence in situ hybridization (FISH) assay as determined by the central laboratory selected by the Sponsor. Patients may have been pre-screened and determined to have ALK marker negative NSCLC by a local test but no molecular testing for MET or ROS1 should have occurred prior to enrollment. As of the Note to File dated 19 June 2012, the requirement that no molecular testing for MET or ROS1 to occur prior to enrollment was removed. However, if MET or ROS1 testing was performed prior to patient enrollment and if the test result for either MET or ROS1 was positive, then the patient could not be enrolled onto this cohort. The results of the negative local test must be confirmed by the central laboratory before entry into the study.

Patient Population:

This clinical trial 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.

Inclusion Criteria:

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. *Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adenosquamous histology). Patients must have received at least one prior chemotherapy regimen. Patients must have been determined to be ALK-negative by the central laboratory but may have been pre-screened and shown to have ALK negative NSCLC by a local test. All patients must either be non-smokers, ex-smokers or light smokers (≤10 pack-years).*

2. *Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1). Patients whose tumors are not measurable may enter the study upon approval by the Sponsor. Target lesions that have been previously irradiated will not be considered measurable (lesion) unless increase in size is observed following completion of radiation therapy.*

3. *Able, in the investigator's opinion, to receive at least 2 cycles of treatment.*

4. *Female or male, 18 years of age or older.*

5. *ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.*

6. *Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).*

7. *Adequate organ function as defined by the following criteria:*

   - *Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.*
   - *Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).*
   - *Absolute neutrophil count (ANC) ≥1500/μL.*
   - *Platelets ≥30,000/μL*
   - *Hemoglobin ≥9.0 g/dL.*
   - *Serum creatinine ≤2.0 x ULN.*

8. *Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.*

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

Exclusion Criteria:

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

1. *Major surgery, radiation therapy, or systemic anti-cancer therapy within 2 weeks of starting study treatment.*

2. *Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.*

3. *Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.*

4. *Current treatment on another clinical trial.*

5. *Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks and not taking medications contraindicated to Exclusion Criteria #11-13.*

6. *Any of the following within the 6 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack, or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 6 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted.*

7. *Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc interval >470 msec.*

8. *Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).*

9. *Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to the use of effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.*

10. *Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, which would make the patient inappropriate for entry into this study.*

11. *Use of drugs that are known strong CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.*

12. *Use of drugs that are known strong CYP3A4 inducers within 12 days prior to the first dose of PF-02341066, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. All concomitant medication must be approved by the Sponsor.*

13. *Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.*

14. *Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.*

15. *Patients with known interstitial fibrosis or interstitial lung disease.*

Sample Size:

To further characterize the anti-tumor activity of PF-02341066 in ALK marker negative NSCLC patients, at least 20 patients will be enrolled into this cohort.

Concomitant Medications:

Refer to Section 5.5 Concomitant Medication(s) for further details.

Administration:

PF-02341066 tablets will be administered at a dose of 250 mg BID. PF-02341066 doses should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study.

Refer to Section 5.2 Trial Treatments for details on Formulation and Packaging (Section 5.2.1), Preparation and Dispensing (Section 5.2.2), Administration (Section 5.2.3) and Compliance (Section 5.2.4).

Schedule of Activities: ALK Marker Negative NSCLC Cohort*

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	*Screening**	**Cycle 1= 21 days****		**Cycle 2 = 21 days****		**Every 3 weeks** (Cycle ≥3)**	**Every 6 Weeks**	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Informed consent[1]	X							
Medical history[2]	X							
Physical examination[3]	X	X		X		X		X
Weight, height, temperature, BP, pulse[4]	X	X		X		X		X
ECOG performance status[5]	X	X		X		X		X
12-Lead electrocardiogram (ECG)[6]	X	X		X				
Registration/Hematology[7]	X	(X)	X	X		X		X
Chemistry[8]	X	(X)	X	X		X		X
Coagulation tests[9]	X	(X)	X	X				
Urinalysis[10]	X	(X)		X		X		
Ophthalmology Examination[21]	X		X			Cycle 3, Cycle 18 & every 17 cycles thereafter		X
Safety assessment (adverse events)[11]	X	X	X	X	X	X		X
*Tumor assessment *. ***[12]	X						X	X
Survival[13]	Until at least 1 year after the final dose							
Concomitant medications[14]	X	X	X	X	X	X		
Contraceptive Check (as applicable)[22]						X		X
Female patients: Pregnancy test[15]	X	X		X		X		X
Special Laboratory Studies								
Two plasma sampling points for PF-02341066 PK[16]		X		X		Cycles 3 and 5		
Blood sample for pharmacogenomics[17]	X							

CCI [redacted]

Protocol Activity	*Screening**	***Cycle 1= 21 days****		***Cycle 2 = 21 days****		***Every 3 weeks** (Cycle ≥3)***	***Every 6 Weeks***	***End of Treatment (28 Days Post Dose)****
	Day –14 to Day 0	***Day 1 (pre-dose)***	***Day 15***	***Day 1***	***Day 15***	***Day 1***		
PF-02341066 treatment[20]		*Twice a day continuously*						

( ) If it has not been performed within 7 days.
** Allowable window for tumor assessment imaging is ±7 days; ±2 days for all other assessments.*
** Allowable window for screening assessments is up to -7 days from Day -14 (ie, Day -21 to Day 0).*
** End of treatment visit should be conducted 28 days postdose ±2 days.*
***Cycle length is 3 weeks (21 days).*
****Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle. Once a patient has completed 15 cycles, tumor imaging may be performed every 12 weeks based on 3-week calendar schedule. Once a patient has completed 35 cycles, tumor imaging may be performed every eighth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit.*

1. *Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.*
2. *Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.*
3. *Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.*
4. *Height need not be collected after the first measurement.*
5. *ECOG performance scale will be available in the Appendix 2 of the protocol.*
6. *12- Lead ECG: Patients will have triplicate ECGs collected at least 2 minutes apart during the screening period; Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hour) and 2-6 hours post-dose, which are corresponding to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.*
7. *Hematology: WBC with differential count, hemoglobin, and platelet count.*
8. *Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail.*
9. *Coagulation: PT and PTT.*
10. *Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.*
11. *Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.*

12. *Tumor Imaging: CT or MRI scan to be performed to assess disease status at screening, every 6 weeks (based on calendar schedule) starting after the first dose, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end/withdrawal from the study. If renal cysts are observed, monitoring with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging.*

