Supplementary Methods

Inclusion Criteria

Patient eligibility was reviewed and documented by an appropriate member of the investigator's study team before patients were included in the study.

Patients met all of the following inclusion criteria to be eligible for enrollment into the *MET* exon 14 cohort:

1. Tumor eligibility: Histologically confirmed advanced malignancies that are 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* and mutations in the intronic regions flanking exon 14 resulting in exon 14 deletion. After IRB/EC approval of Amendment #16, enrollment of patients in this group must be approved by the Sponsor.

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.

Exclusion Criteria

Patients presenting with any of the following were not 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.
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.

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. 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.

15. 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].

Supplementary Table 1. Summary of Local Molecular Testing.

Patients with *MET* exon 14-altered NSCLC	**N = 69**
Sites and/or tests for local laboratory testing — no. (%)	69 (100)
Aichi Cancer Center Hospital	1 (1.4)
Brigham and Women's Hospital Clinical OncoPanel*	5 (7.2)
Foundation Medicine†	13 (18.8)
LC-SCRUM	2 (2.9)
Massachusetts General Hospital – Snapshot*	4 (5.8)
Massachusetts General Hospital – Solid Fusion*,§	4 (5.8)
MSKCC Archer FusionPlex*,§	3 (4.3)
MSKCC IMPACT*	31 (44.9)
Pervenio Lung NGS‡	1 (1.4)
Resolution Bio cfDNA‡	1 (1.4)
UNC McLendon Lab	1 (1.4)
UPMC	1 (1.4)
Weill Cornell	1 (1.4)
Not stated	1 (1.4)

Aichi Cancer Center Hospital and LC-SCRUM performed RT-PCR testing; all others performed NGS testing.
*Indicates site and test used.
†This site performed testing using FoundationOne (tumor tissue; n=12) and FoundationACT (cfDNA; n=1).
‡Indicates test used.
§Indicates RNA-based NGS based testing; all other NGS testing is DNA-based except for UPMC, which is unknown and Pervenio Lung NGS that used RNA/qPCR for detection of *EML4-ALK*, *ROS1* and *RET* translocations.
cfDNA, circulating free deoxyribonucleic acid; LC-SCRUM, Cancer Genome Screening Project for Individualized Medicine in Japan; MSKCC, Memorial Sloan Kettering Cancer Center; NGS, Next-Generation Sequencing; NSCLC, non-small cell lung cancer; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; UPMCS, University of Pittsburgh Medical Center; UNC, University of North Carolina.

Supplementary Table 2. Reasons Best Overall Response was Indeterminate.

Among the 65 patients in the response-evaluable population, 11 patients (17%) were indeterminate for antitumor response to crizotinib as per the study design.

Case	Reason for Indeterminate Response
1	Off-study treatment prior to first on-study tumor assessment secondary to treatment-related grade 3 pneumonitis
2	Off study treatment prior to first on-study tumor assessment secondary to treatment-related grade 2 pneumonitis
3	Off-study treatment prior to first on-study tumor assessment secondary to death due to disease progression
4	Off-study treatment prior to first on-study tumor assessment secondary to withdrawal of consent
5	Off study due to clinical progression before first formal on-study tumor assessment (C2D1); one scan was taken on C1D22 showing stable disease
6	Target lesions could not be measured at each follow-up timepoint due to obscuring pneumonia
7	Off-study treatment prior to first on-study tumor assessment secondary to non-treatment-related grade 3 hypoxia
8	Off study due to treatment-related grade 3 elevated creatinine before first formal on-study tumor assessment (C2D1); one scan was taken on C1D29 showing stable disease
9	Off study secondary to withdrawal of consent before first formal on-study tumor assessment (C2D1); two scans were taken on C1D22 and C1D36, both showed a partial response
10	Target lesions could not be measured at each follow-up timepoint
11	Patient experienced a Grade 4 pneumonitis 13 days after the initiation of study treatment and died 9 days later (prior to first on-study tumor assessment)

Supplementary Table 3. Summary of Objective Response by Baseline Patient Characteristics in the Response-Evaluable Population.*

	MET exon 14-altered NSCLC (N = 65)	
Subgroup	**n/N with objective response†**	**ORR, % (95% CI)‡**
Age Group		
<65 yr	4/16	25.0 (7.3–52.4)
≥65 yr	17/49	34.7 (21.7–49.6)
Number of prior advanced/metastatic therapies		
0	6/24	25.0 (9.8–46.7)
≥1	15/41	36.6 (22.1–53.1)
Smoking history		
Never smoked	5/24	20.8 (7.1–42.2)
Smoker	1/1	100.0 (2.5–100)
Ex-smoker	15/40	37.5 (22.7–54.2)
Histology		
SCC	1/3	33.3 (0.8–90.6)
ACC	17/54	31.5 (19.5–45.6)
Sarcomatoid carcinoma	2/6	33.3 (4.3–77.7)
Other	1/2	50.0 (1.3–98.7)

*The response-evaluable population (N=65) was defined as all patients in the safety population who had an adequate baseline and ≥1 post-baseline disease assessment (≥6 weeks from the first dose), or who withdrew from the study, progressed, or died.
†Objective response was considered to be a confirmed complete or partial response, per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.
‡CIs for the ORR were estimated using an exact binomial method based on the F-distribution.
ACC, adenocarcinoma; CI, confidence interval; ORR, objective response rate; SCC, squamous cell carcinoma.

Supplementary Table 4. Characterization of *MET* exon 14 Alterations in the Response-Evaluable Patient Population.

A) Local Testing*						
Region	Splice Acceptor — no. (%)		Splice Donor — no. (%)		Unknown‡ — no. (%)	Total — no. (%)
Type	Base Substitution	Indel†	Base Substitution	Indel†		
Responder	0	5 (7.7)	12 (18.5)	0	4 (6.2)	21 (32.3)
Non-Responder	0	11 (16.9)	21 (32.3)	4 (6.2)	7 (10.8)	43 (66.2)
Total	0	16 (24.6)	33 (50.8)	4 (6.2)	11 (16.9)	64 (98.5)
P-value§	**0.65**					

B) Central Testing*					
Region	Splice Acceptor — no. (%)		Splice Donor — no. (%)		Total — no. (%)
Type	Base Substitution	Indel†	Base Substitution	Indel†	
Responder	0	4 (11.8)	6 (17.7)	0	10 (29.4)
Non-Responder	0	6 (17.7)	14 (41.2)	3 (8.8)	23 (67.7)
Total	0	10 (29.4)	20 (58.8)	3 (8.8)	33 (97.1)
P-value¶	**0.53**				

*One patient had a whole exon deletion of *MET* exon 14 and was not included in the assessment due to being the only one within the response-evaluable patient population.
†The mutation type "Indel" reported here includes indel and large indel.
‡One patient was enrolled based on the detection of a *GPRC5C-MET* fusion.[1]
§From a 2-sided Fisher's exact test for the association of tumor response with MET exon 14 alteration (splice site region/mutation type, including patients with unknown MET exon 14 alteration status).
¶From a 2-sided Fisher's exact test for the association of tumor response with MET exon 14 alteration (splice site region/mutation type).

Reference

1. Peschard, P. *et al.* Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. *Mol Cell* **8**, 995-1004 (2001).

Supplementary Table 5. *MET* exon 14-Altered NSCLCs with Concurrent *MET* Copy Number Alterations Detected.

Patient	Test used to detect METex14 alteration (local)	METex14 alteration (local)	Test used to detect MET copy number alteration (local)	MET copy number alteration* (local)	MET amplification (central)	Best objective response	Duration of response (months)	Progression-free survival (months)	Duration of therapy (months)
1	MSKCC IMPACT	MET C.2888_2905+47DE LTTCTTTCTCTCTGTT TTAAGATCTGGGCAGTGAATTAG	NGS (IMPACT)	2.3	Detected	SD	-	7.8	6.7
2	Foundation One	MET D1010H	FISH	3.6	Not Analyzable	PR	10.5	12.3	13.0
3	MSKCC IMPACT	MET c.3018_3028+3TTTTC CAGAAGGTA>G	NGS (IMPACT)	NA	Detected	SD	-	1.7	2.9

For local test results, detection of *MET* amplification (any level) was assessed by validated cut points defined by the test used. For central test results (FoundationOne CDx), detection of *MET* amplification was assessed as a copy number ≥6.[1,2] Note that, beyond this table, no other cases of *MET* amplification were detected centrally in all other patients tested of (40/69 patients with tissue available for analysis).
*Represented by *MET*/*CEP7* ratio or *MET* mean copy number.
MSKCC, Memorial Sloan Kettering Cancer Center; NGS, next-generation sequencing; PR, partial response; SD, stable disease.

References

1. Frampton, G. M. *et al.* Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov* **5**, 850-859, doi:10.1158/2159-8290.CD-15-0285 (2015).
2. Schrock, A. B. *et al.* Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations. *J Thorac Oncol* **11**, 1493-1502, doi:10.1016/j.jtho.2016.06.004 (2016).

Supplementary Table 6. Crizotinib-Related Adverse Events Occurring in ≥10% of Patients.

Patients — no. (%) (N=69)	Any Grade	Grade 1	Grade 2	Grade 3§	Grade 4§
Any AE*†	65 (94)	14 (20)	30 (44)	17 (25)	3 (4)
Edema‡	35 (51)	23 (33)	11 (16)	1 (1)	0
Vision disorder‡	31 (45)	30 (44)	1 (1)	0	0
Nausea	28 (41)	20 (29)	8 (12)	0	0
Diarrhea	27 (39)	20 (29)	7 (10)	0	0
Vomiting	20 (29)	18 (26)	2 (3)	0	0
Fatigue	16 (23)	7 (10)	9 (13)	0	0
Constipation	14 (20)	11 (16)	2 (3)	1 (1)	0
Decreased appetite	13 (19)	8 (12)	5 (7)	0	0
Elevated transaminases‡	12 (17)	6 (9)	3 (4)	3 (4)	0
Bradycardia‡	11 (16)	9 (13)	1 (1)	1 (1)	0
Dysgeusia	10 (14)	10 (15)	0	0	0
Neuropathy‡	7 (10)	6 (9)	1 (1)	0	0

*There was 1 treatment-related grade 5 AE (interstitial lung disease, Extended Data Table 2).
†Refers to reports of any frequency of crizotinib-related AE and is not limited to AEs that were reported in ≥10% of patients.
‡Denotes clustered term.
§Grade ≥3 crizotinib-related AEs occurred in 11 (55%) patients receiving prior immunotherapy and in 10 (20%) patients not receiving prior immunotherapy.
AE, adverse event.

CLINICAL PROTOCOL

PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF PF-02341066, A C-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:	73,544
Protocol:	A8081001
Phase:	1

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 23	21 February 2017	Added a separate group of approximately 5 NSCLC patients whose tumors harbor c-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 ROS marker positive NSCLC patients, and NSCLC patients with tumors haboring c-Met gene amplification or c-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 (ROS 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 ROS 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 c-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.

Document	Version Date	Summary of Changes and Rationale
		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 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 c-Met amplification NSCLC (low category closed to enrollment; medium and high categories open to enrollment): 68 planned slots for enrollment ROS 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

Document	Version Date	Summary of Changes and Rationale
Amendment 22	27 April 2016	Added rationale for analysis of NSCLC patients with tumors harboring c-Met Exon 14 alterations in Protocol Summary and Section 1.2; added sample size justification for analysis of NSCLC patients with tumors harboring c-Met Exon 14 alterations in Section 9.1.3.4. Added analysis of NSCLC patients with tumors harboring c-Met Exon 14 alterations in Section 9.2.1.4. Changed "c-Met Exon 14 deletion" terminology to "c-Met Exon 14 alterations" throughout protocol to encompass various types of genetic alterations related to c-Met Exon 14. Closed enrollment of patients into the c-Met Low Amplification category and transferred 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 c-Met amplification categories may trigger transfer of additional enrollment slots from these c-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 c-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.

Document	Version Date	Summary of Changes and Rationale
		Limited circulating free nucleic acids testing only to NSCLC patients with tumors harboring c-Met Exon 14 alterations to be performed only at Screening and End of Treatment in Section 7.5.6, Appendix 9, and Appendix 11. Added analysis of circulating free nucleic acids testing in Section 9.2.5. Clarified survival endpoints in Sections 2.1 and 9.2.1. Extended survival follow-up for ROS marker positive NSCLC patients, and NSCLC patients with tumors haboring c-Met gene amplification or c-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): Added text indicating that all tumor scans from all NSCLC patients with tumors harboring c-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 (c-Met amplified NSCLC cohort): Added text indicating that all tumor scans from all NSCLC patients with tumors harboring c-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.

Document	Version Date	Summary of Changes and Rationale
		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) following Sponsor decision to no longer perform the single dose PK exploratory analysis 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 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.

Document	Version Date	Summary of Changes and Rationale
		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 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. Added collection of plasma samples for circulating nucleic acid analysis for patients enrolled into the c-Met-amplified NSCLC Cohort and Enriched Other Cohort only to explore the predictive and/or pharmacodynamic characteristics of this peripheral blood marker.

Document	Version Date	Summary of Changes and Rationale
		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 c-Met-amplified NSCLC, ROS 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 c-Met-amplified NSCLC Cohort to obtain more robust survival data. A similar change to the survival follow-up period was made to the ROS 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 enroll in the Enriched Other cohort with molecular changes in other than ALK, Met and ROS 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.

Document	Version Date	Summary of Changes and Rationale
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, ROS marker positive NSCLC and c-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 c-Met or ROS testing to occur prior to enrollment was removed. A 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.

Document	Version Date	Summary of Changes and Rationale
		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 the ROS marker positive NSCLC cohort. Increased sample size for ROS 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 ROS marker positive NSCLC cohort, the Enriched Other cohort and the rifampin and

Document	Version Date	Summary of Changes and Rationale
		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, ROS-positive NSCLC, and ALK-negative NSCLC #2 cohorts. Cross referenced 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.

Document	Version Date	Summary of Changes and Rationale
		For c-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 ROS-positive (positive for chromosomal translocations in the ROS gene) NSCLC patients to be enrolled. Clarified the c-Met-amplified NSCLC cohort; enrolling 3 patient categories based on degree of c-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 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 c-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.

Document	Version Date	Summary of Changes and Rationale
		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 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.

Document	Version Date	Summary of Changes and Rationale
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 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 ROS 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.

Document	Version Date	Summary of Changes and Rationale
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 c-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 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.

Document	Version Date	Summary of Changes and Rationale
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 c-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.
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).

c-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 c-Met/HGFR is one of the receptor tyrosine kinases (RTKs) most frequently mutated or otherwise abnormally activated in late-stage human cancer. When activated, c-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 c-Met/HGFR in the regulation of tumor angiogenesis indicates potential for dual anti-tumor and anti-angiogenic mechanisms. Activating mutations in c-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, c-Met/HGFR gene amplification/ overexpression resulting in increased kinase activity has been frequently observed in gastric and colorectal cancer patients. Furthermore, c-Met/HGFR is also activated in human tumors by other mechanisms (eg, autocrine loops, paracrine activation from tumor-associated stroma). Collectively, the dysregulation of c-Met/HGFR in tumors by multiple mechanisms along with the potential role of c-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 c-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 c-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 c-Met Exon 14 alterations. Recently, Paik et al (2015)[21] reported on 4 crizotinib-treated patients with NSCLC harboring alterations leading to c-Met exon 14 skipping. Three (3) out of 4 patients were shown to have a partial response.

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

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

The potency of PF-02341066 against c-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 c-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 c-Met/HGFR and/or were identified in biochemical assays. In these studies, PF-02341066 selectivity for c-Met/HGFR (IC_{50} = 11 nM) was greater than 1000-fold relative to VEGFR2, PDGFRβ, 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 c-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 c-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. c-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 c-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 c-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 c-Met/HGFR phosphorylation at 1 to 8 hours with full recovery by 16 hours.

In summary, c-Met has been shown to be a valid target, and PF-02341066 is a potent and selective inhibitor of c-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.

7. *Perform exploratory evaluation of c-Met/HGFR genotype and expression, pharmacodynamic endpoints, and biomarkers for PF-02341066.*

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

9. Explore the predictive and/or pharmacodynamic characteristics of tumor and peripheral blood biomarkers (including, but not limited to, circulating free nucleic acids) that may be relevant to the mechanism of action of, or resistance to, PF-02341066.

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 and exploratory 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.

6. *To determine the pharmacodynamic effects of PF-02341066 on levels of soluble plasma biomarkers (HGF/Scatter factor, soluble c-Met/HGFR, VEGF, interleukin-8) and on the phosphorylation status of target receptor (c-Met/HGFR) in tumor samples from surgery or biopsy when available.*

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.

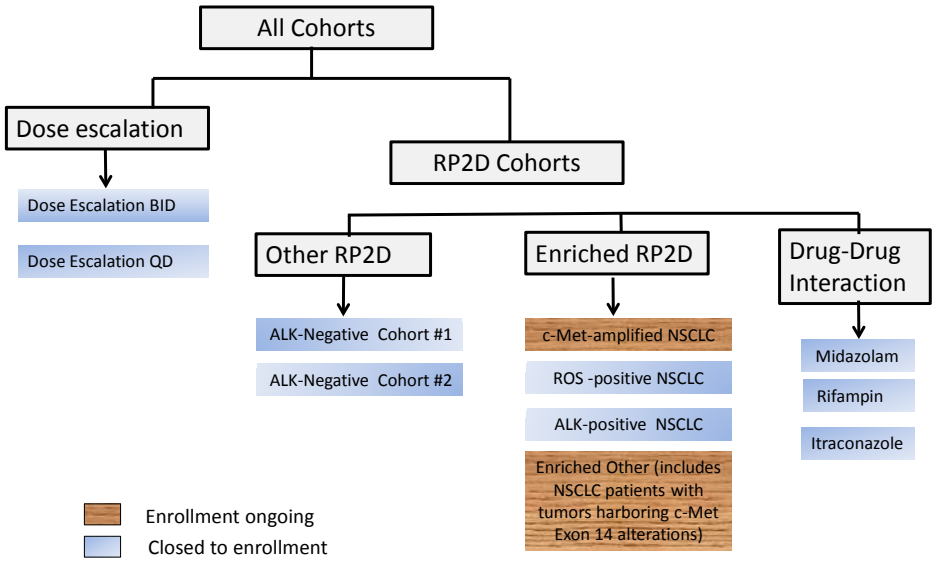
8. Predictive or pharmacodynamic biomarkers in tumor and peripheral blood that may be relevant to the mechanism of action of, or the development of resistance to PF-02341066 (eg, plasma circulating nucleic acid).

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 #23.

Figure 1. Summary of RP2D Cohorts Based on Protocol Amendment #23



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_{0-24} 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 intraconazole 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 470 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 c-Met amplification defined with a MET/CEP7 ratio of ≥5.0 (Group 1), >2.2 to <5.0 (Group 2) and ≥1.8 to ≤2.2 (Group 3, closed to further enrollment as of Note to File 12 October 2015). A total of 68 slots are planned for enrollment. Further details for the c-Met-amplified NSCLC cohort are provided in Appendix 9.

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

    d. Approximately 130 patients with disease with molecular markers (other than ALK marker positive NSCLC and ROS 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 c-Met Exon 14 alterations. Sponsor approval is required for enrollment. Further details for the Enriched Other cohort are provided in Appendix 11.

    e. *<u>ALK Marker Negative NSCLC Cohort #1</u>: 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.

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 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 c-Met or ROS should have occurred prior to enrollment. As of Note to File dated 19 June 2012, the requirement that no molecular testing for c-Met or ROS was to occur prior to enrollment was removed. Thus, c-Met or ROS testing may have been performed prior to patient entry into this cohort. However if the test result for either c-Met or ROS 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.

At least 6 of the enriched population patients will be required to have pre- and post-dose tumor biopsies for the purpose of evaluating pharmacodynamic biomarkers of PF-02341066. See Schedule of Activities, for details. 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 c-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 accessing *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 (c-MET-amplified NSCLC patients), Appendix 10 (ROS marker positive NSCLC patients), and Appendix 11 (Enriched Other cohort).

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
Survival[13]	Until at least 1 year after the patient's final dose (except for c-Met-amplified NSCLC Cohort, ROS marker positive NSCLC Cohort and NSCLC patients with tumors harboring c-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

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**		
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*				
Serum/plasma soluble markers Assessments[24]			*X*	*X*	*X*	*X*	*X (up to Cycle5)*		
Tumor samples (paraffin block)[25]	X								
Fresh tumor biopsy[26]	X				X				X
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 c-Met Exon 14 alterations and will be collected only at screening and End of Treatment)	X		*X*						X
[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*				

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		
Male patients: Hypogonadism Testing for c-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 visit should be conducted 28 days postdose ±2 days.
[ ] 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 patients 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 bilibrubin 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 the study. 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 ROS marker positive NSCLC cohort, c-Met-amplified NSCLC cohort and c-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 c-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 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. 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, c-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 c-Met-amplified NSCLC, ROS 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.*
24. *Serum/Plasma Soluble Markers: blood samples will be collected to assess biomarkers pre-dose and 6 hours post-dose on Days 1 and 15 of Cycle 1; Pre-dose and 6 hours post-dose on Day 1 of Cycle 2; Four to eight hours (Two to eight hours as of May 1, 2007) post-dose on Day 15 of Cycle 2 and Day 1 of Cycles 3 through 5 coinciding with the second PK sample of these days. Biomarkers are: soluble c-Met ectodomain, HGF/Scatter factor, VEGF-A, and IL-8. These samples will no longer be collected once IRB/EC approval of Amendment #17.*
25. Tumor Sample (paraffin block): All patients (except for patients enrolled in the rifampin and itraconaozle DDI sub-studies) must provide a formalin-fixed paraffin-embedded (FFPE) archival tumor specimen for analyses of c-Met/HGFR (including c-Met Exon 14 alteration status), ROS, and/or any candidate biomarker that might confer sensitivity to PF-02341066, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are 5-10 microns thick. If archived FFPE tissue is not available, a de novo (fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies, if possible. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE cell pellet material), is not adequate at screening and should not be submitted. Archived or de novo tumor tissue from bone metastasis, is not adequate at screening and should not be submitted. Refer to the Study Reference Binder for sample processing and shipping instructions. For all patients enrolling into the ALK-marker negative NSCLC Cohort #2, a minimum of 9 slides should be provided, if possible, each containing unstained tissue sections that are 5 microns thick for ROS fusion, c-Met amplification and any candidate biomarker that might confer sensitivity to PF-02341066.
26. Fresh Tumor Biopsy: Optional procedure. Will be performed when possible. Day 1 Cycle 2 biopsy can be done within 14 days after day 1 but not before Day 1 of Cycle 2. A 4-ml blood sample for drug level should be collected prior to biopsy. For patients in the RP2D enriched population cohort, at least 6 patients will be required to have pre- and post-dose tumor biopsies. If a patient discontinues from the study due to disease progression, a tumor biopsy should be obtained, where possible. Refer to the Study Reference Binder for sample processing and shipping instructions.
27. Plasma sample for circulating nucleic acid profiling (c-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 c-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 c-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.

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ITALICIZED TEXT IS OUTDATED INFORMATION AND SHOULD BE DISREGARDED

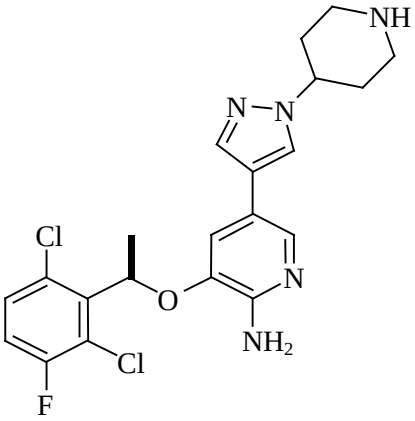
1. INTRODUCTION

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 c-Met/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 c-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 c-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 c-Met/HGFR (including wild-type c-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 c-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 c-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 c-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.

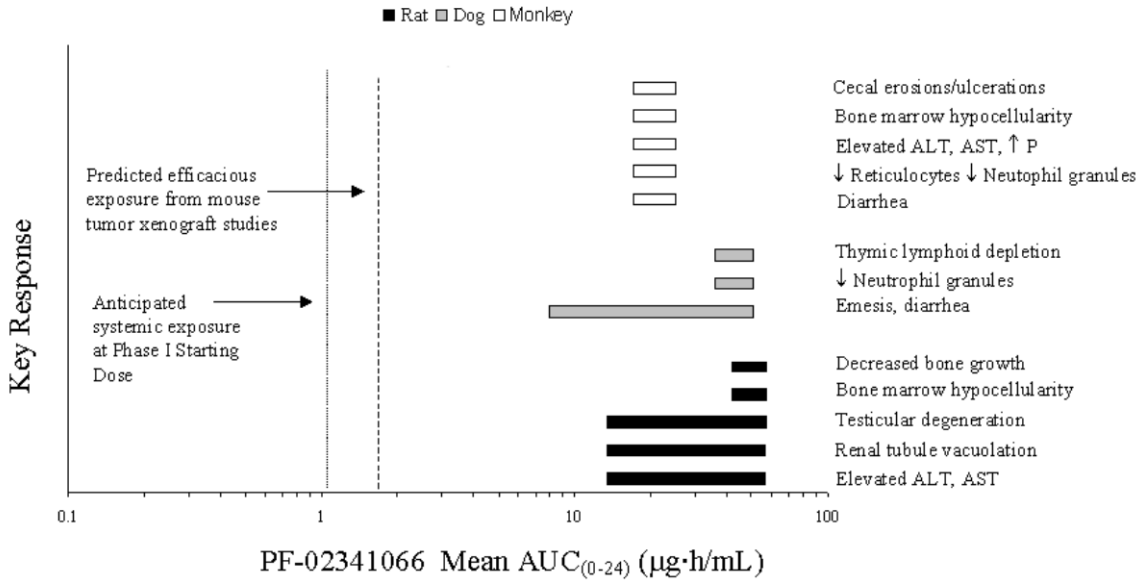
Genotoxic Effects: PF-02341066 was associated with an increased frequency of structural chromosomal aberrations in the in vitro cytogenetics assay with and without metabolic activation under the 3-hour test condition. In addition to the clastogenic response, the kinetochore staining results from the 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

c-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 c-Met/HGFR is one of the receptor tyrosine kinases (RTKs) most frequently mutated or otherwise abnormally activated in late-stage human cancer. When activated, c-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 c-Met/HGFR in the regulation of tumor angiogenesis indicates potential for dual anti-tumor and anti-angiogenic mechanisms. Activating mutations in c-Met/HGFR have been identified in multiple patient populations, including NSCLC, SCLC, renal cancers, head and neck cancers, and hepatocellular cancer. In addition to activation driven by mutation, c-Met/HGFR gene amplification/ overexpression resulting in increased kinase activity has been frequently observed in gastric and colorectal cancer patients. Furthermore, c-Met/HGFR is also activated in human tumors by other mechanisms (eg, autocrine loops, paracrine activation from tumor-associated stroma). Collectively, the dysregulation of c-Met/HGFR in tumors by multiple mechanisms along with the potential role of c-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 c-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 c-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 c-Met Exon 14 alterations. Paik et al (2015) reported on 3 crizotinib-treated

patients with NSCLC harboring alterations leading to c-Met exon 14 skipping. All crizotinib-treated patients were shown to have a partial response.[21]

In conclusion, c-Met has been show to be a valid target, and PF-02341066 is a potent and selective inhibitor of c-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.

7. *Perform exploratory evaluation of c-Met/HGFR genotype and expression, pharmacodynamic endpoints, and biomarkers for PF-02341066.*

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

9. Explore the predictive and/or pharmacodynamic characteristics of tumor and peripheral blood biomarkers (including, but not limited to, circulating free nucleic acids) that may be relevant to the mechanism of action of, or resistance to, PF-012341066.

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.

6. *To determine the pharmacodynamic effects of PF-02341066 on levels of soluble plasma biomarkers (HGF/Scatter factor, soluble c-Met/HGFR, VEGF, interleukin-8) and on the phosphorylation status of target receptor (c-Met/HGFR) in tumor samples from surgery or biopsy when available.*

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.

8. Predictive or pharmacodynamics biomarkers in tumor and peripheral blood that may be relevant to the mechanism of action of, or the development of resistance to PF-02341066 (eg, plasma circulating nucleic acid).

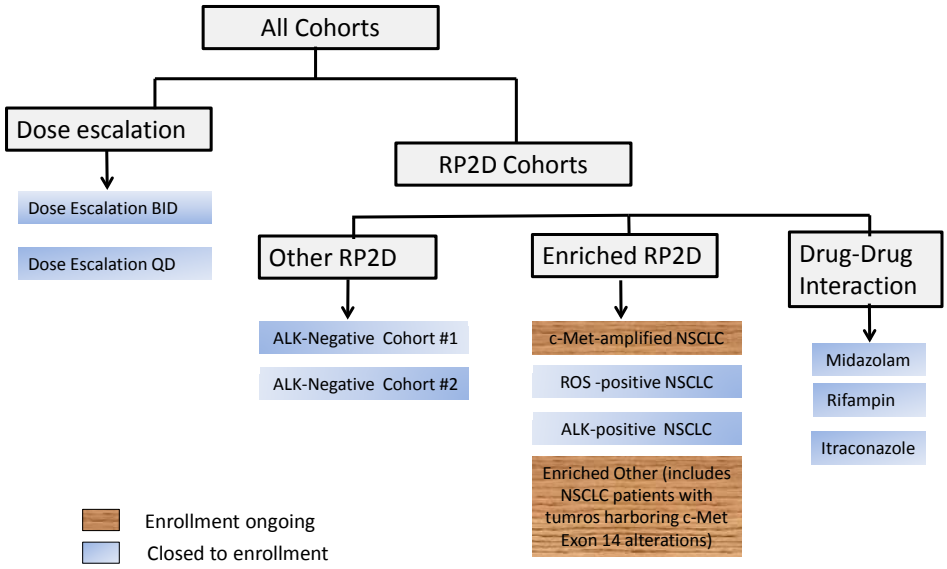
9. Blood testosterone and other blood parameters associated with detecting hypogonadism in males [Appendix 12].

3. TRIAL DESIGN

Open label, multi-center Phase 1 dose escalation, safety, pharmacokinetic and exploratory study.

Figure 3 provides the status of each of the RP2D cohorts of this study, based on Protocol Amendment #23.

Figure 3. Summary of RP2D Cohorts Based on Protocol Amendment #23



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.

c-Met-amplified NSCLC patients: Refer to Appendix 9 for details on patient selection.

ROS 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 c-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 c-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 and mutations in the intronic regions flanking exon 14 resulting in exon 14 deletion. 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 c-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 c-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 *ROS* gene including but not limited to CD74-ROS and SLC34A2-ROS fusion events in NSCLC *and FIG-ROS 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 c-Met dependent tumors, prior therapy specifically directed against c-Met or HGF; for ALK dependent tumors, prior therapy specifically directed against ALK.

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 interefere 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.

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 occur:

- 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;
- 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 and having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for post-menopausal women.

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_{0-24} 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 also evaluate drug-drug interactions. This includes the MDZ, rifampin and intraconazole 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 470 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 c-Met amplification defined as a MET/CEP7 ratio of ≥5.0 (Group 1), >2.2 to <5.0 (Group 2) and ≥1.8 to ≤2.2 (Group 3, closed to further enrollment as of the Protocol Administrative Letter dated 12 October 2015). A total of 68 slots are planned for enrollment. Further detail for the c-Met-amplified NSCLC cohort is provided in Appendix 9.

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

Approximately 130 patients with disease with molecular markers (other than ALK marker positive NSCLC and ROS 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 c-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.

    d. 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.

ALK Marker Negative NSCLC RP2D 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.

ALK Marker Negative NSCLC RP2D Cohort #2:

f. 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 c-Met or ROS may be performed prior to patient enrollment. As of the Note to File dated 19 June 2012, the requirement that no molecular testing for c-Met or ROS to occur prior to patient enrollment was removed. Thus, c-Met or ROS testing may have been performed prior to patient entry into this cohort. However if the test result is either c-Met or ROS 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 ROS fusion, c-Met amplification and any candidate biomarker that might confer sensitivity to PF-02341066. The Sponsor will provide tumor shipment instructions for ROS and c-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.

At least 6 of the enriched population patients will be required to have pre- and post-dose tumor biopsies for the purpose of evaluating pharmacodynamic biomarkers of PF-02341066. See Schedule of Activities, for details.

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 c-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.

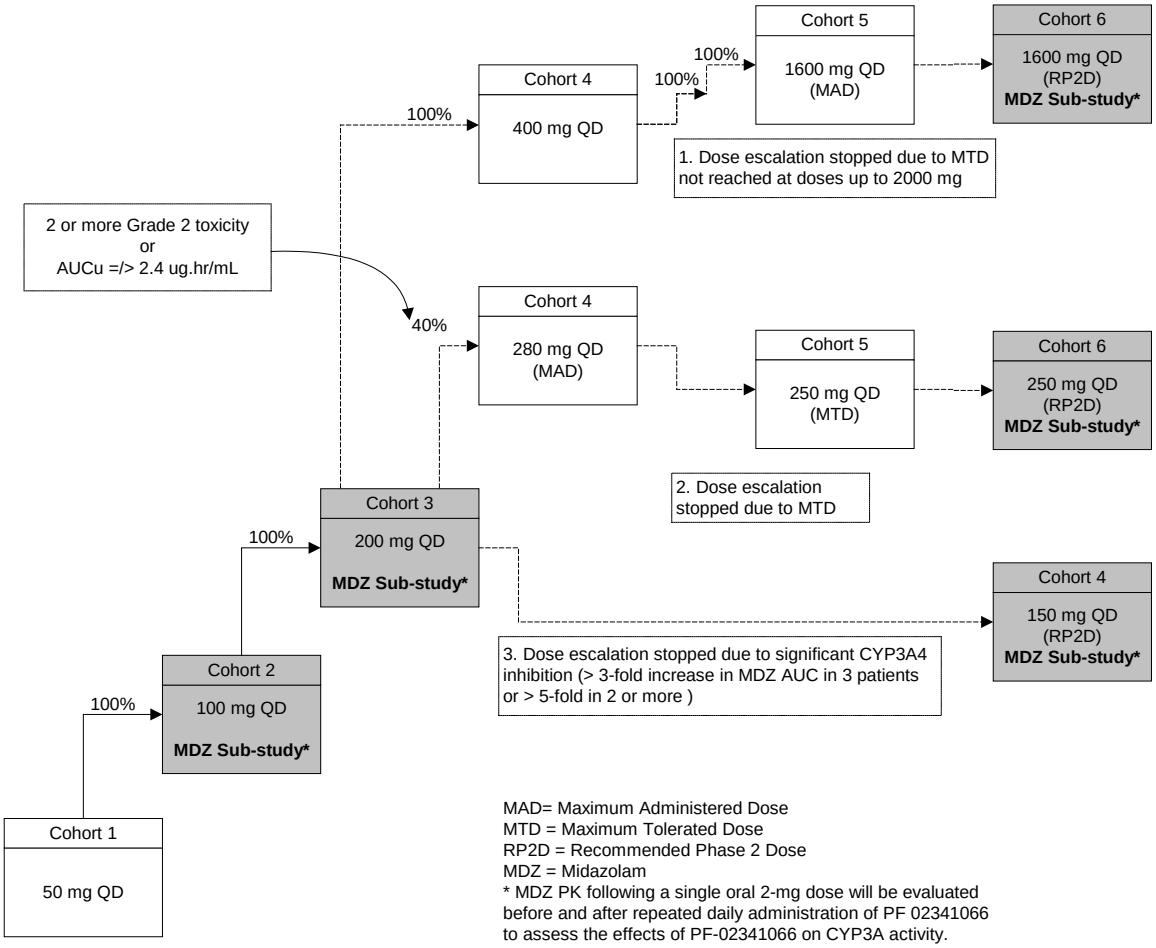
For patients who participate in the fed/fast sub-study, the effect of a high-fat, high-calorie breakfast on PF-02341066 pharmacokinetics will be studied. Each patient will serve as their own control in which PF-02341066 is administered under either "fed" or "fasted" conditions on Day -7 and Day 1 of 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 ROS 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 ROS 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 c-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 c-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.

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 serlogies (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;

- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate;

- 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	See Grade 3.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			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.	
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 abnormalities Continue at the same dose level.	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily. In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade ≥3 recurrence.	Discontinue treatment and do not retreat.
Pneumonitis (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.	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

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate ≥60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60.		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 the same dose level**/*** or reduce by 1 dose level after discussion with Sponsor.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**/***.

* Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.
** Patients who develop Grade 3 or 4 lymphopenia without 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 delayed 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 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Dose Interruption or Delay

The study investigator may implement dose suspension and/or reduction in order to ensure patient safety; however interruption or delay in treatment should last for no more than 6 weeks. If a longer interruption or delay 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.

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).

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.*

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. 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, c-Met-amplified NSCLC Cohort, ROS marker positive NSCLC Cohort, and Enriched Other Cohort please refer to the Schedule of Activities in the corresponding appendices.

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 the trial 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.

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, *c-Met/HGFR genotype and expression*, pharmacodynamic endpoints, and biomarkers (until IRB/EC approval of Amendment #17) 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 the c-Met-amplified NSCLC patients, refer to the Schedule of Activities table in Appendix 9.

For details on the ROS 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.

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

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.

Coagulation: PT and PTT

Urinalysis: For pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrites.

In cases of suspected drug-induced liver injury (DILI) as described in Section 8.6.2 the following laboratory tests should be obtained: albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, 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 c-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.

Refer to Appendix 9 (c-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.

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 ROS 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 ROS 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 c-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- c-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. 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 c-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 c-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 c-Met-amplified NSCLC, ROS 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 c-Met-amplified NSCLC Cohort are provided in Appendix 9.

Further details for the ROS 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.

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.

Samples will be analyzed using a validated analytical method in compliance with Sponsor standard operating procedures. These data will be used for internal exploratory purposes and will not be included in CSR.

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.

7.5.6. Biomarker Analysis

Blood samples for assaying plasma levels of HGF/Scatter factor, soluble c-Met/HGFR ectodomain, VEGFA ELISA, interleukin-8 (IL-8) will be collected at specific time points shown in the table of activities. These samples will no longer be collected once IRB/EC approval of Amendment #17.

A blood sample (4 ml) will be collected at the time points specified in the appropriately labels collection tube. Blood samples will be placed in an ice-bath immediately after collection and processed within 1 hour. Detailed sample collection procedures will be specified in the study manual.

- Blood samples for plasma analysis of circulating nucleic acid (eg, circulating free DNA [cfDNA] or RNA [cfRNA]) will be collected at specific time points shown in the Schedule of Activities. (Refer to Appendix 9 and Appendix 11). As of the Protocol Administrative Clarification Letter dated 12 October 2015, plasma samples for circulating nucleic acid profiling is applicable only to NSCLC patients with tumors harboring c-Met Exon 14 alterations and should be performed only at Screening and End of Treatment.

7.5.7. Tumor Samples/Biopsies

Formalin-fixed, paraffin-embedded (FFPE) blocks collected at the time of the most recent recurrence or at the time of initial diagnosis are preferred, although collection at any time is acceptable. Fresh tumor specimens will also be collected pre-dose (during the screening period) and at Day 1 of Cycle 2 (post-dose) when possible. These samples will be used for exploratory, translational studies that will include somatic mutational status of c-Met/HGFR, immunohistochemistry (IHC) expression analysis for c-Met/HGFR, and c-Met/HGFR FISH (amplicon/copy number) analysis. *Additionally, c-Met/HGFR phospho-Met PD (target inhibition) in fresh pre (screening period), post-dose (Day 1 Cycle 2) and at the time of disease progression (if applicable) biopsies will be analyzed. For patients with anaplastic large cell lymphoma (ALCL), analysis of phospho-ALK (NPM-ALK target inhibition) in fresh pre- and post-dose biopsies of cutaneous lesions or lymph node will be performed instead of phospho-Met.* All patients (except for patients enrolled in the rifampin-- and itraconaozle drug-drug interaction [DDI] sub---studies) must provide a FFPE archival tumor specimen for analyses of c-Met/HGFR (including c-Met Exon 14 alteration status), ROS, and/or any candidate biomarker that might confer sensitivity to PF-02341066, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are 5-10 microns thick. These analyses may include assessment of gene mutational status, gene copy number, gene rearrangement, RNA expression and/or protein expression. If archived FFPE tissue is not available, a de novo (fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies, if possible. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE cell pellet material), is not adequate at screening and should not be submitted. Archived or de novo tumor tissue from bone metastasis, is not adequate at screening and should not be submitted. For fresh biopsies, *ex vivo* handling of the tissue may be required as part of the target inhibition assay. Please refer to Laboratory Manual for further instructions.

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 c-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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as 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

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 c-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 470 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 c-Met-amplified NSCLC patients, Appendix 10 for ROS 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, ROS marker positive NSCLC and c-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. In addition, at least 6 patients will be required to have pre-and post-dose tumor biopsies for the purpose of evaluating pharmacodynamic markers of PF-02341066. 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 ROS or c-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 c-Met or ROS to occur prior to enrollment was removed. However, if c-Met or ROS testing was performed prior to patient enrollment and the test result for either c-Met or ROS 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. c-Met-Amplified NSCLC Cohort

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

- High Level c-Met Gene Amplified Category (MET/CEP7 ratio ≥5.0);
- Medium Level c-Met Gene Amplified Category (MET/CEP7 ratio >2.2 to <5);
- *Low Level c-Met Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2).* Of note, as of Protocol Administrative Clarification Letter dated 12 October 2015, this cohort 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.

Further details for the c-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 c-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 c-Met amplification categories, may trigger transfer of additional enrollment slots from these c-Met gene amplification categories to the Enriched Other cohort.

9.1.3.3. ROS 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 ROS 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 May 2013, 22 objective responses were observed. Based on the number of objective responses (CR, PR) observed, the null hypothesis has been rejected. With Amendment #20, the sample size will be increased to a total of 50 patients in order to provide a more robust estimation of efficacy in this patient population. As of the Note to File dated 12 November 2012, the sample size was increased to a total of 50 patients.

Further details for the ROS 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 130 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 c-Met Exon 14 alterations will be enrolled. In addition, a separate group of approximately 5 NSCLC patients with tumors harboring c-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 c-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. The proportion of responders will be estimated with better precision if the number of evaluable patients exceeds 33 patients.

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 c-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 c-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, ROS marker positive or c-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 c-Met-Amplified NSCLC Categories

For each of the 3 c-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 c-Met-amplified NSCLC cohort are provided in Appendix 9.

9.2.1.3. Analysis of ROS 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 ROS 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 c-Met Exon 14 alterations will be summarized separately from the Enriched Other Cohort. Data from patients with tumors harboring c-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. For each laboratory measurement, the observed values will

be normalized for age using laboratory-provided age-specific means and standard deviations for males. The normalized values and changes from baseline at each assessment timepoint will be summarized using descriptive statistics. The 95% CI based on the t-distribution will be provided for the change from baseline as long as there are at least 10 observations at a specific timepoint. The data will be examined to determine if a log-transformation of the values is appropriate.

Although no formal hypothesis testing will be performed, the interest is in examining change from baseline with primary interest on free testosterone. A decrease of 2 standardized units is considered clinically meaningful.

Observed values and changes/shifts from baseline will be summarized at each timepoint, with values age-adjusted as appropriate. Summaries will be presented for all patients regardless of their enrollment cohort. Additional summaries for each source of enrollment (ie, the c-Met-amplified NSCLC cohort or the Enriched Other cohort) may also be presented if appropriate. Graphical displays may be presented. Data for each hypogonadism parameter may be displayed graphically to show changes over time. Values collected for a patient after the onset of testosterone replacement therapy will not be included in summary statistics but may be included (and specifically identified) on by-patient plots of data over time; all the values will be listed.

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.

9.2.3. Biomarker Analysis

Data from biomarker assays (soluble protein levels and tumor biopsy) will be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA) as appropriate. The statistical approach may include examining correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

9.2.4. Pharmacogenomics Analysis

Data from pharmacogenomic assays will be summarized as applicable.

9.2.5. Circulating Free Nucleic Acids

Data from circulating free nucleic acids testing will be summarized as applicable.

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 or 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.

www.pfizer.com

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

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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 us 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

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. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

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/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

Appendix 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.

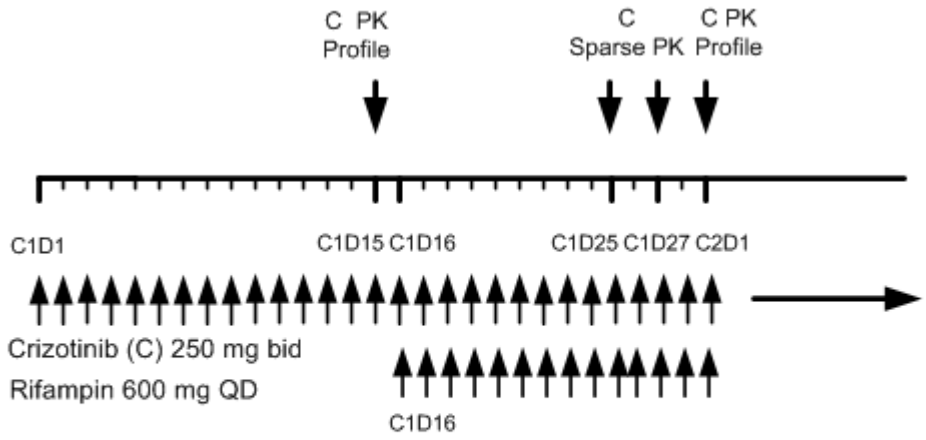
In addition to samples mentioned above, additional blood samples for PK evaluation may be requested from patients experiencing unexpected or serious adverse events; with evidence of disease progression; or with other events where PK sampling is considered useful (upon agreement between investigator and 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



PK profile: pre-dose, 2, 4, 6, 8 and 10 hr post morning dose

PK Trough: pre-dose and 2-6 hr post morning dose

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.

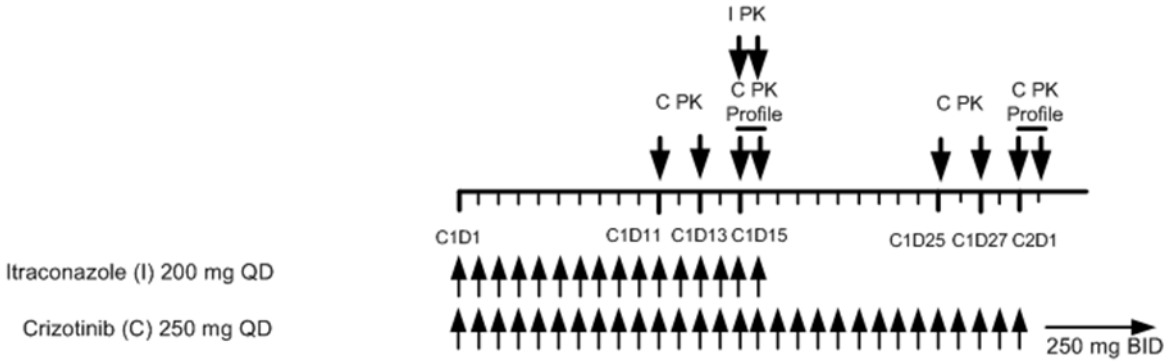
In addition to the time points noted, ECGs should be repeated as clinically indicated.

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.

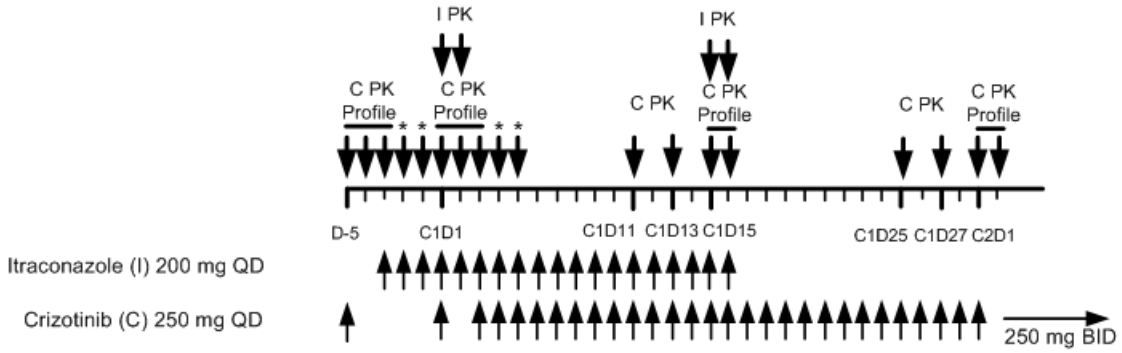
Figure 6. PF 02341066 and Itraconazole Schema: Multiple Dose-Design



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 bilibrubin 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 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*	
Concomitant medications[13]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*		
Contraceptive Check (as applicable)[21]	*X*	*X (Day-5)*					*X*		*X*		*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***		
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 c-Met or ROS should have occurred prior to enrollment. As of the Note to File dated 19 June 2012, the requirement that no molecular testing for c-Met or ROS to occur prior to enrollment was removed. However, if c-Met or ROS testing was performed prior to patient enrollment and if the test result for either c-Met or ROS 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							
Tumor samples (paraffin block) [18]	X							
Fresh tumor biopsy[19]	X			X				X

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 bilibrubin 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.
18. A minimum of 9 slides should be provided, if possible, each containing unstained tissue sections that are 5 microns thick for ROS fusion, c-Met amplification and any candidate biomarker that might confer sensitivity to PF-02341066.
19. Fresh Tumor Biopsy: Optional procedure. Will be performed when possible. Day 1 Cycle 2 biopsy can be done within 14 days after Day 1 but not before Day 1 of Cycle 2. A 4-ml blood sample for drug level should be collected prior to biopsy. If a patient discontinues from the study due to disease progression, a tumor biopsy should be obtained, where possible. Refer to the Study Reference Binder for sample processing and shipping instructions.
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. c-Met-Amplified NSCLC Cohort

To further evaluate the anti-tumor activity of PF-02341066 associated with c-Met amplification, patients with c-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 NSCLC positive for c-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 c-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 interefere 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.

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 c-Met amplification, 10 to 12 patients with c-Met-amplified NSCLC will be enrolled into each of the following 3 categories:

- c-Met Gene Amplified Category (MET/CEP7 ratio ≥5.0).
- c-Met Gene Amplified Category (MET/CEP7 ratio >2.2 to <5).
- *c-Met Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2).* As of the Protocol Administrative Clarification Letter dated 12 October 2015, this category 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 c-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.

Schedule of Activities: c-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.

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							
Tumor samples (paraffin block)[18]	X							
Fresh tumor biopsy[19]	X			X				X
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 cMet amplified NSCLC patients 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 visit should be conducted 28 days postdose ±2 days.

**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 bilibrubin 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 the study. All tumor scans from NSCLC patients with tumors harboring c-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. 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 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 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.

18. Tumor Sample (paraffin block): All patients must provide a formalin-fixed paraffin-embedded (FFPE) archival tumor specimen for analyses of c-Met/HGFR (including c-Met Exon 14 alteration status), ROS, and/or any candidate biomarker that might confer sensitivity to PF-02341066, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are 5-10 microns thick. If archived FFPE tissue is not available, a de novo (fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies, if possible. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE cell pellet material), is not adequate at screening and should not be submitted. Archived or de novo tumor tissue from bone metastasis, is not adequate at screening and should not be submitted. Refer to the Study Reference Binder for sample processing and shipping instructions.

19. Fresh Tumor Biopsy: Optional procedure. Will be performed when possible. Day 1 Cycle 2 biopsy can be done within 14 days after Day 1 but not before Day 1 of Cycle 2. A 4-ml blood sample for drug level should be collected prior to biopsy. If a patient discontinues from the study due to disease progression, a tumor biopsy should be obtained, where possible. Refer to the Study Reference Binder for sample processing and shipping instructions.

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 c-Met amplified NSCLC cohort.

21. Hypogonadism Laboratory Tests (male patients only): All male patients enrolled into the c-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. ROS 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 *ROS* gene (including but not limited to CD74 ROS and SLC34A2 ROS 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 NSCLC positive for chromosomal translocations at *ROS* gene including but not limited to CD74-ROS and SLC34A2-ROS 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 ROS 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 ROS 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 ROS marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review.

Schedule of Activities: ROS 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.

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							
Tumor samples (paraffin block) [18]	X							
Fresh tumor biopsy[19]	X			X				X
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 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 bilibrubin 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 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 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 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/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.
18. Tumor Sample (paraffin block): All patients must provide a formalin-fixed paraffin-embedded (FFPE) archival tumor specimen for analyses of c-Met/HGFR, ROS, and/or any candidate biomarker that might confer sensitivity to PF-02341066, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are 5-10 microns thick. If archived FFPE tissue is not available, a de novo (fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies, if possible. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE cell pellet material), is not adequate at screening and should not be submitted. Archived or de novo tumor tissue from bone metastasis, is not adequate at screening and should not be submitted. Refer to the Study Reference Binder for sample processing and shipping instructions.

19. Fresh Tumor Biopsy: Optional procedure. Will be performed when possible. Day 1 Cycle 2 biopsy can be done within 14 days after Day 1 but not before Day 1 of Cycle 2. A 4-ml blood sample for drug level should be collected prior to biopsy. For patients in the RP2D enriched population cohort, at least 6 patients will be required to have pre- and post-dose tumor biopsies. If a patient discontinues from the study due to disease progression, a tumor biopsy should be obtained, where possible. Refer to the Study Reference Binder for sample processing and shipping instructions.

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 c-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 c-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 and mutations in the intronic region flanking exon 14 resulting in exon 14 deletion. 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 c-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 c-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 ROS gene including but not limited to CD74-ROS and SLC34A2-ROS fusion events in NSCLC and FIG-ROS in glioblastoma. ROS 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:

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

2. Major surgery, radiation therapy, or systemic anti-cancer therapy within 2 weeks of starting study treatment.

3. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.

4. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

5. Current treatment on another clinical trial.

6. 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.

7. 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]

8. 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].

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

10. 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.

11. 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 interefere with the interpretation of study results, and would make the patient inappropriate for entry into this study.

12. 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.

13. 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.

14. 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.

15. Not applicable; included to ensure consistent numbering with exclusion criteria reported in Section 4.2.

16. 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.

17. 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 130 patients will be enrolled including approximately 50 patients with NSCLC harboring c-Met Exon 14 alterations plus a separate group of approximately 5 patients with NSCLC harboring c-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.

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 c-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.

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
Survival[13]	Until at least 1 year after the patient's final dose (except for NSCLC patients with tumors harboring c-Met Exon 14 alterations); For NSCLC patients with tumors harboring c-Met Exon 14 alterations: until two years after the last NSCLC patient with tumors harboring c-Met Exon 14 alterations has discontinued PF-02341066 treatment, unless otherwise notified by the Sponsor. c-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

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] (Optional for patients enrolled in clinical sites in Japan)	X							
Tumor samples (paraffin block) [18]	X							
Fresh tumor biopsy[19]	X			X				X
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 c-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 visit should be conducted 28 days postdose ±2 days.

[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 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 bilibrubin will no longer be collected. If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, obtain repeat ALT orAST 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 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. Upon IRB/IC- approval of Amendment #23, NSCLC patients with tumors harboring c-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 c-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 c-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 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 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 biospecimien (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)
18. Tumor Sample (paraffin block): All patients must provide a formalin-fixed paraffin-embedded (FFPE) archival tumor specimen for analyses of c-Met/HGFR (including c-Met Exon 14 alteration status), ROS, and/or any candidate biomarker that might confer sensitivity to PF-02341066, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are 5-10 microns thick. If archived FFPE tissue is not available, a de novo (fresh) tumor sample should be obtained in accordance with local institutional practice for tumor biopsies, if possible. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE cell pellet material), is not adequate at screening and should not be submitted. Archived or de novo tumor tissue from bone metastasis, is not adequate at screening and should not be submitted. Refer to the Study Reference Binder for sample processing and shipping instructions
19. Fresh Tumor Biopsy: Optional procedure. Will be performed when possible. Day 1 Cycle 2 biopsy can be done within 14 days after Day 1 but not before Day 1 of Cycle 2. A 4-ml blood sample for drug level should be collected prior to biopsy. For patients in the RP2D enriched population cohort, at least 6 patients will be required to have pre- and post-dose tumor biopsies. If a patient discontinues from the study due to disease progression, a tumor biopsy should be obtained, where possible. Refer to the Study Reference Binder for sample processing and shipping instructions.
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 c-Met Exon 14 alterations and will be obtained at Screening and End of Treatment.

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. **Note**: Patients enrolled in clinical sites in Japan will not participate in hypogonadism testing.

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 Amendmetn #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 c-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.

c-Met-amplified NSCLC patients: 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.

PROTOCOL A8081001

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

STATISTICAL ANALYSIS PLAN

(SAP)

Version: 9.0

Author: [redacted]

Date: Final June 30, 2016

[redacted]

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSIONS

The main changes are summarized below. Each revision of the Statistical Analysis Plan (SAP) also includes minor clarifications and corrections.

The main changes from version 8.0 (dated June 13, 2016) described in the current document are as below. All changes pertain to the itraconazole sub-study.

- Clarified details regarding displays of the TEAEs associated with permanent discontinuation and added displays for TEAEs associated with temporary discontinuation of study drug.
- Added displays pertaining to the PK Parameter Evaluable Analysis Population.
- Changed other information for consistency with planned displays.

The main changes in version 8.0 from version 7.0 (dated November 30, 2015) were as follows:

- Made changes consistent with protocol Amendment #22 regarding the itraconazole sub-study.
    - Version 7.0 of SAP was updated to describe the analyses for Multiple Dose Design and Single and Multiple Dose Design, respectively, of the itraconazole sub-study specified in protocol Amendment #20. However protocol Amendment #22 documented the decision that the Single and Multiple Dose Design will no longer be implemented. Because no patients were enrolled in the Single and Multiple Dose Design, all references to the Single and Multiple Dose Design of the itraconazole sub-study are deleted from this version of the SAP with the exception of this section, which describes version changes.
- Added information relating to hypogonadism testing.
- Added information relating to circulating nucleic acid profiling.
- Noted changes to enrollment due to shifting the remaining open enrollment slots from the low c-Met amplification category to the Enriched Other cohort.
- Noted the special attention given to the NSCLC patients who will be enrolled in the Enriched Other population and who have tumors harboring c-Met Exon 14 alterations.
- Updated other changes reflected in protocol Amendments #21 and #22.
- Added subsection numbers in Section 8.2.2 for clarity.
- Included editorial changes to enhance clarity and consistency of text.

The main changes in version 7.0 from version 6 (dated March 31, 2015) were as follows:

- Updated text related to the itraconazole drug-drug interaction sub-study and moved the text to a separate appendix.
- Clarified the evaluable populations for the ophthalmology report.
- Added the cluster terms to be included in the ophthalmology report.
- Augment of the list of AE summary tables for the ophthalmology report.
- Included instructions regarding the summary of pulse rate for patients with an implanted cardiac pacemaker.
- Clarified/updated handling of missing dates.
- Included SAS® code examples for analyses of binary endpoints and of survival data.
- Updated the description of the cohorts for accuracy.
- Included editorial changes to enhance clarity of text.

The main changes in version 6.0 from version 5.0 (dated April 12, 2014) were as follows:

- Updated the document to reflect changes in protocol Amendment #20.
- Streamlined the discussion of plans for the analysis of ROS1-positive NSCLC patients, pointing to the Supplemental SAP for details.
- Updated Section 1 to include a cumulative list of amendments from prior versions.
- Changed naming conventions, updating names from "ROS marker" to "ROS1," from "ALK+ marker" to "ALK-positive," from "ALK-" to "ALK-negative," and from "c-MET" to "c-Met" where appropriate. These changes were *not* implemented in the documentation of changes between previous versions.
- Replaced ketoconazole with itraconazole for the drug-drug interaction sub-study with a CYP3A strong inhibitor based upon FDA guidance.
- Increased the number of patients enrolled for both the rifampin and itraconazole drug-drug interaction sub-studies from a maximum of 15 to a maximum of 25 in order to obtain 8 evaluable patients each.
- Removed reference to the NSCLC Detailed Ophthalmologic Exam 4 Test Sub-set – Evaluable Population because it will not be used in the future.

- Added information in the body of the SAP and added appendices to provide further detail regarding the analyses planned for the ALK-negative NSCLC cohort #2, rifampin drug-drug interaction sub-study, and itraconazole drug-drug interaction sub-study. Cross referenced sections of the body of the main SAP to appendices, as applicable.

- For ALK-negative NSCLC cohort #2 (Section 4.2.1.3), added protocol language to note that the requirement for no c-Met or ROS1 testing to occur prior to enrollment was removed as of a note to file issued 19 June 2012.

- Removed the outdated language regarding ALK-negative Cohort #1 sample size calculations and associated text.

- Reordered sections describing the cohorts for easier flow of the document.

- Added details regarding the imputation of missing dates for adverse events.

- Updated text regarding ophthalmic examinations and made changes for accuracy and consistency.

The main changes in version 5.0 from version 4.0 (dated April 29, 2013) were as follows:

- The description of ophthalmologic analyses for NSCLC patients enrolled under protocol Amendment #17 and beyond has been updated including the description of analysis populations to be used.

The main changes (more minor changes in italics) from in version 4.0 from version 3.0 (dated October 27, 2010) were as follows:

- Description of the definition and analyses for the following cohorts were added and referenced throughout the document where applicable: c-Met amplified NSCLC cohort, ROS-positive NSCLC cohort and ALK-negative NSCLC cohort #2.

- Description of analyses for the following 2 drug-drug interaction sub-studies were added and referenced throughout the document where applicable: rifampin, ketoconazole.

- *Further detail added regarding analysis of data from ophthalmologic tests including additional detailed testing for NSCLC patients.*

- *Rationale added for ALK Negative NSCLC Cohort #2 in Section 4.2.4. In addition, note added regarding recent removal of requirement for no molecular testing for c-MET and ROS prior to enrollment.*

- *Definition of DLT Evaluable Population was clarified in Section 5.3*

- *Further detail regarding the definition of clustered AEs was added in Section 8.2.2.*

- *The definition of 'on-treatment' for the summary of deaths was added in Section 8.2.2.*

- *The definition of the RP2D: Other cohort has been updated to exclude patients who are part of additional cohorts (eg, ROS positive NSCLC cohort, c-Met amplified NSCLC cohort, ALK-negative NSCLC Cohort #2).*

The main changes (more minor changes in italics) from in version 3.0 from version 2.0 (August 20, 2010) were as follows:

- Updates have been made reflecting additional analyses and changes associated with protocol Amendment #15.

- Cohort definitions for categorizing ALK status clarified in Appendix 2.

- Update safety population definition to include patients with at least one dose of PF-02341066 on Cycle 1, Day 1.

- Description of e-DISH scatter plot of maximum ALT vs. maximum total bilirubin added.

- Clarification added that response summaries will be based on investigator assessment for the RP2D: ALK+ NSCLC and RP2D: ALK- NSCLC cohorts but response will be listed for all other cohorts based on the investigator noted response on the 'Disease Status – RECIST Tumor Lesion Measurement' CRF page.

- Analysis of time to response (TTR) updated to be performed by descriptive statistics for subgroup of responders versus Kaplan-Meier method.

- *Clarification added that standard analyses (Section 8.2.1) will be performed using the safety population.*

- *Summary of ocular characteristics at baseline removed. These data will be provided in a listing.*

- *Analyses of AEs updated to included tables by grade group, AEs in ≥5% of patients, and SAEs in ≥2% of patients.*

- *For the ALK+ NSCLC cohort, lab shift tables expanded to include tables for Cycle 2 and Cycle >2. Added shift tables by race group (Asians vs. non-Asians).*

The main change in version 2.0 from version 1.0 (dated June 1, 2006) was as follows:

- Updates have been made reflecting additional analyses and changes associated with protocol Amendments #2 - #14.

2. INTRODUCTION

This document describes the planned statistical analyses for Protocol A8081001 dated December 5, 2005 and subsequent protocol Amendments #2 - #22. This SAP is meant to supplement the study protocol. A Supplemental SAP describes any additional analyses not included in this main SAP that are planned for the ALK-positive NSCLC cohort and the ROS1-positive NSCLC patients identified in Table 5 of Section 8.2. Any deviations from this main analysis plan or the supplemental analysis plan will be described in the Clinical Study Report.

2.1. STUDY DESIGN

Study A8081001 is an open label, multi-center Phase 1 dose escalation, safety, pharmacokinetic and exploratory study of PF-02341066 in patients with advanced cancer. The initial design of the study focused on determining the dose limiting toxicities (DLTs), maximum tolerated dose, and recommended dose for Phase 2 studies (RP2D) for PF-02341066 administered twice a day (BID). Assessments of evidence of antitumor activity were also included.

The study includes a dose escalation component in patients with advanced, solid tumors refractory to standard therapy. The dose escalation component is followed by further evaluation of the RP2D in 2 cohorts. The first RP2D cohort evaluates the potential for CYP3A inhibition due to PF-02341066 using midazolam (MDZ) as a probe. The second RP2D cohort is composed of an enriched population and includes molecularly-defined groups of patients who are predicted to have a clinical response to PF-02341066:

- ALK-positive NSCLC cohort
- c-Met amplified NSCLC cohort
- ROS1-positive NSCLC cohort
- Enriched Other cohort, including NSCLC patients with tumors harboring c-Met Exon 14 alterations (see below)

In addition, 2 ALK-negative NSCLC cohorts are evaluated at the RP2D. A further dose escalation cohort was added to evaluate PF-02341066 administered once a day (QD). Also, 2 drug-drug interaction (DDI) sub-studies were added to assess the effect of the co-administration of rifampin, and separately of itraconazole, on the multiple-dose pharmacokinetics of PF-02341066 BID.

Although patients are enrolled in a single cohort/sub-study, some analyses (eg, analyses of ophthalmic data) are based on groups of patients who are drawn from multiple

cohort/sub-study enrollments. Additionally, patients enrolled in one cohort may also be analyzed with patients in another cohort based on the tumor markers present.

Patients who enroll in the Enriched Other cohort may well be a very diverse group, including patients who are positive for ALK chromosomal translocation (except for patients with NSCLC) or ALK gene amplification; or positive for known c-Met kinase domain activating mutations; or having chromosomal translocations/ fusions that lead to altered transcriptional regulation of c-Met and/or HGF; or positive for chromosomal translocations at the ROS1 gene in other cancer types besides NCSLC; or NSCLC patients with tumors harboring c-Met Exon 14 alterations. In this version of the SAP, references to handling of data pertaining to the Enriched Other cohort should in general be understood to pertain to appropriately-defined subgroups of the Enriched cohort. Such subgroups will be defined when there are a sufficient number of patients who can be meaningfully combined based on their tumors and tumor profiles. At this time only the c-Met Exon 14 alteration subgroup has been identified for specific consideration in the Enriched Other cohort.

Note the aforementioned groups are further defined in Appendix 1.

2.2. STUDY 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 multiple-dose plasma pharmacokinetics of PF-02341066.
7. Perform exploratory evaluation of c-Met/HGFR genotype and expression, pharmacodynamic endpoints, and biomarkers for PF-02341066.
8. Document any evidence of anti-tumor activity of PF-02341066.
9. Explore the predictive and/or pharmacodynamic characteristics of tumor and peripheral blood biomarkers (including, but not limited to, circulating free nucleic acids) that may be relevant to the mechanism of action of, or resistance to, PF-02341066.
10. Evaluate the effect of PF-02341066 on parameters related to hypogonadism in males.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is an open label, single-arm trial for which no formal interim analysis is planned. The final analysis will be performed after the last patient last visit; however, earlier analyses of the data may be performed for publication and regulatory reporting purposes.

4. HYPOTHESIS AND DECISION RULES

A total of at least 565 patients will be enrolled in this study including patients in the dose escalation, RP2D, and DDI cohorts (rifampin and itraconazole). 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 c-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.

4.1. DOSE ESCALATION PHASE

The number of patients 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.

It is anticipated that 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 1, 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 1. Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate (p)	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

* Probability of escalation = (1-p)^3 + 3*p*(1-p)^2

Table 2 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 2. Probability of Failing to Observe Toxicity (at Least One DLT) Given the True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate (p)	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

* Probability = (1-p)^3 ** Probability = (1-p)^6

4.2. RP2D COHORTS

The RP2D cohorts consisted of patients who were to receive the determined recommended phase 2 dose (250 mg BID). These cohorts included:

- RP2D cohorts for NSCLC for molecularly-defined patient groups
    - ALK-positive NSCLC enriched cohort
    - c-Met-amplified NSCLC enriched cohort
    - ROS1-positive NSCLC enriched cohort
    - ALK-negative NSCLC cohort #1
    - ALK-negative NSCLC cohort #2
- Enriched Other cohort
- drug interaction cohorts/sub-studies
    - a MDZ interaction cohort
    - a rifampin DDI sub-study
    - an itraconazole DDI sub-study
- other sub-studies: [^{18}F]-FLT-PET and food effect interaction.

Patients enrolled in one cohort may be analyzed with patients in another cohort, if appropriate. For example, 3 ALK-negative NSCLC patients (in ALK-negative NSCLC cohort #2) were also positive for the ROS1 marker and have also been analyzed with patients in the ROS1-positive NSCLC cohort. See the Supplemental SAP for details. If there are other instances in which it is appropriate to include patients enrolled in one cohort in the analysis with patients in another cohort, summaries and analyses described

below will be modified as appropriate to accommodate different cycle lengths or other differences in data collection. See Appendix 5, for details regarding the itraconazole DDI sub-study.

4.2.1. RP2D NSCLC Cohorts for Molecularly-defined Patient Groups

See the Supplemental SAP for detailed descriptions of the analyses for ALK-positive NSCLC patients and the ROS1-positive NSCLC patients. The Supplemental SAP also includes detail regarding evaluation of response for RP2D cohorts that use RECIST 1.0[3] (ALK-positive NSCLC cohort, c-Met-amplified NSCLC cohort, and ROS1-positive NSCLC patients, and Enriched Other cohort) and separately for those that use RECIST 1.1[4] (ALK-negative NSCLC cohort #1 and ALK-negative NSCLC cohort #2).

4.2.1.1. C-Met-Amplified NSCLC Cohort

In order to evaluate the anti-tumor activity of PF-02341066 in patients with c-Met-amplified NSCLC, patients will be enrolled into one of the following categories:

- High Level c-Met Gene Amplified Category (MET/CEP7 ratio ≥5.0)
- Medium Level c-Met Gene Amplified Category (MET/CEP7 ratio >2.2 to <5.0)
- Low Level c-Met Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2)
  As documented in Amendment # 22, this category was closed to enrollment as of Note to File 12 October 2015; 3 patients had been enrolled at that time.

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 $p \leq 10\%$ versus the alternative $p \geq 30\%$ 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.

4.2.1.2. ALK-Negative NSCLC Cohort #1

The main objective of this ALK-negative NSCLC cohort was to evaluate the objective response in this group of patients and to compare with the objective response observed from ALK-positive NSCLC patients. This objective is now being addressed in the ALK-negative cohort #2.

Further details regarding ALK-negative Cohort #1, including the sample size computations that were relevant at the time, are presented in the protocol.

4.2.1.3. ALK-Negative NSCLC Cohort #2

In order to further characterize the anti-tumor activity of PF-02341066 in ALK-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 by a central laboratory may be eligible for enrollment. Initially, the protocol specified that no molecular testing for c-Met or ROS1 should occur prior to enrollment. As of a Note to File dated 19 June 2012 (at the time only 1 patient had been enrolled into this cohort), the requirement that no molecular testing for c-Met or ROS1 to occur prior to enrollment was removed. Thus, c-Met or ROS1 testing may have been performed prior to patient entry into this cohort. However, if the test result for either c-Met or ROS1 was positive, then the patient could not be enrolled into this cohort.

The ALK-negative cohort #2 was driven partly by the belief that patients whose tumors were negative by the Investigational Use Only (IUO), but positive by the Laboratory Developed Test (LDT) test, could benefit from PF-02341066 treatment. Thus, the rationale for the ALK-negative NSCLC cohort #2 was to address questions regarding activity in the ALK-negative NSCLC population where patients were "purely" negative (ie, if pretesting was done, the local test must be negative and results of the local test needed to be confirmed by the central laboratory before entry into the study).

4.2.2. RP2D Enriched Other Cohort

The RP2D Enriched Other cohort includes all patients in RP2D who do not belong to one of the previously defined cohorts. This enriched population will be used to evaluate the anti-tumor activity of PF-02341066 in patients with other molecular profiles that confer sensitivity to PF-02341066, in particular, patients who are positive for ALK chromosomal translocation (except for patients with NSCLC) or ALK gene amplification; who are positive for known c-Met kinase domain activating mutations; who have chromosomal translocations/ fusions that lead to altered transcriptional regulation of c-Met and/or HGF; or are positive for chromosomal translocations at the ROS1 gene in other cancer types besides NCSLC; or NSCLC patients with tumors harboring c-Met Exon 14 alterations. 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 105 patients will be enrolled. RECIST version 1.0 is used to assess tumor activity in this cohort.

It is anticipated that approximately 40 to 50 NSCLC patients with tumors harboring c-Met Exon 14 alterations will be enrolled in the Enriched Other cohort, and data from these patients may be analyzed separately. With Sponsor written approval and IRB/EC notification, additional patients may be enrolled as described earlier in this section to reach this target enrollment in the event that overall enrollment is achieved prior to reaching this target.

In NSCLC patients with tumors harboring c-Met Exon 14 alterations, an ORR of 10% is considered to be 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 $\geq$ 7 objective responses are observed among the first 33 evaluable patients. The proportion of responders will be estimated with better precision if the number of evaluable patients exceeds 33 patients.

4.2.3. RP2D Midazolam Interaction Cohort

The MDZ Interaction cohort was used to evaluate the potential for CYP3A inhibition due to PF-02341066 using MDZ as a probe. Eight evaluable patients will be required for the MDZ interaction sub-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 the estimated AUC ratio of MDZ (with PF-02341066 vs without PF-02341066) is 2 (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 3) 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 3. 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

4.2.4. RP2D Rifampin DDI Sub-study

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. This study was proposed to evaluate the effect of rifampin (600 mg QD) on multiple-dose PK of PF-02341066 after repeated 250 mg BID dosing. A sample size of 8 evaluable patients, who complete full PK sampling for PF-02341066 on Cycle 1 Day 15 and Cycle 2 Day 1, is recommended for the rifampin DDI sub-study in the RP2D cohort. A total of approximately 25 patients will be enrolled into this cohort to obtain the 8 evaluable patients (to account for loss of patients due to early discontinuations, inadequate dosing, 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 (AUCss), with 80% coverage probability. An approximately 36% decrease in PF-02341066 AUCss is anticipated when co-administered with rifampin. (See Table 4) Table 4 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).

Table 4. 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

4.2.5. Itraconazole DDI Sub-Study

See Appendix 5, for details regarding the itraconazole DDI sub-study.

4.2.6. RP2D Other Sub-studies

Two additional sub-studies will be included in the RP2D 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. In addition, at least 6 patients will be required to have pre-and postdose tumor biopsies for the purpose of evaluating pharmacodynamic markers of PF-02341066. Second, for the food effect sub-study, twelve patients will provide at least 80% power to detect at least a 2-fold change in the AUC or C_{max} between fed and fasting drug administration (assumes an intrapatient CV of 10% for AUC and C_{max}).

5. ANALYSIS SETS

The analysis sets, as described below are defined for the Dose Escalation component and Dose Expansion (RP2D Cohort) component of the study as well as the rifampin DDI sub-study, as applicable. See Appendix 5.3 for details regarding the analysis sets for the itraconazole DDI sub-study.

Patients who did not sign appropriate consent documents at study entry (informed consent forms, HIPAA waivers) will be evaluated and may be omitted from all analyses. Except as noted, other enrollment criteria will not be used to exclude patients from safety analyses. Patients having protocol deviations may be removed from efficacy analyses (eg, due to there being no adequate baseline available) or from PK analyses (eg, due to the timing of dosing relative to blood sampling or the use of interfering concomitant medications), or from both, as appropriate for the particular cohort or sub-study.

5.1. Safety Analysis Set

The safety analysis (SA) set will include all enrolled patients who receive at least one dose of PF-02341066 on Cycle 1, Day 1. This is the primary population for all standard analyses (Section 8.2.1) and safety analyses (Section 8.2.2 and Section 8.1.2 of the

Supplemental SAP). This population is used for all cohorts/sub-studies except for the DDI studies which have sub-study specific safety population definitions as described in Section 5.4.6 (rifampin) and Appendix 5.3 (itraconazole).

5.2. Response-Evaluable (Re) Population

The response evaluable population is defined as all patients in the safety analysis set who have an adequate baseline disease assessment (definition for adequate baseline tumor assessment is reported in Appendices 4 and 5 of the Supplemental SAP).

In addition, for any interim reporting of the data, patients also need to meet 1 of the following 2 criteria:

- had at least one post-baseline disease assessment at least 6 weeks from first dose;
- withdrew from the trial or experienced progression/death at any time on study.

5.3. Dose Limiting Toxicities (DLT) Evaluable Population

The DLT evaluable population is defined as patients in the safety analysis set and dose escalation phase who have received at least 75% of planned dose of PF-02341066 dose in Cycle 1 or experience a treatment-related adverse event that prompts early treatment interruption or discontinuation.

5.4. Other Analysis Sets For PK Analysis

See the Supplemental SAP for information regarding the ROS1-positive NSCLC cohort and the ALK-positive NSCLC cohort. See Appendix 5.3, for details regarding the itraconazole DDI sub-study.

5.4.1. PK Concentration Analysis Set

The PK concentration population of PF-02341066 is defined as all patients treated (including Day -7 dose) who have at least 1 concentration of PF-02341066 (including its active moieties, if appropriate).

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

See the specifics for the rifampin and itraconazole studies in Section 5.4.6 and Appendix 5.3, respectively.

5.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all patients treated (including Day -7 dose) who have at least 1 of the PK parameters of interest for PF-02341066 (including its active moieties, if appropriate).

See the specifics for the rifampin and itraconazole studies in Section 5.4.6 and Appendix 5.3, respectively.

5.4.3. Predose (O H) Populations

These analysis populations are used for the cohorts including but not limited to ALK-positive, ALK-negative, c-Met, and Enriched Other. See the Supplemental SAP for details regarding the ROS1 Cohort,

PK Predose (0 H) Concentration Evaluable Population

Any patient in the safety analysis (SA) population who has at least one predose (0 H) concentration and within the allowable time window (-1.2 H to 0 H of a.m. dosing) or (10.8 H to 13.2 H of previous day p.m. dosing in case of missing a.m. dose) following treatment.

PK Steady State Predose (0 H) Concentration Evaluable Population

Any patient in the PK Predose Concentration Evaluable population who has at least one predose (0 H) concentration on C1D15 and later within the allowable time window (-1.2 H to 0 H of a.m. dosing) or (10.8 H to 13.2 H of previous day p.m. dosing in case of missing a.m. dose) and who has 14 consecutive days of 500 mg daily dose prior to the PK sample collection.

5.4.4. Food Effect Analysis Set

The food effect analysis set is defined as all patients treated (including Day -7 dose) and in the RP2D cohort who have received a dose of PF-02341066 under either fed or fasted conditions as defined in the fed/fast sub-study of the protocol and for which at least 1 PK parameter of interest (C_{max} or AUC) is available.

5.4.5. MDZ Interaction Analysis Set

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

5.4.6. Rifampin Drug-Drug Interaction Sub-study Analysis Sets

The following 3 populations are defined for this sub-study:

Rifampin sub-study safety population: The safety population for the rifampin sub-study includes all patients who receive at least one dose of either PF-02341066 or rifampin. Unless otherwise specified, this population will be used for demographic and baseline characteristics tables and safety tables for this sub-study.

Rifampin sub-study PK concentration population: The PK concentration population for the rifampin sub-study is defined as all patients in the rifampin sub-study safety population who had at least 1 concentration of either PF-02341066 or PF-06260182. This population will be used for all PK concentration tables for this sub-study.

Rifampin sub-study PK parameter population: The PK parameter population is defined as all patients in the rifampin sub-study safety population who satisfy each of the following criteria for **at least one** treatment period:

- Have at least 1 of the primary PK parameters of PF-02341066 (AUC_{tau} and C_{max}) in at least 1 treatment period
- Have received adequate dosing prior to PK sampling in that treatment period (as defined below).

The definition of the treatment periods and the requirements for adequate dosing are described below for each treatment period.

Treatment Period A (reference): When patients completed crizotinib 250 mg BID dosing from the first dose on Cycle 1 Day 1 (C1D1) to the AM dose on Cycle 1 Day 15 (C1D15). A patient is considered to have been adequately dosed if the patient:

- Has received crizotinib 250 mg BID dosing for 3 consecutive days immediately prior to the postdose PK sample collection scheduled on C1D15 and the C1D15 AM dose
- Has received >=90% of the total designated crizotinib dose within 14 days prior to the postdose PK sample collection scheduled on C1D15 including the C1D15 AM dose (ie, at least 6525 mg of the designated 7250 mg total dose)

Treatment Period B (test): When patients completed crizotinib 250 mg BID dosing from PM dosing on C1D15 to the AM dosing on Cycle 2 Day 1 (C2D1) and rifampin 600 mg QD from Cycle 1 Day 16 (C1D16) to the AM dosing on C2D1. A patient is considered to have been adequately dosed if the patient:

- Has received crizotinib 250 mg BID dosing for 3 consecutive days immediately prior to the postdose PK sample collection scheduled on C2D1 and the C2D1 AM dose
- Has received >= 90% of the total designated crizotinib dose within 14 days prior to the postdose PK sample collection scheduled on C2D1 including the C2D1 AM dose (ie, at least 6525 mg of the designated 7250 mg total dose)
- Has received rifampin 600 mg QD dosing for at least 9 consecutive days immediately prior to the postdose PK sample collection scheduled on C2D1 and the AM dose prior to PK sample collection.

5.4.7. Itraconazole DDI Sub-study Analysis Sets

See Appendix 5.3 for details of the analysis sets for the itraconazole DDI sub-study.

5.4.8. ROS1-Positive NSCLC Patients

Additional details regarding the PK and other analyses planned for the ROS1-positive NSCLC patients are provided in the Supplemental SAP.

5.5. Ophthalmologic Exam Evaluable Set (Protocol Amendment #12 and Beyond)

Starting with protocol Amendment #12, an ophthalmology exam was to be performed at screening on all new patients; visual acuity, fundoscopy (vitreous body, retina macula, retina non-macula [peripheral], optic nerve head, and fundus*), biomicroscopy (cornea, iris, lens, anterior chamber), and ocular characteristics were to be recorded. The ophthalmology examination was to be repeated during the study for patients who report a visual disturbance or had an increase in grade for visual disturbances (for all ongoing patients).

*The fundus (normal/abnormal/not done) was not recorded after protocol Amendment #17, which added other expanded ophthalmologic testing.

5.6. "Evaluable" Sets For NSCLC Ophthalmologic Analyses (Protocol Amendment #17 Through and Including Protocol Amendment #21)

All NSCLC patients enrolled under protocol Amendment #17 and beyond were to undergo the following expanded set of ophthalmology 10 assessments:

- Best corrected visual acuity (BCVA)
- Refractive error associated with BCVA
- Pupil size/symmetry under standardized lighting conditions
- Slit lamp biomicroscopy of the anterior segment including lids, conjunctiva, sclera, cornea, anterior chamber, iris and lens
- Intraocular inflammation (cell count and aqueous flare)
- Intraocular pressure (IOP)
- Fundoscopy, including vitreous body, retina macular, peripheral retina non-macular, and optic nerve head
- Dilated fundus photography of the macula, peripheral non-macular and optic nerve head
- Optical coherence tomography (OCT) of the vitreous body and macula
- Ocular characteristics including eye color and documentation of nevi or freckles on the iris or conjunctiva bulbi

These tests were to be performed at screening, Cycle 1 Day 15, Cycle 3 Day 1, and 2-8 weeks after the last dose of study medication (EOT); at protocol Amendment #20,

annual examinations following Cycle 3 Day 1 until EOT were added to the schedule. A total of at least 30 NSCLC patients are required to complete all exams on both eyes at all timepoints. While enrollment will continue until at least 30 NSCLC patients are tested (all examinations, both eyes) at Cycle 3 Day 1, it may be impractical to obtain complete data at the EOT in this patient population.

By the time protocol Amendment #22 was finalized, at least 30 NSCLC patients had completed all examinations on both eyes at screening, Cycle 1 Day 15, and Cycle 3 Day 1. Protocol Amendment #22 specified that the ophthalmic testing would revert to the types of eye examinations and the schedule proscribed in protocol Amendment #12. Accordingly, following the adoption of protocol Amendment #22, the CRFs used following protocol Amendment #17 will be used for all newly enrolled patients, but only for fundoscopy (posterior segment), biomicroscopy anterior segment, ocular characteristics, and visual acuity and only at screening and when changes are noted. Although the tests going forward from protocol Amendment #22 are nominally the same as those collected from protocol Amendments #12 through #16, there are some minor changes in the corresponding CRF pages adopted at protocol Amendment #17; the protocol Amendment #17 versions will be used going forward. The changes are as follows:

- Fundoscopy posterior segment CRF:
    - Eye structures collected per protocol Amendments #12 through #16: vitreous body, retina macula, retina non-macula (peripheral), optic nerve head, fundus
    - Eye structures collected per protocol Amendments #17 and beyond: vitreous body, retina macula, retina non-macula (peripheral), optic nerve head
- Biomicroscopy anterior segment CRF:
    - Eye structures collected per protocol Amendments #12 through #16: cornea, anterior chamber, iris, lens
    - Eye structures collected per protocol Amendments #17 and beyond: lids, conjunctiva, sclera, cornea, anterior chamber, iris, lens

Reports of results for some cohorts may include summaries of ophthalmic parameters based on the safety population for that cohort. For reporting the ophthalmic results across cohorts, the analysis populations are defined below. The population definitions are aligned with the terminology used in the protocol, however the wording will be changed for reporting purposes as appropriate: the word “subject” will replace “patients” to match standard displays, and “crizotinib” will replace “PF-02341066” for consistency in reporting across the program.

NSCLC Detailed Ophthalmologic Exam - ITT Population

The NSCLC Detailed Ophthalmologic Exam – ITT population is defined as all NSCLC patients enrolled under Study Protocol Amendment #17 through Amendment #21 (except those enrolled in the itraconazole DDI sub-study), who received at least one dose of PF-02341066, and who have data for at least one ophthalmology test at any timepoint.

NSCLC Detailed Ophthalmologic Exam 10 Tests – Evaluable Population

The NSCLC Detailed Ophthalmologic Exam 10 Test – Evaluable Population is defined as patients included in the NSCLC Detailed Ophthalmologic Exam ITT population who have complete screening, C1D15, and C3D1 data for all 10 assessments (visual acuity, refractive error, biomicroscopy including intraocular inflammation (cell count and aqueous flare), pupillary diameter, intraocular pressure, fundoscopy, color fundus photography, and ocular coherence tomography) for both eyes.

A patient is considered to have data for the specified ophthalmology test at a visit if the corresponding CRFs for each eye (right and left) report results for all assessments. The summary on this population, which will form the basis of the submission to support the post-marketing requirement, will be performed when there are at least 30 patients with screening, C1D15, and C3D1 data for both eyes on all 10 assessments completed according to the guidelines provided to investigators. The data available for other visits will be listed.

5.7. Hypogonadism Testing Results

Male patients enrolled after IRB/EC approval of protocol Amendment #21 in the c-Met-amplified NSCLC and Enriched Other cohorts were to have additional laboratory tests for hypogonadism. Required tests include: total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone, dihydroepiandosterone sulfate, estradiol, and prolactin. Blood samples were scheduled to be drawn on C1D1, C1D15, C2D1, C4D1, C6D1, and Day 1 of every 3 cycles thereafter as well as at 28 days following the last dose. Blood draws were to 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 was to be as consistent across visits as feasible. If either total testosterone or free testosterone decreased 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 was to be performed at the next clinic visit to confirm hypogonadism.

5.8. Treatment Misallocations

Not applicable.

5.9. Protocol Deviations

Protocol deviations will be described when they appear and relate to the statistical summaries or populations.

6. ENDPOINTS AND COVARIATES

6.1. Endpoints

See Appendix 5, for details regarding the itraconazole DDI sub-study.

6.1.1. Dose-Escalation and RP2D Cohort Endpoints

- Safety endpoints:
  - MTD and phase 2 dose(s) of PF-02341066.
  - Overall safety profile of PF-02341066 including adverse events (AE), as defined and graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0 and first cycle DLTs, as applicable.
  - ECG including heart rate, QT, QT_CB (Bazett's), QT_CF (Fridericia's), PR, and QRS.
  - Ophthalmology examinations including visual acuity, fundoscopy, biomicroscopy (slit lamp examination), and ocular characteristics (all patients protocol Amendment #12 and beyond). Expanded ophthalmology tests include BCVA, refractive error associated with BCVA, pupil size/symmetry under standardized lighting conditions, slit lamp biomicroscopy of the anterior segment, intraocular inflammation (cell count and aqueous flare), IOP, fundoscopy, dilated fundus photography, OCT, and ocular characteristics (all NSCLC patients enrolled under protocol Amendment # 17 and beyond).
  - Blood testosterone and other blood parameters associated with detecting hypogonadism in males
- Efficacy endpoints:
  - The following efficacy endpoints will be evaluated for each cohort, as appropriate.
    - Objective response according to RECIST 1.0 (RECIST 1.1 will be used for the ALK-negative NSCLC cohorts)
    - Objective response rate
    - Duration of response (DR)
    - Time to response (TTR)
    - Disease control rate at weeks 8 and 16
    - Disease control rate at weeks 6 and 12 (ALK-negative NSCLC cohorts)

- Progression-free survival (PFS) (analysis based on safety population)
- 6-month PFS (analysis based on safety population)
- Overall survival (OS) (analysis based on safety population)
- Probability of survival at 6-and 12-months (analysis based on safety population)

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. All tumor scans from NSCLC patients with tumors harboring c-Met Exon 14 alterations and c-Met gene amplification will also 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.

- Other endpoints:
  - For interaction studies: Plasma concentrations of PF-02341066 (including its active moieties, if appropriate) and other drugs studied for interaction effects (ie, midazolam, rifampin, or itraconazole, as appropriate); PK parameters of PF-02341066 (including its active moieties, if appropriate) including AUC_{inf}*, AUC_{tau}, AUC_{last}, C_{trough}, C_{max}, T_{max}, $t_{1/2}$*, CL/F*, V/F* for plasma and Ae and Ae% for urine, as appropriate; and PK parameters of other drugs studied for interaction effects including AUC_{last}, AUC_{inf} *, C_{max}, and T_{max} as appropriate. (* if data permit).
  - For cohorts including but not limited to ALK-positive, ALK-negative, c-Met, ROS1, and Enriched Other cohorts, the following PK endpoints may be calculated:
    - Mean steady state predose concentration or mean steady state trough concentration ($C_{trough, ss, mean}$) for PF-02341066 and PF-06260182 calculated by using the arithmetic mean of all evaluable plasma predose concentrations (C_{trough}) for that patient
    - The PF-06260182 to PF-02341066 molar ratio calculated by [(concentration of PF-06260182) / (concentration of crizotinib)] × [(molecular weight of crizotinib (450.34)/molecular weight of PF-06260182 (464.33)].
  - Pharmacodynamic biomarkers of PK-02341066 including levels of soluble plasma biomarkers (HGF/Scatter factor, soluble c-Met/HGFR, VEGF, interleukin-8) in tumor samples from surgery or biopsy when available. (Soluble biomarkers were no longer collected as of protocol Amendment #17.)

- Urine 6 beta-hydroxycortisol/cortisol ratio. Urine samples for this endpoint will be collected prior to dosing on Days 1 and 15 of Cycle 1 and Day 1 of Cycle 2. These samples were no longer required once IRB/EC approval of protocol Amendment #17 was obtained.

- Predictive or pharmacodynamic biomarkers in tumor and peripheral blood that may be relevant to the mechanism of action of, or the development of resistance to PF-02341066 (eg, plasma circulating nucleic acid). For patients enrolling in the c-Met-amplified NSCLC and Enriched Other cohorts after the approval of protocol Amendment #21, blood biospecimen for nucleic acid analysis (eg, circulating free DNA [cfDNA] or RNA [cfRNA]) will be collected. Administrative Clarification Letter dated 12 October 2015 limited collection of samples for circulating nucleic acid profiling to NSCLC patients with tumors harboring c-Met Exon 14 alterations only, with collection times limited to Screening and End of Treatment only.

6.1.2. Rifampin DDI Sub-study Endpoints

- Concentrations of PF-02341066 and PF-06260812

- The following PK parameters will be calculated for PF-02341066 and PF-06260812 from the concentration-time data on C1D15 and C2D1 using standard noncompartmental methods:

PK Parameter	Analysis Scale	PF-02341066	PF-06260812
AUC_{tau}	ln	A, D	A, D
C_{max}	ln	A, D	A, D
C_{trough}	R	D	D
T_{max}	R	D	D
CL/F	R	D	D
$MRAUC_{tau}$	R		D
MRC_{max}	R		D
MRC_{trough}	R		D

A=analyzed using statistical model, D=displayed with descriptive statistics
ln=natural-log transformed, R=raw (untransformed)

6.2. Covariates

Not applicable.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, imputation methods apply to partial dates. If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing day. Similarly, if both the day and month are missing, the first day of the year is used. For stop dates, the last day of the month or the last day of the year is used if the day or both the day and month are missing, respectively. These

rules are used unless the calculations result in negative time durations (eg, date of resolution cannot be prior to date of onset). In these cases, the dates resulting in 0 time duration will be used. For PFS, OS, TTR, and DR, if conventions result in a negative duration, duration will be reset to 1 day. For imputations for pharmacokinetic, ECG, and pharmacodynamics analyses, see Sections 7.2, 7.3, and 7.4.

7.2. Pharmacokinetics

Concentrations below the limit of quantification

In all data presentations (except listings and plots presenting log-transformed concentrations), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings and plots using log-transformed measurements BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

Deviations, missing concentrations and anomalous values

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

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample)

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist

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

Pharmacokinetic parameters

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

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

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

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

7.3. ECG Parameters

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

7.4. Pharmacodynamic/Pharmacogenomic Parameters

Missing data for the pharmacodynamic and pharmacogenomic parameters will be treated as such and no imputed values will be derived.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

No formal hypothesis testing will be performed in this exploratory study. Estimates and confidence intervals will be generated as indicated, but p-values will not be computed unless otherwise indicated.

8.1.1. Analyses of Binary Endpoint

The point estimates of the rates of binary endpoints will be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on the F-distribution.

Assume that each observation has a binomial response recorded in variable *resp* in dataset *xx*. Then the desired output, along with an output dataset *yy*, can be computed in SAS as shown below.

```
proc freq data=xx;
  table  resp / binomial alpha = 0.05;
  output out= yy  binomial;
run;
```

The confidence interval will be given for the response category with the lower value (0 rather than 1, "N" rather than "Y"). To obtain the CI for the higher value, sort in descending order and use the ORDER=DATA option.

8.1.2. Analyses of Continuous and Categorical Data

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. The number and percentage of patients in each category will be presented for categorical variables.

8.1.3. Analyses of Time-to-Event Endpoints

Time-to-event endpoints (including DR, PFS, and OS) will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times

(and other quartiles) and 2-sided 95% confidence intervals for each quartile will be provided (Brookmeyer R and Crowley JJ).[1] TTR will be summarized using descriptive statistics.

Assume that the dataset *xx* has variables *duration* and *censor* for each patient, recording the time to event and censoring variable (0=not censored, 1=censored). The desired output can be generated using SAS PROC LIFETEST, and saved in dataset *yy*, as follows:

```
proc lifetest data = xx method =KM conftype = linear;
  time duration*censor_(1);
  survival out=yy  conftype = linear;
run;
```

8.2. Statistical Analyses

Table 5 displays cohorts/subgroups that will be referenced in the following sections. Analyses will be performed separately for these cohorts/subgroups unless otherwise specified. Additional subgroup analyses (eg, by race) will be provided, as appropriate.

Appendix 1 provides definitions of the cohorts/subgroups in Table 5 based on the CRF. Appendix 2 provides a summary of analyses by cohorts/subgroups.

The analyses for the ALK-positive NSCLC and ROS1-positive NSCLC cohorts are specified in the Supplemental SAP.

Table 5. List of Cohorts

Cohorts
1. Dose Escalation cohort (BID and QD)
2. RP2D: ALK-positive NSCLC *
3. RP2D: ALK-negative NSCLC cohort #1
4. RP2D: ALK-negative NSCLC cohort #2 **
5. RP2D: c-Met-amplified NSCLC cohort
6. RP2D: ROS1-positive NSCLC cohort *, +
7. RP2D: Enriched Other***

Note: The interaction sub-studies for rifampin and itraconazole are discussed in Appendix 4 and Appendix 5, respectively.
* Additional details are provided in the Supplemental SAP.
**See Appendix 3.
+ For the purposes of reporting, patients in the ALK negative cohort who are ROS1-positive and received at least one dose of PF-02341066 on Cycle 1, Day 1 will also be included in the analyses with patients from the ROS1-positive cohort. See the Supplemental SAP for details.
***This cohort is defined as all patients in RP2D who are not in one of the other RP2D cohorts.

The above cohorts are defined for enrollment purposes but the cohorts are not necessarily mutually exclusive for purposes of analysis. A patient who is enrolled to a specific cohort (eg, an ALK-negative NSCLC cohort) at the time of study entry may subsequently

be determined through molecular testing to be positive for a marker relevant to another cohort (eg, ROS1-positive NSCLC or c-Met amplified NSCLC). In this case, such patients may be pooled in the other cohort and/or summarized as a subgroup within their initial cohort as appropriate as long as the patient meets the definitions as described in Appendix 1 for the relevant cohort for analysis.

8.2.1. Standard Analyses

The safety analysis set will be used for all standard analyses except for the overall disposition table which will be presented for all enrolled patients.

Descriptive statistics will be used to summarize study conduct, patient disposition, baseline characteristics, and treatment administration/compliance. Analyses will be presented separately based on the cohorts in Table 5.

Study Conduct and Patient Disposition

An accounting of the study patients will be tabulated. The number and percentage of patients in each of the cohorts listed in Table 5 will be presented.

Reasons for discontinuations during the treatment period will be summarized based on the *Subject Summary CRF*. Patients discontinuing during the treatment period will also be listed along with the reasons for discontinuation. Disposition by cycle will also be presented for specific cohorts, as appropriate.

Demographics and Baseline Characteristics

Demographic characteristics including age, age category (<65, ≥65), gender, race, height (cm), and weight (kg) will be summarized. Weight is based on information collected at screening from the demography CRF page.

Baseline and disease characteristics will be summarized including smoking classification, primary diagnosis, time (years) from primary diagnosis to first day of dosing, current disease stage, histological classification, ECOG performance status, prior therapy, and medical history (past/present); best response to prior therapy may also be summarized. Time (years) from primary diagnosis to Day 1 of study is calculated as first dose date minus date of primary diagnosis plus 1 divided by 365.25. For ECOG performance status, baseline is the Cycle 1 Day 1 value, unless it is missing, in which case the screening value is used.

For the RP2D cohorts summaries of prior therapy may include the following:

1. number of prior regimens [categories 0, 1, 2, 3, …, K-1, ≥ K, as appropriate]
2. number of prior metastatic regimens [categories as appropriate, see above]
3. prior radiation therapy [yes/no]
4. prior cancer surgery [yes/no]

5. type of prior treatment regimen (neoadjuvant/adjuvant, advanced/metastatic)

6. type of prior metastatic therapy (eg, platinum-based therapies, EDFR TKIs, other TKIs, hormonal as available in the data, with subcategories neoadjuvant/adjuvant, advanced/metastatic, as applicable for the data being summarized)

7. best response to prior metastatic therapy by type of therapy, as appropriate

Treatment Administration/Compliance

Study drug administration will be described in terms of the following items, as appropriate (cohort/sub-study specific details below):

1. total number of cycles started
2. the median number (range) of cycles started
3. duration of treatment (weeks or months)
4. duration of treatment categories
5. dose reductions
6. dose interruptions
7. dose intensity
8. dose intensity by cycle

Reports for different RP2D cohorts and sub-studies will include different summaries:

ALK-negative NSCLC #1 cohort: items 1, 2, 4, 5, 6
ALK-negative NSCLC #2 cohort: items 1-6
ALK-positive NSCLC cohort: items 1-4, 6-8
ROS1-positive NSCLC cohort: items 3, 4, 5, 6, 7
Enriched Other cohort: items 1-7 as appropriate
(Note that the Enriched Other cohort may be summarized in various subsets of patients with similar characteristics; different subsets may have different reporting requirements.)
Rifampin sub-study: items 1, 2, 5, 6, with period-specific summaries as appropriate
Itraconazole sub-study: items 1, 2, 5, 6, with period-specific summaries as appropriate

8.2.2. Safety Analyses

Safety data will be summarized using the safety analysis population.

8.2.2.1. Dose Limiting Toxicities

Dose limiting toxicities will be presented by dose level for the dose escalation cohorts.

8.2.2.2. Adverse Events (AEs)

All AEs reported after initiation of treatment (Cycle 1, Day 1) and pre-existing conditions that worsen after the initiation of treatment will be considered as treatment emergent (Treatment Emergent Adverse Event: TEAE). AEs will be coded by system organ class (SOC) and preferred term (PT) according to MedDRA terminology. AE severity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated 12 December 2003.

An overall summary table of AEs will be provided. This table will include the number and percentage of patients who experienced any: AE, serious AE (SAE), grade 3 or 4 AE, grade 5 AE, and discontinued the study associated with an AE. Summaries will be presented by dose level for the Dose Escalation cohort. Treatment-related AEs are those judged by the investigator to have a reasonable possibility of being related to the study drug.

Emphasis in the analyses will be placed on TEAEs. TEAEs will be summarized by MedDRA SOC and PT. A summary will also be provided by MedDRA SOC, PT and maximum CTC severity grade and by maximum CTC grade group (Grade 1-2, Grade 3-4, Grade 5), as appropriate. Tables may also be presented for Cycle 1 and Cycle >1 or other periods, as specified in Appendix 2. A summary of TEAEs by PT (decreasing frequency) will also be presented. The aforementioned summaries will also be presented by relationship to study drug. Summary tables may also be generated for clustered adverse events which are events which combine several PTs associated with an event of interest (eg, events associated with visual disturbance). The clustered events are described in a list in the product's Safety Review Plan maintained by the Sponsor.

Patient deaths will be summarized by presenting the number and percentage of patients for each cause of death. Deaths will be presented separately "on-treatment" and during follow-up. Deaths that occurred on or after first dose of study medication and within 28 days after the last dose of study medication are defined as on-treatment deaths. Patients who died will also be listed.

Summaries will also be provided for AEs associated with dose reduction, dose interruptions, AEs associated with discontinuation of treatment, and SAEs associated with discontinuation of treatment. Patients who withdrew from study treatment because of an AE will be listed.

SAEs and treatment-related SAEs will be summarized by MedDRA SOC and PT. Patients who experienced a SAE will be listed.

The most commonly experienced AEs (5% or more of patients) will also be summarized by PT. Similarly, the most commonly experienced SAEs (2% or more of patients) will be summarized by PT.

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

occurring between Day -7 and Cycle 1, Day 1 for patients receiving a dose of PF-02341066 prior to Cycle 1 Day1, as is the case for some interaction studies.

8.2.2.3. Laboratory Data

Laboratory data values for complete blood counts (hemoglobin, platelets, and WBC with differentials-- neutrophils, eosinophils, lymphocyte, monocytes, and basophils) and serum chemistry will be summarized for shift changes from baseline as appropriate; urinalysis summaries may also be presented. Shift tables of laboratory parameters will also be presented as appropriate. Lab shift tables may also be summarized separately for Cycle 1, Cycle 2, and > Cycle 2 or other specified periods, as appropriate. An e-DISH scatter plot of maximum ALT vs. maximum total bilirubin on study based on the upper limit of normal (ULN) also may be presented to check for cases of Hy's Law; a similar plot for maximum AST vs maximum total bilirubin on study may also be presented.

8.2.2.4. Vital Signs

Vital signs include pulse rate (beats per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), and weight (kg). Descriptive statistics will be presented by timepoint for each vital sign and for change from baseline.

The number and percent of patients meeting the criteria for each of the following categories during the study will also be presented:

- Pulse Rate
  - On-study values: maximum >120 bpm or minimum <50 bpm
  - Change from baseline (increase or decrease) of ≥30 bpm

- Blood Pressure
  - Change from baseline (increase or decrease) in SBP of ≥40 mmHg
  - Change from baseline (decrease) in SBP of ≥60 mmHg
  - Change from baseline in DBP (increase or decrease) of ≥20 mmHg
  - Change from baseline in DBP (decrease) of ≥40 mmHg

- Body Weight
  - Percent change from baseline (increase or decrease) of ≥10%

Patients who have a cardiac pacemaker implanted prior to enrollment will be excluded from all summaries of pulse rate. All data will be listed, and an appropriate footnote will be added to all relevant displays if there are any patients removed from summaries due to a cardiac pacemaker.

8.2.2.5. ECOG Performance Status

ECOG Performance Status data will be summarized. Shift tables for ECOG performance status from baseline to worst on study will be presented.

8.2.2.6. 12-Lead ECG

12-lead ECGs will be performed as per protocol. The focus of these analyses will be to use changes in QTc from baseline to evaluate the frequency of patients experiencing QTc prolongation.

At each time point, triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. QT measurements corrected by heart rate will be used for the data analysis and interpretation. The commonly used Bazett's and Fridericia's correction methods will be applied. A study specific correction (QTcS) may also be applied. The exponent for the study specific correction will be derived from a population modeling (further described in a separate document) and applied to present the descriptive and central tendency analyses described in this SAP.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize absolute values and changes from baseline in heart rate, QT, QTc (including but not limited to QTcB and QTcF), PR interval and QRS complex by dose and nominal postdose time points. For each patient and by dose, the maximum change from baseline for these parameters will be calculated as well as the maximum post-baseline value across time-points.

Overall central tendency analysis of the QTc data will be conducted and summarized as follows: Summary statistics (including 90% confidence limits) of changes from baseline in QTcB, QTcF, and possibly QTcS will be presented for patients who received 250 mg BID dosing, as applicable, at each post-treatment time point.

Categorical analysis of ECG data will also be conducted. All planned and unplanned postdose time points will be counted in these categorical summaries. Patients with QTc values of grade ≥ 3, >500 ms, or with maximum increase from baseline ≥60 ms will separately be listed.

Categorical analysis of the QTcF/QTcB data will be conducted and summarized as follows:

1. The number and percentage of patients with maximum increase from baseline in QTcF/QTcB (<30, 30- <60, and ≥ 60 ms)

2. The number of and percentage patients with maximum postdose QTcF/QTcB (<450, 450-<480, 480- <500, and ≥500 ms)

3. PR interval changes from baseline ≥ 50% if absolute baseline value was < 200 ms, and ≥ 25% if absolute baseline value was ≥ 200 ms

4. QRS complex changes from baseline ≥ 50% if absolute baseline value was < 100 ms, and ≥ 25% if absolute baseline value was ≥ 100 ms

Individual patient ECG data listings (including a listing of qualitative results) will be generated.

8.2.2.7. Concomitant Medications

All medications received during the study will be considered as concomitant medications and will be coded by WHO medical dictionary. The version of the WHO dictionary used may vary by study cohort/sub-study due to changes over time in the standard applied. Concomitant medications will be summarized by therapeutic class and WHO PT. Because each drug taken by one or more patients is included in the summary for all therapeutic classes in the WHO dictionary, the same concomitant drug treatment may be included in multiple therapeutic classes.

Patients who received concomitant medications will be listed.

8.2.2.8. Ophthalmologic Testing (Protocol Amendment #12 – All Patients)

The discussion in this section pertains to analyses performed using the NSCLC Detailed Ophthalmologic analysis datasets described in Section 5.5 and 5.6. As noted in that section, reports concentrating on individual cohorts may summarize the ophthalmologic data based on the cohort-specific safety population. In those cases, the ophthalmologic summaries may deviate from the details provided below. In particular, for some cohorts, the overall results taking into consideration both eyes (as distinct from separate results for the right and left eyes) may be omitted, and some parameters may not be summarized.

As of protocol Amendment #12, the following ophthalmologic examinations will 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: visual acuity, fundoscopy (vitreous body, retina macula, retina non-macula [peripheral], optic nerve head, and fundus), biomicroscopy (slit lamp examination: cornea, iris, lens, and anterior chamber), and ocular characteristics (eye color and freckles/nevi). Using these examinations, the analyses listed in this section will be applied to the Ophthalmologic Exam Evaluable population. If there are few patients with data available for inclusion in a particular summary (eg, for visits having <10 non-missing values for the patients included in the report), summaries of those visits may be omitted, but all data will be listed.

In the following, baseline is defined as the assessment performed at screening. Analyses for visual acuity at baseline and ocular characteristics at baseline will be performed separately for each eye (right/left). Analyses for visual acuity worst change from baseline, fundoscopy posterior segment, biomicroscopy (slit lamp) exams, and change from baseline in ocular characteristics will be performed separately for each eye (right/left) and overall across eyes. The overall summary represents the worst category across both eyes. Unscheduled assessments are included in the evaluation of the worst change from baseline category across both eyes. For analyses of change from baseline in ocular characteristics, the overall summary counts a patient once if there is a change in either eye.

- **BCVA**

  Baseline: For baseline, the percentage of patients falling into each category (20/10, 20/13, etc.) based on Snellen equivalent will be summarized for each eye. All values for BCVA will be converted to the Snellen equivalent measured in feet as needed for summary purposes. Fractions that are recorded in meters are converted to feet by representing the recorded value as the ratio (20/3.28*y) where y is the value of the denominator in meters recorded on the CRF and the resulting denominator is rounded to the nearest whole number.

  Worst Change from Baseline: The worst change from baseline in BCVA will be summarized for each eye separately and for the total across eyes using the following categories: ≥ 3 line loss, 2 line loss, +1/-1 line, and > 1 line increase. A change in line of "+1/-1 line" represents no change from baseline in visual acuity. This summary will include patients with both a screening and at least one post-baseline assessment. The overall summary will count patients once in the worst change category from baseline across both eyes.

  If visual acuity at screening is provided as corrected, only corrected visual acuity data are evaluable on study; otherwise changes cannot be assessed. Similarly, if uncorrected visual acuity is collected at screening; on treatment data should be considered only if uncorrected.

- **Fundoscopy Posterior Segment**

  Summaries will be provided separately for each item on the CRF applicable for the group of patients included in the summary. Patients enrolled under protocol Amendments #12 - #16 had slightly different testing than those enrolled under protocol Amendment #17 or later; see Section 5.5 and 5.6.

  Baseline: For baseline, percentage of patients falling into each category of the examination status (normal, abnormal: not reported, abnormal: mild, abnormal: moderate, abnormal: severe, not done, not reported) will be summarized for each eye structure by eye and for the overall across eyes. "Abnormal: Not Reported" includes patients who reported "abnormal" results but with missing severity. "Not Done" includes patients who marked the "Not done" check box on the CRF page for the exam. "Not Reported" includes patients for which the CRF page was completed but there are missing results for the specific summary. For the overall summary, patients are counted once in the worst category across both eyes at baseline.

  Worst Change from Baseline: For post-baseline results, percentage of patients falling into each category of the worst examination status on study (new finding/worsening of findings, no change, improvement of findings, not done) will be summarized for each eye structure by eye and for the overall across eyes. For the total summary, patients are counted once in the worst category across both eyes on study.

- **Biomicroscopy (Slit Lamp) Examination Results**

  Summaries will be provided separately for each item on the CRF applicable for the group of patients included in the summary. Patients enrolled under protocol Amendments #12 - #16 had slightly different testing than those enrolled under protocol Amendment #17 or later; see Section 5.5 and 5.6.

  Baseline: For the baseline, percentage of patients falling into each category of the examination status (normal, abnormal: not reported, abnormal: mild, abnormal: moderate or abnormal: severe, not done, not reported) will be summarized for each eye structure by eye and for the total across eyes. For the overall summary, patients are counted once in the worst category across both eyes at baseline.

  Worst Change from Baseline*:* For post-baseline results, percentage of patients falling into each category of the worst examination status on study (new finding/worsening of findings, no change, improvement of findings, not done) will be summarized for each eye structure by eye and for the overall across eyes. For the overall summary, patients are counted once in the worst category across both eyes on study.

- **Ocular Characteristics**

  Baseline: The number and the percentage of patients in each group of iris color will be calculated for each eye. In addition, whether or not a patient has nevi or freckles on the iris (yes/no/not reported) and separately on the conjunctiva bulbi (yes/no/not reported) will be summarized.

  Change from Baseline: The change from baseline in ocular characteristics will be presented by eye and for the total across eyes. Patients are counted once in each category if there is a change in: eye color, nevi or freckles (on iris), and nevi or freckles (on conjunctiva bulbi). For the overall summary, patients are counted once if there is a change in either eye in the aforementioned categories. Patients are counted as having a change in nevi or freckles if "No" was reported at baseline and "Yes" was reported at a subsequent visit during the study.

8.2.2.9. Expanded Ophthalmologic Testing (Protocol Amendment #17 – NSCLC Patients)

The discussion in this section pertains to analyses performed using the NSCLC Detailed Ophthalmologic analysis datasets described in Section 5.6. As noted above, reports concentrating on individual cohorts may summarize the ophthalmologic data based on the cohort-specific safety population and the summaries may deviate from those described below.

This version of the SAP describes the analyses planned for the resubmission of the A8081001 Ophthalmology Report. The original ophthalmology report (19Jun2014) included fewer than 30 patients who had completed all 10 tests, and the FDA requested a resubmission including results for at least 30 patients who had complete data. Version

5 of the Statistical Analysis Plan (12Apr2014) described the analyses for the original report.

Note that all NSCLC patients enrolled after protocol Amendment #17 approval will undergo the following expanded set of 10 ophthalmology assessments: BCVA, refractive error associated with BCVA, pupil size/symmetry under standardized lighting conditions, slit lamp biomicroscopy of the anterior segment, intraocular inflammation (cell count and aqueous flare), IOP, fundoscopy, dilated fundus photography, OCT, and ocular characteristics. These tests are to be performed at screening, Cycle 1 Day 15, Cycle 3 Day 1, and 2-8 weeks after the last dose of study medication (EOT); at protocol Amendment #20, annual examinations following Cycle 3 Day 1 until EOT were added to the schedule. Patients enrolled after approval of protocol Amendment #22 were no longer required to undergo the expanded testing, as described in Section 5.6.

A total of at least 30 NSCLC patients are required to complete all examinations through Cycle 3, Day 1. Due to patient inability/unwillingness to submit to the EOT testing, it may be impractical to achieve a sample size of 30 at later timepoints. In order to adequately describe the data available at the time of reporting, the following analyses will be repeated for the populations described in Section 5.6 unless otherwise specified: NSCLC Detailed Ophthalmologic Exam - ITT Population and NSCLC Detailed Ophthalmologic Exam All 10 Tests – Evaluable Population.

Given that NSCLC patients enrolled under protocol Amendment #17 and beyond include patients with a variety of molecular markers, summaries will also be presented overall and across cohorts: ROS1-positive NSCLC cohort, c-Met-amplified NSCLC cohort, ALK-negative NSCLC cohort #2, Rifampin sub-study (if NSCLC), and Enriched Other NSCLC cohort (as applicable). Additional summaries may be presented for separate cohorts.

The following tests of continuous measures will be summarized separately for right and left eyes: refractive error (spherical equivalent), intraocular pressure, optical coherence tomography (center point), and external eye exam (pupillary diameter/symmetry). The following tests for categorical measures will be summarized separately for right and left eye and summarized for the overall across eyes: fundoscopy of the posterior segment, biomicroscopy of the anterior segment (including anterior chamber grading of aqueous flare and cell count), dilated fundus photography, and optical coherence tomography. Data at baseline for each assessment will be summarized by eye with worst change from baseline presented by eye and for the overall across eyes. Unscheduled assessments are included in the evaluation of the worst change from baseline category across both eyes.

The analyses of visual acuity, fundoscopy of the posterior segment, biomicroscopy of the anterior segment, and ocular characteristics will be performed as described previously for all patients following adoption of protocol Amendment #12 as described in Section 5.5 and 5.6.

Analyses of additional endpoints are described below:

- **Refractive error**: Using the reported spherical numeric result (in diopters) and the numeric cylinder result (in diopters), the spherical equivalent will be calculated. The spherical equivalent is defined as: spherical result + ½ cylinder result. The spherical equivalent and change from baseline in spherical equivalent will be summarized using descriptive statistics for each timepoint separately by eye (right/left). For each eye, the spherical equivalent will be calculated as ([0.5 × cylinder] + spherical).

- **External eye exam (including pupil size under standard lighting conditions)**: The pupillary diameter (in millimeters) and change from baseline in pupillary diameter will be summarized using descriptive statistics for each timepoint separately by eye (right/left). Patients with a change (increase or decrease) in pupillary diameter >2mm at any time on study will be listed.

- **Cell count:** For each timepoint, the percentage of patients falling into each category of grading of cells in the aqueous humor (no cells, 1-5, 6-10, 11-20, >20, not done) will be summarized by eye. A shift table of change from baseline category to worst category on study will also be presented by eye. This summary will include patients with a baseline and at least one post-baseline assessment.

- **Flare grading:** For each timepoint, the percentage of patients falling into each category of grading of aqueous flare (0, 1+, 2+ 3+, 4+, not done) will be summarized by eye and for the total across eyes. For the total summary, patients are counted once for the worst grade across eyes. A shift table of change from baseline grade to worst grade on study will also be presented by eye. This summary will include patients with a baseline and at least one post-baseline assessment.

- **Intraocular pressure:** For each patient, at least 2 measures of intraocular pressure will be obtained for each eye (a third reading will be obtained if the first 2 measurements are more than 2mm Hg of each other). The average intraocular pressure will be calculated for each patient by timepoint and eye using all available measurements (including repeat measurements). Using these averages, descriptive statistics will be calculated for intraocular pressure and change from baseline in intraocular pressure at each timepoint separately by eye (right/left). Patients with an intraocular pressure > 22 mmHg will be listed.

- **Dilated fundus photographs (FP):**

  Baseline: For baseline, the percentage of patients falling into each category of the examination status (normal, abnormal: not reported, abnormal: mild, abnormal: moderate, abnormal: severe, not done, not reported) will be summarized for each eye structure by eye and for overall across eyes by each eye structure. For the overall summary, patients are counted once for the worst category across both eyes at baseline.

  Worst Change from Baseline: For post-baseline results, percentage of patients falling into each category of the worst examination status on study (new finding/worsening of findings, no change, improvement of findings, not done) will be summarized for each eye structure by eye and for the total across eyes by each eye structure. Eye structures include: retina macula, retina non-macula (peripheral), and

optic nerve head. For the overall summary, patients are counted once for the worst category across both eyes on study.

- **Optical coherence tomography of the macula (OCT):**

  Baseline: For baseline, the percentage of patients falling into each category of the examination status (normal, abnormal: not reported, abnormal: mild, abnormal: moderate, abnormal: severe, not done, not reported) will be summarized for each eye structure by eye and for the overall across eyes. For the overall summary, patients are counted once for the worst category across both eyes at baseline.

  Worst Change from Baseline: For post-baseline results, percentage of patients falling into each category of the worst examination status on study (new finding/worsening of findings, no change, improvement of findings, not done) will be summarized for each eye structure by eye and for the total across eyes by each eye structure. For the overall summary, patients are counted once for the worst category across both eyes on study. Eye structures include: vitreous body and retina macula. Center point thickness (micron) and change from baseline in center point thickness will be summarized using descriptive statistics at each timepoint separately by eye. Patients with a center point of > 50 um will be listed.

In order to further describe the safety and baseline characteristics associated with these ophthalmologic exams, additional analyses will be performed. These include a summary of subject disposition, demographic characteristics, treatment emergent adverse events (all causality) of eye disorders by PT and maximum CTC grade in descending order of frequency, and treatment emergent adverse events (treatment-related) related to eye disorders by PT and maximum CTC grade in descending order of frequency. Similar tables will be generated for all causality AEs associated with permanent treatment discontinuation, those associated with temporary treatment discontinuation, and those associated with dose reduction; separate tables for treatment-related AEs associated with permanent treatment discontinuation, those associated with temporary treatment discontinuation, and those associated with dose reduction will also be provided. In these AE summaries, the PTs associated with the SOC of Eye Disorders plus the clustered terms VISION DISORDER and VISUAL LOSS will be shown, as applicable; the PTs that define the clustered terms VISION DISORDER or VISUAL LOSS will not be individually listed in these tables. However, additional tables of all causality and treatment-related AEs by clustered term including the individual PTs within cluster for the VISION DISORDER and VISUAL LOSS clustered terms will be provided. Details of these analyses are described in Section 8.2.2.2. Subject disposition, treatment-emergent AEs (all causality) of all eye-related AEs, including the treatment emergent AEs included in the VISION DISORDER or VISUAL LOSS clustered terms, will be provided in the listings.

To further describe the ophthalmology data available, a summary of patients by visit (total across cohorts) will present the number of patients who have completed the exam for at least one eye at each visit for each of the ophthalmology tests.

An examination of the relationship between ophthalmologic exam abnormalities and adverse events related to eye disorders and visual disturbances will be presented.

The following are the definitions of abnormality:

- Visual acuity: >= 2 line loss in either eye.
- Fundoscopy, dilated fundus photography, optical coherence tomography, or biomicroscopy: a new finding/worsening of findings from baseline in either eye.
- Grading of cells in the aqueous (cell count): a shift from baseline to a greater number of cells using the following categories (no cells, 1-5 cells, 6-10 cells, 11-20 cells, > 20 cells).
- Anterior chamber grading of aqueous flare: an increase in grade from baseline for either eye using the following grades (0, 1+, 2+, 3+, 4+).
- Additional freckles/nevi
- Changes in eye color
- Change in intraocular pressure >22 mm Hg
- Change in center point of > 50 microns

If there are few patients with data available for inclusion in a particular summary (eg, for visits having <10 non-missing values for the patients included in the report), summaries may be omitted.

Data listings will be based on the NSCLC Detailed Ophthalmology Exam - ITT population.

8.2.2.10. Hypogonadism Testing

Male patients enrolled following IRB/EC approval of protocol Amendment #21 in the c-Met-amplified NSCLC and Enriched Other cohorts will have additional blood tests for hypogonadism. The target is approximately 20 to 25 male patients available for hypogonadism evaluation. Required tests include: total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone, follicle stimulating hormone, dihydroepiandosterone sulfate, estradiol and prolactin.

The statistical analysis of hypogonadism parameters 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. For each laboratory measurement, the observed values will be normalized for age using laboratory-provided age-specific means and standard deviations for males. The normalized values and changes from baseline at each assessment timepoint will be summarized using descriptive statistics. The 95% CI based on the t-distribution will be provided for the change from baseline as long as there are at least 10 observations at a specific timepoint. The data will be examined to determine if a log-transformation of the values is appropriate.

Although no formal hypothesis testing will be performed, the interest is in examining change from baseline with primary interest on free testosterone. A decrease of 2 standardized units is considered clinically meaningful.

Observed values and changes/shifts from baseline will be summarized at each timepoint, with values age-adjusted as appropriate. Summaries will be presented for all patients regardless of their enrollment cohort. Additional summaries for each source of enrollment (ie, the c-Met-amplified NSCLC cohort or the Enriched Other cohort) may also be presented if appropriate. Graphical displays may be presented. Data for each hypogonadism parameter may be displayed graphically to show changes over time. Detailed by-patient plots of data over time may be presented. All the values will be listed.

8.2.3. Pharmacokinetic Analyses

8.2.3.1. PF-02341066 PK Analyses

Analyses will be performed by subgroups as defined in Appendix 2 except for the ROS1-positive NSCLC patients; PK analyses for the ROS1-positive NSCLC patients are described in detail in the Supplemental SAP. Descriptive statistics for PK parameters will also be presented by ethnicity and/or race group (eg, Asians vs. non-Asians) for the RP2D cohort.

Pharmacokinetic Concentrations

PK concentrations of PF-02341066 (including its active moieties, if appropriate) will be listed, summarized and plotted for patients in the PK analysis set as defined in Section 5.4.1. For summary statistics and mean/median plots by sampling time, the nominal PK sampling time will be used; for individual patient plots by time, the actual PK sampling time will be used. Presentations for concentrations will include but not be limited to:

- Listing of all concentrations sorted by dose, day of assessment, patient ID and nominal time post dose. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- Summary of concentrations by dose, day of assessment and nominal time post dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (CV), minimum, maximum, and the number of concentrations above the lower limit of quantification.

- Linear plots of median/mean concentrations against nominal time post dose by dose and day of assessment (based on the summary of concentrations by dose, day of assessment and time post dose).

- Semi-log plots of median/mean concentrations against nominal time post dose by dose and day of assessment (on the same plot as above).

- Plots of individual concentrations against actual time post dose by day of assessment (there will be separate plots for each dose).

Pharmacokinetic Parameters

PK parameters detailed in Section 6.1 will be estimated using noncompartmental analysis for patients in the PK analysis set as defined in Section 5.4.2. Actual PK sampling times will be used in the derivation of PK parameters. Missing values will be handled as detailed in Section 7.2. All calculations will follow the Pfizer Clinical Pharmacology Guidances[2] "Pharmacokinetic Data Handling and Non-Compartmental Analysis Conventions."

Standard plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), predose plasma concentration (C_{trough}), area under the plasma concentration versus time curve from zero time to the time of the last measurable concentration (AUC_{last}), area under the plasma concentration versus time curve from zero time to time τ, the dose interval (AUC_{tau}), accumulation ratio (Rac), and metabolite to parent ratio for PF-02341066 and its metabolite(s) (if applicable) will be estimated using non-compartmental analysis. Standard urine pharmacokinetic parameters including cumulative amount of drug recovered unchanged in the urine (Ae) and cumulative total amount of drug recovered unchanged in the urine, expressed as fraction of administered dose (Ae%). If data permit, area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F) and apparent volume of distribution (V/F) will be also estimated. Each PK parameter will be summarized by dose and will include the set of summary statistics as specified in the table below:

Parameter	Summary statistics
AUC_{last}, AUC_{inf}*, AUC_{tau}, C_{max}, C_{trough}, CL/F*, V/F*,	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$, Rac*, Ae and Ae (%)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

* if data permit

To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf}, AUC_{last}, AUC_{tau}, and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual patient values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented.

In addition, plasma concentrations may be listed, summarized, and plotted for analyses of sets of patients, including but not limited to the ALK-positive NSCLC cohort, ALK-negative cohorts, c-Met-amplified NSCLC cohort, ROS1-positive NSCLC cohort,

and Enriched Other cohort (or subset thereof, as appropriate). Data presentations may include the following:

- Listing of all concentrations sorted by patient identification number and nominal time postdose. The listing of concentrations includes the actual collection times. Deviations from the nominal time are given in a separate listing;
- Summary of predose (0H) concentrations by visit and ethnicity with descriptive statistics;
- Summary of $C_{trough,\ ss,\ mean}$ by ethnicity with descriptive statistics;
- Linear plots of median/mean predose (0H) concentrations against visit, by ethnicity.

8.2.3.2. Effect of Food on PF-02341066 PK

Analysis Set: Food Effect Analysis Set as in Section 5.4.4

Natural log transformed AUC and C_{max} will be analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and patient within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The fasted state is the Reference treatment and the fed state is the Test treatment.

Individual and descriptive statistics of PF-02341066 plasma concentrations at each nominal time point by fed and fasted condition will be listed and plotted as described in Section 8.2.3.1. Individual and summary statistics of plasma PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf} (if data permit) will be provided in tabular form by fed and fasted condition as described in Section 8.2.3.1.

8.2.3.3. Interaction of PF-02341066 with Midazolam (MDZ)

Analysis set: MDZ Interaction Analysis Set as in Section 5.4.5.

In order to assess the effect of PF-02341066 on CYP3A activity in the GI tract and the liver, the PK of midazolam following a single oral 2 mg dose was evaluated before and after repeated administration of PF-02341066.

The primary PK parameter AUC_{last} of MDZ will be utilized to estimate the effect of multiple doses of PF-02341066 on a single dose of MDZ. The parameter AUC_{last} will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect and patient as the random effect. Ninety percent confidence intervals for the ratio of geometric means of MDZ AUC_{last} in presence of PF-02341066 (Cycle 2 Day 1 when MDZ is administered in combination with PF-02341066) and MDZ alone (Day -7) will be computed to assess the interaction with MDZ alone as the Reference treatment.

8.2.3.4. POPPK Modeling Analysis

A POPPK modeling analysis using pooled PK data from the A8081001 and A8081005 studies will also be performed. The results of these analyses will be presented in a separate document.

8.2.3.5. Effect of Rifampin on PF-02341066 PK

The analyses planned for the rifampin DDI sub-study are described in detail in Appendix 4.

8.2.3.6. Effect of Itraconazole on PF-02341066 PK

The analyses planned for the itraconazole DDI sub-study are described in detail in Appendix 5.

8.2.4. Population PK/PD Analysis

Population pharmacokinetic analysis of samples collected in this study will be performed in accordance with the FDA guidance on Population Pharmacokinetics (February 1999)[19]. 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, and 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.

8.2.5. Efficacy Analyses

For the purposes of efficacy analyses, the term "on study" includes the period from the date of the first dose (Cycle 1, Day 1) until 35 days after the last dose of study medication (28 days + 1 week allowance). However, deaths will be included in the progression-free survival (PFS) analysis if they occur within 16 weeks (14 weeks for the ALK-negative NSCLC cohort, which had 21-day cycles instead of 28-day cycles) from the last tumor assessment on study and will be included in the OS analysis irrespective from their timing of occurrence. As of protocol Amendment #22 survival follow-up was extended for three patient groups: (1) the c-Met amplified NSCLC cohort, (2) the ROS1-positive NSCLC cohort, and (3) patients in the Enriched Other cohort with NSCLC who have tumors harboring c-Met Exon 14 alterations. Within each patient group, survival follow-up will continue until 1 year after the last patient's last dose.

Response will be derived based on the investigator assessment according to the rules described in Appendices 4 and 5 of the Supplemental SAP for the following groups:

ALK-positive NSCLC cohort, ALK-negative NSCLC cohort #1, ALK-negative NSCLC cohort #2, c-Met-amplified NSCLC cohort, ROS1-positive NSCLC cohort, and patients in the Enriched Other cohort with NSCLC. Best response will then be summarized for patients in the response evaluable populations for these cohorts. As noted in Section 2.1, subgroups of the Enriched Other cohort will be defined for purposes of analysis. In particular, for the group of NSCLC patients in the Enriched Other cohort with tumors harboring c-Met Exon 14 alterations, 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 response-evaluable patients, will be provided along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.

Additional details of the efficacy analysis for the ALK-positive NSCLC cohort ROS1-positive NSCLC patients are described further in the Supplemental SAP and includes the following endpoints: overall response rate, duration of response, time to response, disease control rate at 8 and 16 weeks, progression-free survival, probability of survival at 6 and 12 months and overall survival. These endpoints will also be analyzed for other cohorts, as appropriate.

Analysis for ALK- negative NSCLC cohorts #1 and #2 will use RECIST version 1.1 and is further described in Section 8.2.6.

8.2.6. Analysis of ALK-Negative NSCLC Cohorts

The best response (confirmed complete response [CR], confirmed partial response [PR], stable disease [SD] or progressive disease [PD]) per RECIST version 1.1 (detailed in protocol Appendix 5 of the Supplemental SAP) will be summarized. ORR calculated as the number of treated patients with a best response of CR or PR divided by the total number of response-evaluable patients in the ALK-negative cohort will be provided, along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution. The disease control rate at 6 and 12 weeks may also be calculated for the ALK-negative cohorts. If the number of patients in either of the ALK-negative NSCLC cohorts is small, listings may be provided for best response.

For ALK-negative NSCLC cohort #2, ORR of the ALK-negative cohort may be compared against the ORR of ALK-positive patients in the PF-02341066 treatment arm of Study A8081007 and/or A8081005. The difference in ORR between the two studies may be provided and its 95% confidence interval calculated based on the normal approximation.

Further detail regarding analyses planned for the ALK-negative NSCLC cohort #2 is provided in Appendix 3.

8.2.7. Analysis of c-Met-Amplified NSCLC Categories

For each of the 3 c-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 4.2.1.1. The best overall response (confirmed CR, confirmed PR, SD or 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. For each category, summaries will be presented for the first group of 10 patients (or for all the patients, if fewer than 10 enroll) and separately for all the patients if more patients are enrolled in each category.

8.2.8. Analysis of ROS1-Positive NSCLC Cohort

Additional details regarding the analyses planned for the ROS-positive NSCLC cohort are provided in the Supplemental SAP.

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

Urine 6 beta-Hydroxycortisol/Cortisol (6β-OHC/C) Ratio data will be summarized using graphical methods and descriptive statistics in tabular form, as appropriate.

8.2.10. Pharmacogenomic Assays

Data from pharmacogenomic assays will be summarized as applicable.

8.2.11. Biomarker Analysis

Data from biomarker assays (soluble protein levels and tumor biopsy) may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA) as appropriate. The statistical approach may include examining correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy. (Soluble biomarkers were no longer collected as of protocol Amendment #17.)

8.2.12. Circulating Nucleic Acid Profiling

Data from circulating free nucleic acids testing will be summarized as applicable.

9. REFERENCES

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

2. Pfizer Clinical Pharmacology Guidances, Pfizer Inc., 5 May 2005.

3. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000.

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

10. APPENDICES

Appendix 1. COHORT and OTHER SUBGROUP DEFINITIONS

An enrollment tracker maintained by the Sponsor identifies the cohort or sub-study associated with the enrollment of each patient. The following describes how cohorts that will be used for analyses will be identified based on the data:

Dose-escalation cohort

BID: Patient has an enrollment number between 1 and 37 or equal to 39.
QD: Patient has a "Dosing Cohort Frequency"=QD on the *Subject Randomization CRF*.

RP2D cohort

Patients who have the following:

- Enrollment number of 38 or > 39 **AND**
- Assigned to 250 mg BID crizotinib

Patients in the RP2D cohort will be further assigned to the following analysis cohorts according to the guidelines below.

a. **RP2D: ALK-Negative NSCLC Cohort #1** – Enrolled in Randomization Subgroup = "SUBGROUP 9 (Non-small Cell Lung Cancer – ALK marker negative)" on the *Subject Randomization CRF* AND NSCLC AND laboratory (Abbott Lab, US Labs, or Esoterix) test for ALK was negative.

b. **RP2D: ALK-Positive NSCLC Cohort -** If ALK marker is "Positive" AND primary diagnosis is non-small cell lung cancer AND identified on the enrollment tracker maintained by the Sponsor as being in this cohort.

In addition, the following analysis cohorts are also defined:

c. **ALK-Negative NSCLC Cohort #2** – Patients in the RP2D cohort with Randomization Subgroup= "SUBGROUP 10 (Non-small Cell Lung Cancer – ALK marker negative cohort 2)" on *the Subject Randomization* CRF. These patients can also be defined as patients who have a patient ID in the form of "SSID xxxx4xxx".

d. **c-Met Positive NSCLC Cohort** – Patients in the RP2D cohort with "Result Classification" = "Positive" on the *Diagnostic Marker Test – cMET CRF* AND primary diagnosis is NSCLC per the enrollment tracker. Subgroups of this cohort were identified in the protocol:

- High Level c-Met: MET/CEP7 Ratio ≥5
- Medium Level c-Met: MET/CEP7 ratio >2.2 to <5
- Low Level c-Met: MET/CEP7 ratio ≥1.8 to ≤2.2

e. **ROS1-Positive NSCLC Cohort** – Patients in the RP2D cohort with "Result Classification" = "Positive" on the *Diagnostic Marker Test – ROS CRF* AND primary diagnosis is non-small cell lung cancer. For these patients, Subgroup = "SUBGROUP 14 (Non-small Cell Lung Cancer - ROS)" on the Subject Randomization CRF.

f. **RP2D: Enriched Other Cohort** – All other patients in the RP2D cohort who are NOT in one of the previously defined RP2D cohorts and NOT in the itraconazole DDI sub-study; see below for the c-Met Exon 14 subgroup of this cohort.

g. **RP2D: Enriched Other Cohort, c-Met Exon 14 Alteration Patients** – Have a "POSITIVE" finding on the DIAGNOSTIC MARKER TEST - CMET EXON 14 DELETION CRF page (UNPL_DIAG_CMET3).

For the RP2D: ALK-positive NSCLC cohort, summaries will be performed by further identifying the following:

- Patients tested as ALK-positive by MGH (originally or re-tested) – These are defined as patients with a test where result classification = "Positive" on a MGH test (using either the Diagnostic Marker Test CRF with Location="LDT-MGH" OR a test documented in the MGH data source). The MGH data source should be used as a preferred source for summary purposes if information is available (eg, percent positivity).

- Patients tested as ALK-positive based on original test who are re-tested by MGH – These are defined as patients who will have data from both the Diagnostic Marker Test CRF AND the MGH data source. The MGH data source should be used as a preferred source for summary purposes if information is available (eg, percent positivity).

In addition, subgroups pertaining to additional sub-studies are defined as follows:

Food Effect subgroup: Patients in the RP2D cohort who are enrolled into the Food effect subgroup based on indicating "SUBGROUP 2 (Food Effect)" on the *Subject Randomization CRF*.

Midazolam subgroup: Patients in the RP2D cohort who are enrolled into the Midazolam subgroup based on indicating "SUBGROUP 1 (Midazolam)" on the *Subject Randomization CRF*. Patients may also be in other RP2D cohorts, as applicable, if the primary diagnosis was NSCLC.

Rifampin interaction subgroup: Patients in the RP2D cohort who are enrolled into the rifampin subgroup based on indicating "SUBGROUP 11 (Rifampin Interaction Sub-study)" on the *Subject Randomization CRF*. These patients can also be defined as patients who have a patient ID in the form of "SSID xxxx5xxx".

Itraconazole interaction subgroup: Patients in the RP2D cohort who are enrolled into the itraconazole subgroup based on indicating SUBGROUP 15 on the *Subject Randomization CRF*. These patients can also be defined as patients who have a patient ID in the form of "SSID xxxx7xxx".

Although patients are enrolled in a single cohort/sub-study, some analyses are based on groups of patients who are drawn from multiple cohort/sub-study enrollments. In particular:

- Patients who are enrolled in one marker-specific cohort who are also positive for another maker may be reported with all relevant cohorts. For example, 3 patients in ALK-negative #2 cohort were also ROS1-positive and were included in the report with those patients; one ALK-positive NSCLC patient also received midazolam.

- The patients used to analyze ophthalmic data are drawn from the patients enrolled after the adoption of protocol Amendment #17 in all of the following cohorts: ROS1-positive NSCLC, c-Met-amplified NSCLC, and ALK-negative NSCLC cohort #2, Rifampin cohort (if NSCLC) as well as the Enriched Other cohort. Additional summaries may be presented for separate cohorts.

Appendix 2. SUMMARY OF ANALYSES BY COHORTS

The analyses of DDI cohorts (rifampin and itraconazole) are discussed in subsequent appendices.

Analyses	COHORTS						
	Dose-Escalation	RP2D Cohort					
	Total and By Dose*	ALK-Positive NSCLC	ALK-Negative NSCLC #1	ALK-Negative NSCLC #2	c-Met amplified NSCLC §	ROS1-Positive NSCLC §	Enriched Other**, §
Standard Analyses							
Patient disposition	X	X	X	X	X	X	X
Patient disposition by Cycle		X		X		X	X
Demographic and Baseline Characteristics (including Prior Therapies)	X	X	X	X	X	X	X
Diagnostic Biomarker Results		X	X	X	X	X	X
Treatment Administration	X	X	X	X	X	X	X
Safety Analyses							
DLTs	X						
AE summaries	X	X	X	X	X	X	X
AEs (Cycle 1, Cycle >1)	X	X				X #	
Lab summaries	X	X		X	X	X	X (?)
Labs (Cycle 1, Cycle 2, Cycle >2)	X	X					
Time to AE, duration, etc.		X				X	
Efficacy Analyses							
Best overall response	Listings only	X	X***	X***	X***	X	X***
Objective response rate		X	X	X	X	X	
Duration of response		X	X	X	X****	X	
Duration of SD		X	X	X	X	X	X
Time to response		X	(Listed)	(Listed)	X****	X	
Disease control rate at 8 and 16 weeks (6 and		X		X	X****	X	

Analyses	COHORTS						
	Dose-Escalation	RP2D Cohort					
	Total and By Dose*	ALK-Positive NSCLC	ALK-Negative NSCLC #1	ALK-Negative NSCLC #2	c-Met amplified NSCLC §	ROS1-Positive NSCLC §	Enriched Other**, §
12 for ALK-negative NSCLC)							
PFS, 6 month PFS		X			X****	X	
OS, 6 and 12 month OS		X			X****	X	
PK Analyses	X	X	X	X	X	X	X

Note that the above cohorts are defined for analysis purposes. The cohorts are not necessarily mutually exclusive.
*: for each schedule (QD [original]/BID), summaries are done separately for each dose and a grand total across all dose levels and schedules is included.
**: This cohort is defined as all patients in the RP2D cohort who are NOT in one of the previously defined RP2D cohorts including the drug-drug interaction sub-studies, ROS1- positive NSCLC cohort, c-Met-amplified NSCLC cohort, ALK-positive NSCLC cohort, ALK-negative NSCLC cohort #1 and ALK-negative NSCLC cohort #2. The cohort may be analyzed by appropriately-defined subgroups. In particular, separate summaries will be provided for the NSCLC patients with tumors harboring c-Met Exon 14 alterations, 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 response-evaluable patients, will be provided along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on the F distribution.
***: Listings will be provided for early reporting purposes only or if numbers are too small to support summaries.
****: As data permits, the additional efficacy analyses (DR, TTR, DCR, PFS, TTP, and OS) may also be analyzed for c-Met amplified NSCLC cohort.
§For patients in the c-Met amplified NSCLC cohort, follow-up will continue until 1 year after the final dose of the last patient enrolling in that cohort. For patients in the ROS1-positive NSCLC cohort, follow-up will continue until 1 year after the final dose of the last patient enrolling in that cohort. For patients with NSCLC who have tumors harboring c-Met Exon 14 alterations, follow-up will continue until 1 year after the final dose of the last patient enrolling in that group of patients.

Instead of cycles 1 and >1, summaries for week intervals (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, ≥25) were provided for treatment-related and all causality TEAEs for clustered preferred terms of special interest.

Appendix 3. ALK-NEGATIVE NSCLC COHORT #2

The purpose of this appendix is to provide detail regarding the analyses planned for the ALK negative NSCLC cohort #2. All supportive data will be listed.

Analysis Populations

In addition to the analysis populations used by other cohorts (Safety Population, Response Evaluable Population), the ALK-negative NSCLC cohort #2 will also use the PK Predose (0 H) Concentration Evaluable Population and the PK Steady State Predose (0 H) Concentration Population as defined in Section 5.4.3 Note that all patients initially enrolled in the ALK-negative NSCLC cohort #2 will be included in the main analyses described below even if subsequent testing was positive for ROS1 or c-Met.

Demographics and Baseline Characteristics

Standard demographic and baseline characteristics (ie, sex, age, age category [<65, >=65], and race) will be presented for the Safety Population as described in Section 8.2.1. For the PK Concentration Population and PK Steady State Predose Concentration Population, the following additional demographic characteristics may also be summarized overall and by sex: body mass index (kg/m^2), body surface area (m^2), lean body weight (kg), and renal impairment category (normal, mild, moderate or severe) based on creatinine clearance. For renal impairment, the categories are as follows: normal (CLcr $\geq$ 90mL/min), mild (60mL/min $\leq$CLcr<90mL/min), moderate (30mL/min $\leq$ CLcr < 60mL/min), and severe (CLcr < 30mL/min. The body mass index, body surface area, lean body weight, and creatinine clearance will be calculated based on the Quetelet, Mosteller, James, and Cockcroft-Gault formulae respectively.

Additional standard summaries presented for the Safety Population include: subject disposition, weight, height, smoking classification, current disease stage, histology, number of prior cancer systemic regimens, types of prior therapies, duration of treatment (in weeks, and by cycles started), and ECOG performance status.

Biomarker Testing of Tumor Tissue

The test results (positive, negative, uninformative, insufficient, no tumor, not done) for ALK, c-Met, and ROS1 based on central testing will be summarized for the Safety Population. In addition the ALK percentage of positive cells based on central testing will be summarized using descriptive statistics as a continuous variable and also using the following categories: 0-3, 4-6, 7-9, 10-12, 13-15, and Not Done. A cross tabulation will also summarize ALK central vs. local lab testing results. Note that ALK central testing is based on Abbott results and ALK local testing is based on the initial testing performed at the site.

Efficacy

The best response category, overall response rate, disease control rates at weeks 6 and 12, and waterfall plot of best percentage change from baseline in target lesion tumor size by best overall response will be presented as described in the Supplemental SAP for the

Response Evaluable Population. In addition, in order to assess the relationship between ALK percentage of positive cells and response, descriptive statistics for the ALK percentage of positive cells will be presented by each best response category, and a graph of percentage positivity by best overall response will be presented.

The overall response rate observed in Study 1005 will be compared descriptively to the overall response rate of patients in ALK-negative NSCLC cohort #2 and historical controls of unselected patients as applicable.

Additional summaries may be presented to assist in the interpretation of the results. In particular, additional summaries of patients with ALK-negative NSCLC (patients for whom a low response rate would be expected) may be presented for the subset of those patients whose tumors are also documented as being neither ROS1-positive nor c-Met-amplified.

Safety

Adverse Events

The following summaries will be presented:

- TEAEs associated with permanent discontinuation by SOC and PT (all causality)
- TEAEs associated with permanent discontinuation by SOC and PT (treatment related)
- TEAEs by PT and grade in descending order (all causalities)
- TEAEs by PT and grade in descending order (treatment-related)
- Serious TEAEs by PT and grade in descending order (all causalities)
- Serious TEAEs by PT and grade in descending order (treatment-related)

Laboratory and Vital Sign Data

Laboratory data and vital signs will be summarized at a later time: the change in category shift table will be presented for vital signs, and shift tables for hematology and for chemistry will be presented. Laboratory shifts in grade will note shifts from missing/not reported, Grades 0-4 at baseline to Grade 0-5 post-baseline, omitting Grade 5 if it is always missing.

For vital signs, the maximum post-baseline changes post-baseline will be summarized as then number and percentage of patients in each of the following categories (percentages based on the number of patients having both baseline and post-baseline data):

Blood Pressure (BP)
Maximum Increase from Baseline in Systolic BP >= 40 mmHg
Maximum Decrease from Baseline in Systolic BP <= -40 mmHg
Maximum Decrease from Baseline in Systolic BP <= -60 mmHg

Maximum Increase from Baseline in Diastolic BP >= 20 mmHg
Maximum Decrease from Baseline in Diastolic BP <= -20 mmHg
Maximum Decrease from Baseline in Diastolic BP <= -40 mmHg

Pulse Rate
Maximum Pulse Rate On-study > 120 bpm
Minimum Pulse Rate On-study < 50 bpm

Maximum Increase from Baseline in Pulse Rate >= 30 bpm
Maximum Decrease from baseline in Pulse Rate <= -30 bpm

Body Weight
Maximum Increase from Baseline >= 10%
Maximum Decrease from Baseline <=-10%

For the laboratory and vital sign data, both planned and unplanned post-baseline measurement obtained during the indicated treatment periods will be included in the summary.

PK Analyses

Plasma concentrations of PF-02341066 and PF-06260182 will be listed, summarized, and plotted. Data presentation will include:

- Listing of all concentrations sorted by patient identification number and nominal time postdose. The listing of concentrations includes the actual collection times. Deviations from the nominal time are given in a separate listing.
- Summary of predose (0H) concentrations by visit and ethnicity with descriptive statistics.
- Summary of $C_{trough, ss, mean}$ by ethnicity with descriptive statistics.

Appendix 4. RIFAMPIN DDI SUB-STUDY

The purpose of this appendix is to provide detail regarding the analyses planned for the rifampin DDI sub-study. All supportive data will be listed.

Analysis Populations

Note that of the patients who were enrolled in this cohort, 3 patients (10035001, 10035002 and 10035005) did not sign HIPAA authorization. No data from these 3 patients will be included in the summaries for the rifampin DDI sub-study.

The following populations will be used specifically for the rifampin DDI sub-study and are described further in Section 5.4.6: Rifampin Sub-study Safety Population, Rifampin Sub-study PK Concentration Population, and Rifampin Sub-study PK Parameter Population. The number and percentage of patients in the rifampin DDI sub-study that are in each of these populations will be summarized.

Demographics and Baseline Characteristics

In addition to the standard demographic and baseline characteristics described in Section 8.2.1 (ie, sex, age, age category, race, height, weight, ECOG performance status, current disease stage), the following additional demographic characteristics will be summarized for this sub-study: body surface area (m^2), body mass index (kg/m^2), creatinine clearance, and renal impairment category (normal, mild, moderate or severe). For renal impairment, the categories are as follows: normal (CLcr≥90mL/min), mild (60mL/min ≤ CLcr < 90mL/min), moderate (30mL/min ≤ CLcr < 60mL/min), and severe (CLcr < 30mL/min. Summaries will be provided separately for the Rifampin Safety and PK Parameter populations.

Additional standard summaries presented for the Rifampin Safety Population will include subject disposition and primary diagnosis.

PK Analysis

Statistical Methods (PK)

The interactive effect on PK parameters will be determined by constructing 90% confidence intervals (CIs) around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS® PROC MIXED, with REML estimation method and Kenward-Roger degrees of freedom algorithm

Statistical Analysis (PK)

The primary pharmacokinetic (PK) parameters AUC_{tau} and C_{max} of PF-02341066 from the Rifampin Sub-study PK Parameter Population will be utilized to estimate the effect of rifampin on multiple-dose PK of PF-02341066. The primary parameters will be log transformed and analyzed using a mixed-effect model with treatment as the fixed effect

and patient as the random effect. Estimates of adjusted mean differences (Test-Reference) and corresponding 90% CIs for the primary parameters obtained from the model will be exponentiated to provide the ratios (Test/Reference) of adjusted geometric means and 90% CIs for the ratios for PF-02341066. PF-02341066 alone will be the Reference and PF-02341066 in the presence of rifampin will be the Test.

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

Presentation for the PK Parameter Population

The following PK parameters in the Rifampin Sub-study PK Parameter Population will be summarized for PF-02341066 and PF-06260182, respectively, by treatment (C1D15 and C2D1), as applicable.

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

* calculated by ([(AUC_{tau} or C_{max} or C_{trough}) of PF-06260182] / [(AUC_{tau} or C_{max} or C_{trough}) of PF-02341066]) × ([molecular weight of PF-02341066 {450.34}/molecular weight of PF-06260182 {464.33}]).

Box and whisker plots for individual patient parameters (AUC_{tau} and C_{max}) of PF-02341066 from the Rifampin Sub-study PK Concentration Population will be presented by treatment (C1D15 and C2D1) and overlaid with geometric means.

In addition, a listing of all PK parameters of PF-02341066 and PF-06260182, respectively, sorted by subject ID and treatment (C1D15 and C2D1) for the Rifampin Sub-study PK Concentration Population will be presented.

Presentation for the PK Concentration Population

Presentations for PF-02341066 and PF-06260182 concentrations and their molar ratios in the Rifampin Sub-study PK Concentration Population will include the following:

- A listing of all plasma concentrations of PF-02341066 and its metabolite PF-06260182 (including metabolite-to-parent ratios) sorted by subject ID, visit and nominal time postdose. The listing of plasma concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of plasma concentrations by visit and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation (SD), coefficient of variation (CV), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Median plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by visit (all visits on the same plot per scale, based on the summary of plasma concentrations by treatment and time postdose).
- Mean plasma concentrations time plots (on both linear and semi-log scales) against nominal time postdose by visit (all visits on the same plot per scale, based on the summary of plasma concentrations by treatment and time postdose).
- Individual plasma concentration time plots by visit (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each visit per scale).

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual patient plots by time, the actual PK sampling time will be used with predose time set to zero.

Safety

Adverse Events

The standard overall summary tables of AEs will be provided for (1) all causality AEs, (2) PF-02341066-related AEs, and (3) rifampin-related AEs.

TEAEs associated with permanent discontinuation of PF-02341066, (2) of rifampin, or (3) of either PF-02341066 or rifampin will be provided; frequencies of AEs within SOCs and of PTs within SOC will be presented.

Additionally, the following summaries will be presented separately for categories: (1) all causalities, (2) PF-02341066 treatment-related, (3) rifampin treatment-related, (4) PF02341066 or rifampin treatment-related, and (5) both PF-02341066 and rifampin treatment-related:

- TEAEs by PT and grade in descending order
- Serious TEAEs by PT and grade in descending order

Vital Signs

Maximum post-baseline changes through Cycle 2 Day 1 in vital signs will be summarized as then number and percentage of patients in each of the following categories (percentages based on the number of patients having both baseline and post-baseline data):

Blood Pressure (BP)
Maximum Increase from Baseline in Systolic BP >= 40 mmHg
Maximum Decrease from Baseline in Systolic BP <= -40 mmHg
Maximum Decrease from Baseline in Systolic BP <= -60 mmHg

Maximum Increase from Baseline in Diastolic BP >= 20 mmHg
Maximum Decrease from Baseline in Diastolic BP <= -20 mmHg
Maximum Decrease from Baseline in Diastolic BP <= -40 mmHg

Pulse Rate
Maximum Pulse Rate On-study > 120 bpm
Minimum Pulse Rate On-study < 50 bpm

Maximum Increase from Baseline in Pulse Rate >= 30 bpm
Maximum Decrease from baseline in Pulse Rate <= -30 bpm

Body Weight
Maximum Increase from Baseline >= 10%
Maximum Decrease from Baseline <=-10%

Laboratory Data

For each laboratory value (hematology and chemistry), the maximum CTC grade shift from baseline to post-baseline value will be presented for 2 post-baseline periods: Cycle 1 Day 1 to Cycle 1 Day 15, and Cycle 1 Day 1 through Cycle 2 Day 1. CTC Version 3 criteria will be used.

ECG Data

ECG change from baseline data will be presented for 2 post-baseline treatment periods: Cycle 1 Day 1 to Cycle 1 Day 15, and Cycle 1 Day 1 to Cycle 2 Day 1. For the treatment period "Cycle 1 Day 1 to Cycle 1 Day 15," the baseline value is the mean of the measurements at C1/D1/0H (or the mean at screening, if C1/D1/0H is missing). The number and percentage of patients in the categories of each parameter shown below will be presented (percentages based on the number of patients having both baseline and post-baseline data):

Maximum QTCB INTERVAL (BAZETT'S CORRECTION) (msec):
Change categories: <450, 450-<480, 480-<500, ≥500

Maximum PR INTERVAL Increase from Baseline (msec)
Change≥25% and Baseline Value≥200 msec
Change≥50% and Baseline Value<200 msec
None of the above

QTCF INTERVAL (FRIDERICIA'S CORRECTION) (msec)
Maximum Increase from baseline < 30 msec
Maximum Increase from baseline 30 - <60 msec
Maximum Increase from baseline >= 60 msec

QTCB INTERVAL (BAZETT'S CORRECTION) (msec)
Maximum Increase from baseline < 30 msec
Maximum Increase from baseline 30 - <60 msec
Maximum Increase from baseline >= 60 msec

HR Decrease to <50 bpm

For the vital sign, laboratory, and ECG data, both planned and unplanned post-baseline measurement obtained during the indicated treatment periods will be included in the summary.

All data will be listed for ECG and laboratory data; vital signs in specific categories will also be listed.

Appendix 5. ITRACONAZOLE DDI SUB-STUDY

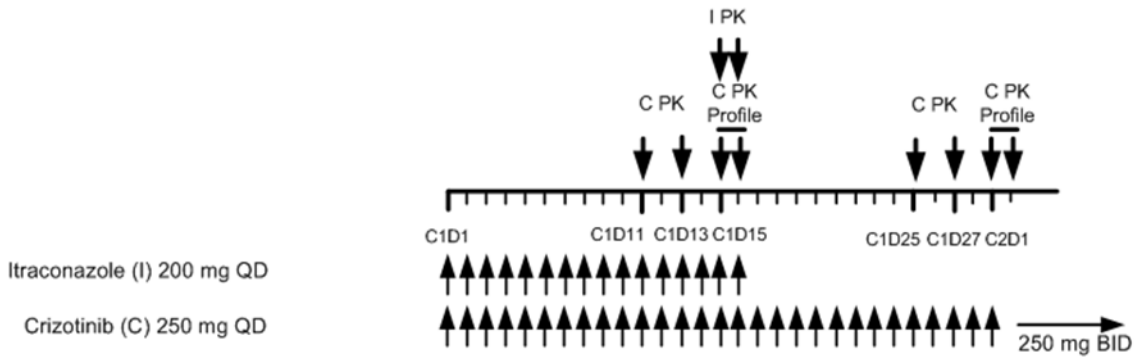
The details of the SAP as they pertain to the itraconazole DDI sub-study are included in this appendix.

Appendix 5.1. Description of the Itraconazole DDI Sub-study

This objective of this sub-study is to evaluate the effects of itraconazole on the multiple-dose plasma pharmacokinetics of PF-02341066.

The study is based on 28-day cycles and is designed to evaluate the effect of itraconazole on the multiple-dose PK of PF-02341066 (Figure 1). Approximately 25 patients will be enrolled to obtain at least 8 evaluable patients 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.

Figure 1. 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

Each patient is scheduled to receive treatment for two treatment periods in the Multiple Dose Design (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.

Following Cycle 2 Day 1, PF-02341066 250 mg BID dosing will be initiated for the remainder of the patient's participation.

Appendix 5.2. Sample Size

A total of approximately 25 patients will be enrolled into the itraconazole sub-study to obtain at least 8 PK-evaluable patients, as defined in Appendix 5.3. Eight evaluable patients will provide 90% CIs for the difference between treatments of ± 0.276 on the natural log scale for the steady state area under the curve (AUCss), with 80% coverage probability. An approximately 2-fold increase in PF-02341066 AUC_{ss} is anticipated when co-administered with itraconazole. Table 6 presents the width of 90% CIs for the AUC ratio for different estimated effects, assuming that the within-patient coefficient of variation (CV) is 25%. Sample size calculations are based on a 2-sided paired t-test with 80% tolerance probability (nQuery, Version 7.0).

Table 6. Expected Precision for Effect of Itraconazole on PF-02341066 Assessed by AUC Ratio (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

Appendix 5.3. Analysis Populations

For all patients enrolled in the itraconazole DDI sub-study, safety and PK data up to but not including the first day of PF-02341066 BID dosing (that is, data from the DDI evaluation period) will be included in the itraconazole DDI sub-study report; all PK data associated with the nominal Cycle 2 Day 1 sampling time (including the 24-hour sample) will be included or excluded together, as appropriate. Additionally, if there are any deaths that occurred within 28 days of the last day of QD dosing, they will be reported. Data not included in the DDI sub-study report will be reported separately.

Four patient populations for the analyses are defined as follows:

Safety Population: defined as all patients who received at least one dose of either PF-02341066 or itraconazole.

PK Concentration Population: defined as all patients included in the Safety Population who had at least one plasma concentration of any of the following: PF-02341066, PF-06260182, itraconazole or any itraconazole metabolites.

PK Parameter Population: defined as all patients included in PK Concentration Population who had at least one PK parameter for either PF-02341066 or PF-06260182 in at least 1 treatment period.

PK Parameter Evaluable Analysis Population: defined as all patients included in the PK Parameter Population who satisfy each of the following criteria:

- Have at least one of the PK parameters of PF-02341066 (AUC_{tau} or C_{max}) for either Treatment Period A or B; and

- Have received 10 consecutive doses of both crizotinib (250 mg QD) and itraconazole (200 mg QD) immediately prior to the end of Treatment Period A as well as 10 consecutive doses of crizotinib (250 mg QD) prior to the end of Treatment Period B.

Appendix 5.4. Itraconazole DDI Sub-study Endpoints

The PK endpoints are as follows:

- Primary PK endpoints: AUC_{tau} and C_{max} of PF-02341066 for Treatment Periods A and B.

- Secondary PK endpoints:

    - C_{min}, T_{max}, and CL/F of PF-02341066 for Treatment Periods A and B

    - AUC_{tau}, C_{max}, T_{max}, MRC_{max}, and $MRAUC_{tau}$ of PF-06260182 for Treatment Periods A and B

    - C_{trough} of PF-02341066 and PF-06260182 for Treatment Periods A and B

    - C_{trough} of itraconazole and its metabolites for Treatment Period A

Safety endpoints include the following:

- Overall safety profile of PF-02341066 including treatment-emergent AEs, as defined and graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0

- ECG, including heart rate, QT interval, QT_C, QT_CB (Bazett's correction), QT_CF (Fridericia's correction), PR interval, and QRS complex.

- Vital signs: pulse rate (beats per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C) and weight (kg).

- Laboratory values: hematology (hemoglobin, platelets, WBC, lymphocyte [absolute], neutrophils [absolute]) and serum chemistry (albumin, alkaline phosphatase, ALT, AST, bicarbonate, total bilirubin, creatinine, glucose, calcium, potassium, sodium, phosphate).

Appendix 5.5. Handling of Missing Values

Appendix 5.5.1. Concentrations Below the Limit of Quantitation

In all data presentations (except listings), PK concentrations below the limit of quantitation (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

Appendix 5.5.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set PK concentrations to missing if 1 of the following cases is true:

1. A PK concentration has been reported as ND (ie, not done) or NS (ie, no sample).
2. A deviation in sampling time is of sufficient concern or a PK concentration has been flagged anomalous by the pharmacokineticist.

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

Appendix 5.5.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters, with the following exceptions: if time of dose is missing, nominal time postdose may be used; if sample collection time is missing, the concentration may be excluded from the analysis.

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

In summary tables, statistics will be calculated by setting NC values to missing; statistics will be presented for a particular treatment period with ≥3 evaluable measurements. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing; analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual patient has a known biased estimate of a PK parameter (eg, due to missing dose(s) of PF-02341066 or itraconazole, or an unexpected event such as vomiting before all the compound was adequately absorbed in the body), this issue will be footnoted in summary tables and the value will not be included in the calculation of summary statistics or statistical analyses.

Protocol deviations that may impact estimate of a PK parameter, such as taking prohibited concomitant medications, non-compliance of dose administration of itraconazole (not taking with a standard meal), will be flagged and the potentially affected data values may or may not be included in the calculation of summary statistics or statistical analyses based upon the discretion of clinician and clinical pharmacologist. A decision not to include a particular PK parameter result will be documented.

Appendix 5.5.4. Calculation of Pharmacokinetic Parameters

Pharmacokinetic parameters for PF-02341066 and its metabolite, PF-06260182, will be calculated for each patient, as applicable, using noncompartmental analysis as shown in Table 7 and Table 8. C_{trough} values of PF-02341066, PF-06260182, itraconazole and itraconazole metabolites will be obtained for each patient, as applicable, by programming as defined in Table 7 and Table 9.

Table 7. Pharmacokinetic Parameter Definitions and Calculation Methods

Parameter	Definition	Method of Determination[†]
C_{max}	Maximum observed plasma concentration	Observed directly from data
C_{min}	Minimum observed plasma concentration	Observed directly from data
T_{max}	Time of Cmax	Observed directly from data as time of first occurrence
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval, where τ = 24 hours for QD dosing.	Linear/Log trapezoidal method.
C_{trough}[†]	Trough (predose) concentration	Observed directly from data
CL/F	Apparent clearance	Dose / AUCtau
MRC_{max}	Metabolite ratio for C_{max}	$(C_{max}/MW(parent))/(C_{max}/MW(metabolite)$[a]
$MRAUC_{tau}$	Metabolite ratio for AUC_{tau}	AUC_{tau}(parent) / AUC_{tau}(metabolite) * MW(metabolite) / MW(parent)[a]

[*] If data permit.
[†] All parameters will be derived by using noncompartmental analysis except for $C_{trough.}$
[a] MW = Molecular weight = 450.34 for parent PF-02341066, and 464.33 for metabolite PF-06261082.

Table 8. Non-compartmental PK Parameters and Types of Analysis for PF 02341066 and PF 06260182

Treatment Period: Visit	PF-02341066 PK Parameters	PF-06261082 PK Parameters	Analysis Type