13. *Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the final dose.*

14. *Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.*

15. *Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/EC or if required by local regulations. As of IRB/EC approval of Protocol Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely performed at every cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2 for further detail. Note: At the time of the required inclusion of additional pregnancy testing, no patients are being enrolled in this cohort and all ongoing patients are beyond Cycle 2.*

16. *PK samples will be collected on Day 1 of Cycle 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. See Section 7.5.1.1.*

17. *A single blood sample will be collected at baseline (within 2 weeks prior to the first dose) to genotype the alleles of cytochrome P450 enzymes and drug transport proteins.*

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20. *PF-02341066 will be administered at a dose of 250 mg BID.*

21. *As of Protocol Amendment #17, all patients will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor. As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. All ophthalmology examinations should be performed by an ophthalmologist. Ophthalmology examination(s) should be repeated if visual disturbances are observed or if there is an increase in grade for a visual side effect. The time points of this special testing is designated by "[ ]" in the Schedule of Activities Table and includes Screening, Cycle 1 Day 15, Cycle 3 Day 1, 1 year, yearly thereafter, and then at 2 - 8 weeks after discontinuation of PF-02341066. For NSCLC patients on a 3-week cycle, 1 year would be Cycle 18 Day 1 and every 17 cycles thereafter. There is a ±2 week window for the yearly ophthalmology examination.*

22. *Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.*

Appendix 9. MET-Amplified NSCLC Cohort

To further evaluate the anti-tumor activity of PF-02341066 associated with MET amplification, patients with MET-amplified NSCLC will be enrolled.

Patient Population:

This clinical trial 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.

Inclusion Criteria:

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. Histologically confirmed advanced NSCLC positive for MET amplification. Patients must have a MET/CEP7 ratio of ≥1.8.

2. Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.0). However, patients whose tumors are not measurable may enter the study upon approval by the Sponsor. Target lesions that have been previously irradiated will not be considered measurable (lesion) unless increase in size is observed following completion of radiation therapy.

3. Able, in the investigator's opinion, to receive at least 2 cycles of treatment.

4. Female or male, 18 years of age or older.

5. ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.

6. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).

7. Adequate organ function as defined by the following criteria:

    - Serum aspartate transferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.

    - Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).

- Absolute neutrophil count (ANC) ≥1500/μL.
- Platelets ≥30,000/μL.
- Hemoglobin ≥9.0 g/dL (≥8.0 g/dL after IRB/EC approval of Amendment #21).
- Serum creatinine ≤2.0 x ULN.

8. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment. For Sites using WIRB, patients who lack capacity to consent for themselves will be excluded from this study.

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

Exclusion Criteria:

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

1. Major surgery, radiation therapy, or systemic anti-cancer therapy within 2 weeks of starting study treatment.

2. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.

3. Prior therapy specifically directed against MET or HGF.

4. Current treatment on another clinical trial.

5. Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks and not taking medications contraindicated to Exclusion Criteria #11-13.

6. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 3 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted. [Implement 3 month guidance upon IRB/EC approval of Amendment #20].

7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc >470 msec. Upon agreement between the Investigator and Sponsor, patients with a QTc >470 msec but <490 msec in the

presence of a right bundle branch block or with an implanted cardiac pacemaker may enter the study [Implement upon IRB/EC approval of Amendment #20].

8. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

9. Pregnant female patients, breastfeeding patients, male patients with pregnant female partners who are unwilling or unable to use a condom for the duration of the pregnancy, female and male patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of study treatment and for 90 days after the last dose of investigational product.

10. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior) or end-stage renal disease on hemodialysis or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and would make the patient inappropriate for entry into this study.

11. Use of drugs that are known strong CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.

12. Use of drugs that are known strong CYP3A4 inducers within 12 days prior to the first dose of PF-02341066, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. All concomitant medication must be approved by the Sponsor.

13. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.

14. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

15. Patients with known interstitial fibrosis or interstitial lung disease. After IRB/EC approval of Amendment #20: History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, , obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

16. Patients who are investigational site staff members directly involved in the conduct of the study 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 study [Implement upon IRB/EC approval of Amendment #20].

Sample Size:

To further evaluate the anti-tumor activity of PF-02341066 associated with MET amplification, 10 to 12 patients with MET-amplified NSCLC will be enrolled into each of the following 3 categories:

- *High Level MET Gene Amplified Category (MET/CEP7 ratio ≥5.0; Group 1)*: As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to ≥4.0). As per the PACL dated 11 September 2018, this group was closed to further enrollment. The remaining 14 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

- *Medium Level MET Gene Amplified Category (MET/CEP7 ratio >2.2 to <5; Group 2):* As per the PACL dated 15 May 2017, the MET/CEP7 ratio cut-off for this group was revised to >2.2 to <4.0 and this group was closed to further enrollment. The remaining 13 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort;

- *Low Level MET Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2; Group 3)*: As per the PACL dated 12 October 2015, this group was closed to further enrollment.

For further details refer to Section *9.1.3.2*.

Concomitant Medications:

Refer to Section *5.5* Concomitant Medication(s) for further details.

Administration:

PF-02341066 tablets will be administered at a dose of 250 mg BID. PF-02341066 doses should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study.

Refer to Section *5.2* Trial Treatments for details on Formulation and Packaging (Section *5.2.1*), Preparation and Dispensing (Section *5.2.2*), Administration (Section *5.2.3*) and Compliance (Section *5.2.4*).

Independent Radiology Review:

All tumor scans from NSCLC patients with tumors harboring MET gene amplification will be collected and held at the investigative site. With Sponsor approval and IRB/EC notification, the Sponsor may request tumor scans from these patients to be submitted to an independent radiology laboratory for review at a later date. As per PACL dated 9 March 2018, all tumor scans for patients enrolled in the MET-amplified NSCLC cohort will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Amendment #24, tumor scans from patients with MET-amplified NSCLC will no longer be collected and submitted to an independent radiology review laboratory.

Schedule of Activities: MET-Amplified NSCLC Cohort ***

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

NOTE: Upon IRB/EC approval of Protocol Amendment #24, ongoing patients will follow a Reduced Schedule of Activities as indicated in Appendix 13.

Protocol Activity	Screening*	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks**	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Informed consent[1]	X							
Medical history[2]	X							
Physical examination[3]	X	X		X		X		X
Weight, height, temperature, BP, pulse[4]	X	X		X		X		X
ECOG performance status[5]	X	X		X		X		X
12-Lead electrocardiogram (ECG)[6]	X	X		X				
Registration/Hematology[7]	X	(X)	X	X		X		X
Chemistry[8]	X	(X)	X	X	X	X		X
Coagulation tests[9]	X	(X)	X	X				
Urinalysis[10]	X	(X)		X		X		
Ophthalmology Examination[23]	X		*X*			*Cycle 3, Cycle 14 & every 13 cycles thereafter*		*X*
Safety assessment (adverse events)[11]	X	X	X	X	X	X		X
Tumor assessment *, ***[12]	X						X	X
Survival[13]	Until two years after the last patient enrolled has discontinued PF-02341066 treatment, unless otherwise noted by the Sponsor							
Concomitant medications[14]	X	X	X	X	X	X		
Contraceptive check (as applicable)[24]	X	X		X		X		X
Female patients: Pregnancy test[15]	X	X		X		X		X

Protocol Activity	Screening*	Cycle 1= 28 days**		Cycle 2 = 28 days**		Every 4 weeks** (Cycle ≥3)	Every 8 Weeks	End of Treatment (28 Days Post Dose)*
	Day –14 to Day 0	Day 1 (pre-dose)	Day 15	Day 1	Day 15	Day 1		
Special Laboratory Studies								
Two plasma sampling points for PF-02341066 PK[16]		X		X		Cycles 3 & 5; also at disease progression if patient is still taking PF-02341066.		
Blood sample for pharmacogenomics[17]	X							
CCI [redacted]	[redacted]							
Plasma sample for circulating nucleic acid profiling[20] (As of the Protocol Administrative Clarification Letter dated 12 October 2015, collection of plasma samples for circulating nucleic acid profiling in patients with MET-amplified NSCLC is no longer required.)	*X*	*X*						*X*
Male Patients: Hypogonadism Testing[21]		X	X	X		Cycles 4, 6 and every 3 cycles thereafter		X
PF-02341066 treatment[22]		Twice a day continuously						

( ) If it has not been performed within 7 days.

* Allowable window for tumor assessment imaging is ±7 days; ±2 days for all other assessments.

* Allowable window for screening visits is up to -7 days from Day -14 (ie, Day -21 to Day 0).

* End of Treatment (EOT) visit should be conducted 28 days postdose ±2 days. If a patient withdraws from study treatment and new anticancer therapy is subsequently administered, the EOT visit should occur prior to the initiation of new anticancer therapy.

**Cycle length is 4 weeks (28 days).

***Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle**.** Once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle. Once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit.

1. Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.
2. Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.

3. Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.
4. Height need not be collected after the first measurement.
5. ECOG performance scale will be available in the Appendix 2 of the protocol.
6. 12- Lead ECG: Patients will have triplicate ECGs collected at least 2 minutes apart during the screening period; Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hour) and 2-6 hours post-dose, which are corresponding to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.
7. Hematology: WBC with differential count, hemoglobin, and platelet count.
8. Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat AST or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail. C2D15 chemistry required after approval of Amendment #20.
9. Coagulation: PT and PTT.
10. Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.
11. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable,” whichever is later. Serious adverse events should be monitored and reported as described in the protocol.
12. Tumor Imaging: CT or MRI scan to be performed to assess disease status at screening, every 8 weeks (based on calendar schedule) starting after the first dose, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end/withdrawal from study treatment. *All tumor scans from NSCLC patients with tumors harboring MET gene amplification will be collected and held at the investigative site. With Sponsor written approval and IRB/EC notification, the Sponsor may request tumor scans to be submitted to an independent radiology laboratory for review at a later date.* As per PACL dated 9 March 2018, all tumor scans for patients enrolled in the MET-amplified NSCLCcohort were to be collected and submitted to an independent radiology laboratory for review. As of IRB/EC approval of Amendment #24, tumor scans from all patients with MET-amplified NSCLC will no longer be collected for and submitted to an independent radiology review laboratory. If renal cysts are observed, monitoring with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging.
13. Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the patient’s final dose. As of IRB/EC approval of Amendment #22, all patients enrolled into this cohort should be followed for survival every 3 months after discontinuing study treatment until one year after the last patient in this cohort has discontinued PF-02341006 treatment, unless otherwise notified by the Sponsor. As of IRB/EC approval of Amendment #23, all patients enrolled into this cohort should be followed for survival every 3 months after discontinuing study treatment until two years after the last patient in this cohort has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor.
14. Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from study treatment, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.

15. Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/EC or if required by local regulations. As of IRB/EC approval of Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting study therapy; once at Screening and once at Cycle 1 Day 1 before PF-02341066 administration. Pregnancy tests will also be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2 for further detail.

16. PK samples will be collected on Day 1 of Cycle 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. See Section 7.5.1.1. As of IRB/EC approval of Amendment #21, a PK sample should be taken around the time that disease progression is confirmed as long as the patient is on PF-02341066.

17. Blood sample for pharmacogenomics: A single whole blood biospecimen (4 mL) will be collected at baseline (within 2 weeks prior to the first dose) for possible analysis of DNA sequence variation in genes that may affect PK of the study drugs, may be associated with specific adverse events or toxicities, or may correlate with efficacy.

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20. *Plasma sample for circulating nucleic acid profiling: As of IRC/EC approval of Amendment #21, blood biospecimen (10 mL) for nucleic acid analysis (eg, circulating free DNA [cfDNA] or RNA [cfRNA]) will be collected*. As of the Protocol Administrative Clarification Letter dated 12 October 2015, plasma sample for circulating nucleic acid profiling will no longer be required for patients enrolled in the MET amplified NSCLC cohort.

21. Hypogonadism Laboratory Tests (male patients only): All male patients enrolled into the MET-amplified NSCLC Cohort after IRB/EC approval of Amendment #21 will have hypogonadism laboratory tests. Required blood tests include: total testosterone, free testosterone, SHBG, luteinizing hormone, follicle stimulating hormone, dihydroepiandrosterone sulfate, estradiol and prolactin. Blood draws **MUST** be taken before PF-02341066 dosing and between 07:00 and 10:00 a.m. and, for each individual patient, the time of the draw should be as consistent across visits as feasible. If either total testosterone or free testosterone decrease to a value that is .both 25% lower than baseline and below the lower limit of normal, then a repeat laboratory test of both these parameters must be performed at the next clinic visit to confirm hypogonadism. See Section 7.2 for further details.

22. PF-02341066 will be administered at a dose of 250 mg BID.

23. *As of Protocol Amendment #17, all patients will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor.* As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. All ophthalmology examinations should be performed by an ophthalmologist. Ophthalmology examination(s) should be repeated if visual disturbances are observed or if there is an increase in grade for a visual side effect. *The time points of this special testing is designated by "[ ]" in the Schedule of Activities Table and includes Screening, Cycle 1 Day 15, Cycle 3 Day 1, 1 year, yearly thereafter, and then at 2 - 8 weeks after discontinuation of PF-02341066. For NSCLC patients on a 4-week cycle, 1 year would be Cycle 14 Day 1 and every 13 cycles thereafter. There is a ±2 week window for the yearly ophthalmology examination.*

24. Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.

Appendix 10. ROS1 Marker Positive NSCLC Cohort

To further evaluate the anti-tumor activity of PF-02341066 in patients with NSCLC positive for a chromosomal translocation in the *ROS1* gene (including but not limited to CD74 ROS1 and SLC34A2 ROS1 fusion events).

Patient Population:

This clinical trial 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.

Inclusion Criteria:

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

1. Histologically confirmed advanced NSCLC positive for chromosomal translocations at *ROS1* gene including but not limited to CD74-ROS1 and SLC34A2-ROS1 fusion events.

2. Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.0). However, patients whose tumors are not measurable may enter the study upon approval by the Sponsor. Target lesions that have been previously irradiated will not be considered measurable (lesion) unless increase in size is observed following completion of radiation therapy.

3. Able, in the investigator's opinion, to receive at least 2 cycles of treatment.

4. Female or male, 18 years of age or older.

5. ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.

6. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).

7. Adequate organ function as defined by the following criteria:

    - Serum aspartate aminotransferase (AST) and serum aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.

    - Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).

    - Absolute neutrophil count (ANC) ≥1500/μL.

- Platelets ≥30,000/μL.
- Hemoglobin ≥9.0 g/dL.
- Serum creatinine ≤2.0 x ULN.

8. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.

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

Exclusion Criteria:

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

1. Major surgery, radiation therapy, or systemic anti-cancer therapy within 2 weeks of starting study treatment.

2. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.

3. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

4. Current treatment on another clinical trial.

5. Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks and not taking medications contraindicated to Exclusion Criteria #11-13.

6. Any of the following within the 6 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack, or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 6 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted.

7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc interval >470 msec.

8. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

9. Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to the use of effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.

10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, which would make the patient inappropriate for entry into this study.

11. Use of drugs that are known strong CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.

12. Use of drugs that are known strong CYP3A4 inducers within 12 days prior to the first dose of PF-02341066, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. All concomitant medication must be approved by the Sponsor.

13. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.

14. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

15. Patients with known interstitial fibrosis or interstitial lung disease.

Sample Size:

To further evaluate the anti-tumor activity of PF-02341066 in patients with NSCLC positive for a chromosomal translocation in the ROS1 gene, approximately 50 patients will be enrolled.

For further details refer to Section 9.1.3.3.

Concomitant Medications:

Refer to Section 5.5 Concomitant Medication(s) for further details.

Administration:

PF-02341066 tablets will be administered at a dose of 250 mg BID. PF-02341066 doses should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study.

Refer to Section 5.2 Trial Treatments for details on Formulation and Packaging (Section 5.2.1), Preparation and Dispensing (Section 5.2.2), Administration (Section 5.2.3) and Compliance (Section 5.2.4).

Independent Radiology Review:

All tumor scans from ROS1 marker positive NSCLC patients enrolled will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Protocol Amendment #23, tumor scans from ROS1 marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review.

Schedule of Activities: ROS1 Marker Positive NSCLC Cohort ***

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

NOTE: Upon IRB/EC approval of Protocol Amendment #24, ongoing patients will follow a Reduced Schedule of Activities as indicated in Appendix 13.

Protocol Activity	Screening*	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks**	**End of Treatment (28 Days Post Dose)***
	Day –14 to Day 0	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Informed consent[1]	X							
Medical history[2]	X							
Physical examination[3]	X	X		X		X		X
Weight, height, temperature, BP, pulse[4]	X	X		X		X		X
ECOG performance status[5]	X	X		X		X		X
12-Lead electrocardiogram (ECG) [6]	X	X		X				
Registration/Hematology[7]	X	(X)	X	X		X		X
Chemistry[8]	X	(X)	X	X		X		X
Coagulation tests[9]	X	(X)	X	X				
Urinalysis[10]	X	(X)		X		X		
Ophthalmology Examination[21]	X		*X*			*Cycle 3, Cycle 14 & every 13 cycles thereafter*		*[X]*
Safety assessment (adverse events) [11]	X	X	X	X	X	X		X
Tumor assessment *, ***[12]	X						X	X
Survival[13]	Until two years after the last patient enrolled in this cohort has discontinued PF-02341006 treatment, unless otherwise notified by the Sponsor							
Concomitant medications[14]	X	X	X	X	X	X		
Contraceptive Check (as applicable) [22]						X		X
Female patients: Pregnancy test[15]	X	X		X		X		X

Protocol Activity	Screening*	Cycle 1= 28 days**		Cycle 2 = 28 days**		Every 4 weeks** (Cycle ≥3)	Every 8 Weeks	End of Treatment (28 Days Post Dose)*
	Day –14 to Day 0	Day 1 (pre-dose)	Day 15	Day 1	Day 15	Day 1		
Special Laboratory Studies								
Two plasma sampling points for PF-02341066 PK[16]		X		X		Cycles 3 & 5 and at disease progression (if patient is still taking PF-02341066)		
Blood sample for pharmacogenomics[17]	X							
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PF-02341066 treatment[20]		Twice a day continuously						

( ) If it has not been performed within 7 days.
* Allowable window for tumor assessment imaging is ±7 days; ±2 days for all other assessments.
* Allowable window for screening assessments is up to -7 days from Day -14 (ie, Day -21 to Day 0).
* End of Treatment (EOT) visit should be conducted 28 days postdose ±2 days. If a patient withdraws from study treatment and new anticancer therapy is subsequently administered, the EOT visit should occur prior to the initiation of new anticancer therapy.
**Cycle length is 4 weeks (28 days).
***Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle**.** Once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle. Once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit.

1. Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.
2. Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.
3. Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.
4. Height need not be collected after the first measurement.
5. ECOG performance scale will be available in the 0 of the protocol.
6. 12-Lead ECG: Patients will have triplicate ECGs collected at least 2 minutes apart during the screening period; Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hour) and 2-6 hours post-dose, which are corresponding to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.
7. Hematology: WBC with differential count, hemoglobin, and platelet count.

8. Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail. C2D15 chemistry required after approval of Amendment #20.
9. Coagulation: PT and PTT.
10. Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.
11. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.
12. Tumor Imaging: CT or MRI scan to be performed to assess disease status at screening, every 8 weeks (based on calendar schedule) starting after the first dose, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end/withdrawal from study treatment. If renal cysts are observed, monitoring with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging.
13. Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the patient's final dose. As of IRB/EC approval of Amendment #22, all patients enrolled into this cohort should be followed for survival every 3 months after discontinuing study treatment until one year after the last patient in this cohort has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. As of IRB/EC approval of Amendment #23, all patients enrolled into this cohort should be followed for survival every 3 months after discontinuing study treatment until two years after the last patient in this cohort has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor.
14. Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from study treatment, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.
15. Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations. As of IRB/EC approval of Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely performed at every cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. See Section 7.2. for further details. Note: At the time of the required inclusion of additional pregnancy testing, no patients were being enrolled in this cohort and all ongoing patients are beyond Cycle 2.
16. PK samples will be collected on Day 1 of Cycle 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. See Section 7.5.1.1. As of IRB/EC approval of Amendment #21, a PK sample should be taken around the time that disease progression is confirmed as long as the patient is on PF-02341066.
17. A single blood sample will be collected at baseline (within 2 weeks prior to the first dose) to genotype the alleles of cytochrome P450 enzymes and drug transport proteins.

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20. PF-02341066 will be administered at a dose of 250 mg BID.

21. *As of Protocol Amendment #17, all patients will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor.* As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. All ophthalmology examinations should be performed by an ophthalmologist. Ophthalmology examination(s) should be repeated if visual disturbances are observed or if there is an increase in grade for a visual side effect. *The time points of this special testing is designated by "[ ]" in the Schedule of Activities Table and includes Screening, Cycle 1 Day 15, Cycle 3 Day 1, 1 year, yearly thereafter, and then at 2 - 8 weeks after discontinuation of PF-02341066. For NSCLC patients on a 4-week cycle, 1 year would be Cycle 14 Day 1 and every 13 cycles thereafter. There is a ±2 week window for the yearly ophthalmology examination.*

22. Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.

Appendix 11. Enriched Other Cohort

To further evaluate the anti-tumor activity of PF-02341066 in patients with molecular profiles that could potentially rendering disease sensitive to PF-022341066.

Patient Population:

This clinical trial 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.

Inclusion Criteria:

Patient eligibility should be reviewed and documented by an appropriate 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 trial:

1. Tumor eligibility:

    - Histologically confirmed advanced malignancies that meet one of the following criteria:

    - Positive for MET amplification by FISH (excluding polysomy). After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

    - Positive for ALK chromosomal translocations or gene amplification including but not limited to NPM-ALK positive anaplastic large cell lymphoma, inflammatory myofibroblastic tumors, echinoderm microtubule-associated protein-like 4 (EML4)-ALK positive non-small cell lung cancer or ALK-positive melanoma. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor. After IRB/EC approval of Amendment #18 patients with NSCLC that is positive for ALK chromosomal translocations or gene amplifications will not be allowed to enter the enriched cohort.

    - Positive for known MET kinase domain activating mutations including but not limited to V1110L, H1112L, H1112Y, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, M1268T, P1009S, T1010I, R988C, V941L but excluding Y1248C, Y1248H, Y1248D, Y1253D; mutations in the intron/exon splice site regions flanking exon 14 resulting in exon 14 deletion and Y1003X mutations in exon 14 affecting binding of the E3 ubiquitin ligase, CBL. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

- Chromosomal translocations/fusions that lead to altered transcriptional regulation of MET and/or HGF including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma. Patients with these tumors may enter the study without prior confirmation of MET and/or HGF alterations. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

- Positive for chromosomal translocations at ROS1 gene including but not limited to CD74-ROS1 and SLC34A2-ROS1 fusion events in NSCLC and FIG-ROS1 in glioblastoma. ROS1 marker positive NSCLC patients may not be enrolled onto this cohort.

- Other molecular changes for which there are data to suggest a biologic rationale for PF-02341066 treatment, eg, TRK1 fusions.

2. Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.0). However, patients whose tumors are not measurable may enter the study upon approval by the Sponsor. Target lesions that have been previously irradiated will not be considered measurable (lesion) unless increase in size is observed following completion of radiation therapy.

3. Able, in the investigator's opinion, to receive at least 2 cycles of treatment.

4. Female or male, 18 years of age or older. For patients enrolled in clinical sites in Japan: Female or male, 20 years of age or older.

5. ECOG performance status 0 or 1. However, patients with an ECOG performance status of 2 may enter the study upon agreement between the investigator and Sponsor.

6. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).

7. Adequate organ function as defined by the following criteria:

   - Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.

   - Total serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome; however enrollment must be approved by the Sponsor).

   - Absolute neutrophil count (ANC) ≥1500/μL.

   - Platelets ≥30,000/μL.

   - Hemoglobin ≥9.0 g/dL (≥8.0 g/dL after IRB/EC approval of Amendment #21).

- Serum creatinine ≤2.0 x ULN.

8. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment. For Sites using WIRB, patients who lack capacity to consent for themselves will be excluded from this study.

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

Exclusion Criteria:

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

1. Major surgery, radiation therapy, or systemic anti-cancer therapy within 2 weeks of starting study treatment.

2. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.

3. For MET dependent tumors, prior therapy specifically directed against MET or HGF; for ALK dependent tumors, prior therapy specifically directed against ALK; for ROS1 dependent tumors, prior therapy specifically directed against ROS1.

4. Current treatment on another clinical trial.

5. Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease unless appropriately treated and neurologically stable for at least 2 weeks and not taking medications contraindicated to Exclusion Criteria #11-13.

6. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, cerebrovascular accident including transient ischemic attack, or pulmonary embolus. However, upon agreement between the investigator and Sponsor, the 3 month post-event-free period for a patient with a pulmonary embolus can be waived if due to advanced cancer. Appropriate treatment with anticoagulants is permitted. [Implement 3 month guidance upon IRB/EC approval of Amendment #20]

7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or QTc >470 msec. Upon agreement between the Investigator and Sponsor, patients with a QTc >470 msec but <490 msec in the presence of a right bundle branch block or with an implanted cardiac pacemaker may enter the study [Implement upon IRB/EC approval of Amendment #20].

8. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

9. Pregnant female patients, breastfeeding female patients (including patients who intend to interrupt breastfeeding), male patients with pregnant female partners who are unwilling or unable to use a condom for the duration of the pregnancy, female and male patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of study treatment and for 90 days after the last dose of investigational product.

10. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior) or end stage renal disease on hemodialysis or laboratory abnormality that would impart, in the judgment of the investigator and/or Sponsor, excess risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and would make the patient inappropriate for entry into this study.

11. Use of drugs that are known strong CYP3A4 inhibitors within 7 days prior to the first dose of PF-02341066, including but not limited to atazanavir, clarithromycin, ketoconazole, itraconazole, telithromycin, troleandomycin, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and voriconazole. Grapefruit or grapefruit juice should also be avoided. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. All concomitant medication must be approved by the Sponsor.

12. Use of drugs that are known strong CYP3A4 inducers within 12 days prior to the first dose of PF-02341066, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort. All concomitant medication must be approved by the Sponsor.

13. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*withdrawn from U.S. market). All concomitant medication must be approved by the Sponsor.

14. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

15. Patients with known interstitial fibrosis or interstitial lung disease. After IRB/EC approval of Amendment #20: History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis. As of IRB/EC approval of Protocol Amendment #24, this exclusion criterion is as follows: History of extensive disseminated/bilateral or known presence of any grade interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity

pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

16. Patients who are investigational site staff members directly involved in the conduct of the study 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 study [Implement upon IRB/EC approval of Amendment #20].

Sample Size:

To further evaluate the anti-tumor activity of PF-02341066 in patients who have tumors with molecular alterations potentially conferring sensitivity to PF-02341066, approximately 171 patients will be enrolled including approximately 103 patients with NSCLC harboring MET Exon 14 alterations including patients with NSCLC harboring MET Exon 14 alterations who are enrolled in clinical sites in Japan.

For further details refer to Section 9.1.3.4.

Concomitant Medications:

Refer to Section 5.5 Concomitant Medication(s) for further details.

Administration:

PF-02341066 tablets will be administered at a dose of 250 mg BID. PF-02341066 doses should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study.

Following IRB/EC approval of Amendment #25 (Japan specific amendment), PF-02341066 formulated capsules can also be administered at a dose of 250 mg BID. PF-02341066 doses should be administered approximately 12 hours apart. PF-02341066 may be given with or without food throughout the study.

Refer to Section 5.2 Trial Treatments for details on Formulation and Packaging (Section 5.2.1), Preparation and Dispensing (Section 5.2.2), Administration (Section 5.2.3) and Compliance (Section 5.2.4).

Independent Radiology Review:

As of IRB/EC approval of Protocol Amendment #23, all tumor scans from all NSCLC patients with tumors harboring MET Exon 14 alterations will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor.

Schedule of Activities: Enriched Other Cohort ***

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to TRIAL PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

NOTE: Upon IRB/EC approval of Protocol Amendment #24, ongoing patients will follow a Reduced Schedule of Activities as indicated in Appendix 13.

Protocol Activity	Screening*	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks**	**End of Treatment (28 days Post Dose)***
	Day –14 to Day 0	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Informed consent[1]	X							
Medical history[2]	X							
Physical examination[3]	X	X		X		X		X
Weight, height, temperature, BP, pulse[4]	X	X		X		X		X
ECOG performance status[5]	X	X		X		X		X
12-Lead electrocardiogram (ECG)[6]	X	X		X				
Registration/Hematology[7]	X	(X)	X	X		X		X
Chemistry[8]	X	(X)	X	X	X	X		X
Coagulation tests[9]	X	(X)	X	X				
Urinalysis[10]	X	(X)		X		X		
Ophthalmology Examination[22]	X *[X]*		*[X]*			*[X] [Cycle 3, one year and yearly thereafter]*		*[X]*
Safety assessment (adverse events) [11]	X	X	X	X	X	X		X
Tumor assessment *, ***,[12]	X						X	X

Protocol Activity	Screening*	**Cycle 1= 28 days****		**Cycle 2 = 28 days****		**Every 4 weeks** (Cycle ≥3)**	**Every 8 Weeks**	**End of Treatment (28 days Post Dose)***
	Day –14 to Day 0	**Day 1 (pre-dose)**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Survival[13]	Until at least 1 year after the patient's final dose (except for NSCLC patients with tumors harboring MET Exon 14 alterations); For NSCLC patients with tumors harboring MET Exon 14 alterations: until two years after the last NSCLC patient with tumors harboring MET Exon 14 alterations has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. MET Exon 14 alteration patients enrolled in clinical sites in Japan will be followed for survival as a separate group.							
Concomitant medications[14]	X	X	X	X	X	X		
Contraceptive check (as applicable) [23]	X	X		X		X		X
Female patients: Pregnancy test[15]	X	X		X		X		X
Special Laboratory Studies								
Two plasma sampling points for PF-02341066 PK[16]		X		X		Cycles 3 & 5 and at disease progression (if patient is still taking PF-02341066)		
Blood sample for pharmacogenomics[17] (Optional for patients enrolled in clinical sites in Japan)	X							
CCI [redacted]								
Plasma sample for circulating nucleic acid profiling[20] *(As of the Protocol Administrative Clarification Letter dated 12 October 2015, only applicable to NSCLC patients with tumors harboring MET Exon 14 alterations and required only at Screening and End of Treatment)*	*X*	*X*						*X*
Hypogonadism Testing [21] *(Patients enrolled in clinical sites in Japan will not participate in hypogonadism testing)*		*X*	*X*	*X*		*Cycles 4, 6 and every 3 cycles thereafter*		*X*
PF-02341066 treatment[22]		Twice a day continuously						

( ) If it has not been performed within 7 days

* Allowable window for tumor assessment imaging is ±7 days, ±2 days for all other assessments.

* Allowable window for screening visit assessments is up to -7 days from Day -14 (ie, Day -21 to Day 0).

* End of Treatment (EOT) visit should be conducted 28 days postdose ±2 days. If a patient withdraws from study treatment and new anticancer therapy is subsequently administered, the EOT visit should occur prior to the initiation of new anticancer therapy.
[X] Special ophthalmology tests for all NSCLC patients enrolled until written notification by Sponsor. As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. See Section 7.3 for additional details.
**Cycle length is 4 weeks (28 days).
***Once a patient has completed 10 cycles, clinic visits may be every other cycle. Laboratory tests will still be performed on Day 1 of each cycle. If a patient does not have a clinic visit, a telephone contact is required before initiating the next cycle**.** Once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle. Once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit.

1. Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 14-day screening period.
2. Medical/Oncology History: To include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure.
3. Physical Examination: During Screening, on Day 1 of each cycle and at the end of treatment: examination of major body systems.
4. Height need not be collected after the first measurement.
5. ECOG performance scale will be available in the 0 of the protocol.
6. 12-Lead ECG: Patients will have triplicate ECGs collected at least 2 minutes apart during the screening period; Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hour) and 2-6 hours post-dose, which are corresponding to PK time points. ECGs should be performed before PK blood draws at respective time points. In addition to the time points noted, ECGs should be repeated as clinically indicated.
7. Hematology: WBC with differential count, hemoglobin, and platelet count.
8. Blood Chemistry: Total and indirect bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, CO_2 (bicarbonate), calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Upon IRB/EC approval of Amendment #23, indirect bilirubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1. See Table 2b for further detail. C2D15 chemistry required after approval of Amendment #20.
9. Coagulation: PT and PTT.
10. Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite at baseline, then Day 1 of each cycle thereafter.
11. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable,” whichever is later. Serious adverse events should be monitored and reported as described in the protocol.
12. Tumor Imaging: CT or MRI scan to be performed to assess disease status at screening, every 8 weeks (based on calendar schedule) starting after the first dose, whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the end/withdrawal from study treatment. If renal cysts are observed, monitoring with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging. Upon IRB/IC- approval of Amendment #23, NSCLC patients with tumors harboring MET Exon 14 alterations will have scans collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor.

13. Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the patient's final dose. NSCLC patients with tumors harboring MET Exon 14 alterations only: As of IRB/EC approval of Amendment #22, patients should be followed for survival every 3 months after discontinuing study treatment until one year after the last NSCLC patient with cMet Exon 14 alterations in the cohort (excluding patients enrolled in clinical sites in Japan) has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. As of IRB/EC approval of Amendment #23, patients should be followed for survival every 3 months after discontinuing study treatment until two years after the last NSCLC patient with cMet Exon 14 alterations in the cohort (excluding patients enrolled in clinical sites in Japan) has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. For NSCLC patients with tumors harboring MET Exon 14 alterations enrolled in clinical sites in Japan: survival shall be followed every 3 months after discontinuing study treatment until two years after the last patient has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor.
14. Concomitant Medications: Concomitant medications will be recorded from 14 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from study treatment, concomitant medications and treatments should be recorded for 28 days or until all study drug-related toxicities have resolved, whichever is later.
15. Pregnancy Test (Serum or Urine): Women of reproductive potential must be tested within 14 days of the first treatment. This test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/EC or if required by local regulations. As of IRB/EC approval of Amendment #21, for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy; once at Screening and once at Cycle 1 Day 1 before PF-02341066 administration. Pregnancy tests will also be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2. for further detail.
16. PK samples will be collected on Day 1 of Cycle 1, 2, 3 and 5 at pre-dose (0 hour) and 2-6 hours post-dose. See Section 7.5.1.1. As of IRB/EC approval of Amendment #21, a PK sample should be taken around the time that disease progression is confirmed as long as the patient is on PF-02341066. Refer to the Study A8081001 Laboratory Manual for Special Research-Related Testing for sample processing and shipping instructions.
17. Blood sample for pharmacogenomics: A single whole blood biospecimen (4 mL) will be collected at baseline (within 2 weeks prior to the first dose) for possible analysis of DNA sequence variation in genes that may affect PK of the study drugs, may be associated with specific adverse events or toxicities, or may correlate with efficacy. (For patients enrolled in clinical sites in Japan: blood sample for pharmacogenomics is optional). Refer to the Study A8081001 Laboratory Manual for Special Research-Related Testing for sample processing and shipping instructions.

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20. *Plasma sample for circulating nucleic acid profiling: As of IRC/EC approval of Amendment #21, blood biospecimen (10 mL) for nucleic acid analysis (eg, circulating free DNA [cfDNA] or RNA [cfRNA]) will be collected.* As of the Protocol Administrative Clarification Letter dated 12 October 2015, plasma sample for circulating nucleic acid profiling is only required for NSCLC patients with tumors harboring MET Exon 14 alterations and will be obtained at Screening and End of Treatment. Refer to the Study

A8081001 Laboratory Manual for Special Research-Related Testing for sample processing and shipping instructions. Upon IRB/EC approval of Protocol Amendment #24, collection of plasma samples for circulating nucleic acid profiling is no longer required.

21. Hypogonadism Laboratory Tests (male patients only): All male patients enrolled into the Enriched Other Cohort after IRB/EC approval of Amendment #21 will have hypogonadism laboratory tests. Required blood tests include: total testosterone, free testosterone, SHBG, luteinizing hormone, follicle stimulating hormone, dihydroepiandosterone sulfate, estradiol and prolactin. Blood draws **MUST** be taken before PF-02341066 dosing and between 07:00 and 10:00 a.m. and, for each individual patient, the time of the draw should be as consistent across visits as feasible. If either total testosterone or free testosterone decrease to a value that is .both 25% lower than baseline and below the lower limit of normal, then a repeat laboratory test of both these parameters must be performed at the next clinic visit to confirm hypogonadism. See Section 7.2, for further details. Refer to the Study A8081001 Covance Central Laboratory Services Manual for sample processing and shipping instructions. **Note**: Patients enrolled in clinical sites in Japan will not participate in hypogonadism testing. Upon IRB/EC approval of Protocol Amendment #24, collection of hypogonadism samples is no longer required.

22. PF-02341066 will be administered at a dose of 250 mg BID. An ophthalmology examination will be performed at screening for all patients. The ophthalmology examination should be repeated during the study when visual disturbances have been observed and when there is an increase in grade for visual disturbances. The ophthalmology examination should include ocular characteristics, visual acuity, fundoscopy and slit lamp examination. *As of Protocol Amendment #17, all NSCLC patients enrolled will undergo additional special ophthalmological testing as described in Section 7.3 until written notification by the Sponsor.* As of the Note To File issued 18 March 2016, the following ophthalmologic tests (added in Protocol Amendment #17) are no longer required for NSCLC patients: refractive error, pupil size, intraocular pressure, ocular coherence tomography, dilated fundus photography. All ophthalmology examinations should be performed by an ophthalmologist. *Time points of this special testing are designated by "[ ]" in the Schedule of Activities Table and are performed at Screening, Cycle 1 Day 15, Cycle 3 Day 1, one year, and yearly thereafter. The yearly ophthalmology examination will be done at Cycle 14 Day 1, and every 13 cycles thereafter. These tests should also be done within 2-8 weeks after discontinuation of PF-02341066. There is a ±2 week window for the yearly ophthalmology examination.*

23. Contraceptive Check: As of IRB/EC approval of Amendment #21, male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and, upon IRB/EC approval of Amendment #23, the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.

Appendix 12. Hypogonadism Testing

Hypogonadism testing was included based upon a publication reporting hypogonadism secondary to PF-02341066 use in men with metastatic non-small cell lung cancer.[20] Therefore laboratory Testing has been added to the MET-amplified NSCLC cohort (Appendix 9) and the Enriched Other cohort (Appendix 11); the additional tests include:

- *Total testosterone.*
- *Free testosterone.*
- *SHBG.*
- *Luteinizing hormone.*
- *Follicle stimulating hormone.*
- *Dihydroepiandrosterone sulfate.*
- *Estradiol.*
- *Prolactin.*

*Note that blood draws **MUST** be taken before PF-02341066 dosing and between 7:00 and 10:00 a.m. and, for each patient, every attempt should be made to draw blood at approximately the same time across visits. Blood draws are also to be done pre-PF-02341066 dose.*

Patients with MET-amplified NSCLC: Refer to Schedule of Activities in Appendix 9 for additional details.

Enriched Other cohort: Refer to Schedule of Activities in Appendix 11 for additional details.

Note: Patients enrolled in clinical sites in Japan will not participate in hypogonadism testing.

Refer to the Study A8081001 Covance Central Laboratory Services Manual for sample processing and shipping instructions.

Appendix 13. Reduced Schedule of Activities

Upon IRB/EC approval of Protocol Amendment #24, ongoing patients in the ALK marker positive NSCLC cohort, the ROS1 marker positive NSCLC cohort, the MET-amplified NSCLC cohort, and the Enriched Other cohort (including NSCLC patients with MET Exon 14 alterations) will follow a Reduced Schedule of Activities. Refer to TRIAL PROCEDURES and ASSESSMENTSsections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the reduced schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

Protocol Activity	**Study Treatment[1]**		**End of Treatment ****	
	For Cycles 1-10, Visits on Day 1 (±4 days) of each Cycle	**For Cycles >10, Visits on Day 1 (±4 days)of Alternate Cycles (except as noted below)**	**End of Txt/Withdrawal**	**Post Txt Follow-up**
Physical examination[2]	X	X	X	
Weight, blood pressure and pulse rate	X	X	X	
Ophthalmology Examination[3]	X			
Laboratory Studies				
Hematology and Blood Chemistry, excluding Liver Function Tests (LFTs)[4]	As per local clinical practice.			
LFTs: ALT/AST/alkaline phosphatase/total bilirubin[5]	X	Day 1 of each cycle (±4 days)	X	
Contraceptive Check (as applicable)[6]	X	X	X	X
Female patients: Pregnancy test[7]	X	X	X	
Disease Assessments				
Tumor assessments for NSCLC patients with tumors harboring MET Exon 14 alterations only*, [8]	X	X	X	
Tumor assessment for all other cohorts (ALK marker positive cohort, ROS1 marker positive cohort, MET-amplified cohort, and Enriched Other cohort [excluding NSCLC patients with tumors harboring MET Exon 14 alterations])[9]	As per local clinical practice.			

Protocol Activity	Study Treatment[1]		End of Treatment **	
	For Cycles 1-10, Visits on Day 1 (±4 days) of each Cycle	For Cycles >10, Visits on Day 1 (±4 days)of Alternate Cycles (except as noted below)	End of Txt/Withdrawal	Post Txt Follow-up
Other Clinical Assessments				
Safety assessment (adverse events)[10]	X	X	X	X
Concomitant Medications/Treatments[11]	X	X	X	X
Survival (for NSCLC patients with tumors harboring MET Exon 14 alterations only)[12]				X
PF-02341066 treatment	Twice a day continuously			

* Allowable window for tumor assessment imaging is ±7 days.
** End of Treatment (EOT) visit should be conducted 28 days postdose ±2 days. If a patient withdraws from study treatment and new anticancer is subsequently administered, the EOT visit should occur prior to the initiation of new anticancer therapy.

1. All assessments should be performed prior to dosing with study medication unless otherwise indicated. All cycles are 4 weeks in duration. Sufficient study medication for 2 cycles of treatment will be dispensed at each clinic visit. During the non-clinical visit cycles, the Investigator is responsible for ensuring the patient contacts the clinical site in order to provide an update of adverse events and concomitant medications.
2. Physical Examination: Includes an examination of major body systems.
3. Ophthalmology examination: Includes ocular characteristics, visual acuity, fundoscopy and slit lamp examination and should be performed by an ophthalmologist. The ophthalmology examinations should be performed at Sceening and repeated during the study when a visual change occurred or when there is an increase in grade for a visual change.
4. Hematology and Blood Chemistry, excluding Liver Function Tests (LFTs): Will be repeated at the frequency as per local clinical practice, and will no longer be recorded on the CRF. However, lab information should be retained in the pateint's file for documentation purposes. NOTE: For Blood Chemstiry, LDH and uric acid are not required to be collected as part of the Reduced Schedule of Activities.
5. LFTs: If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST ≤ Grade 1.
6. Contraceptive Check: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation and the patient's affirmation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See Section 4.5.1 for further detail.
7. Pregnancy Test (Serum or Urine): For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely repeated at every treatment cycle, at the end of treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the

case of a positive confirmed pregnancy, the patient will be withdrawn from study medication. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. See Section 7.2 for further detail.

8. Once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle. Once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). If tumor imaging was done within 6 weeks of the last dose of PF-02341066, it is not required to be repeated at the End of Treatment visit. If renal cysts are observed, monitoring with appropriate imaging should be performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging. NSCLC patients with tumors harboring MET Exon 14 alterations will have scans collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor.

9. Tumor Assessments: For ongoing patients in the ALK marker positive cohort, the ROS1 marker positive cohort, the MET amplified cohort, and the Enriched Other cohort (excluding NSCLC patients with tumors harboring MET Exon 14 alterations) tumor assessments will be repeated at the frequency as per local clinical practice, and will no longer be recorded on the CRF. However, tumor assessment information should be retained in the patient's file for documentation purposes.

10. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.

11. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded up to 28 days post the last dose of study treatment.

12. Survival: Upon IRB/EC approval of Protocol Amendment #24: Post-study survival status is no longer required for patients (excluding NSCLC patients with tumors harboring MET Exon 14 alterations). NSCLC patients with tumors harboring MET Exon 14 alterations should be followed for survival every 3 months after discontinuing study treatment until two years after the last patient has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor.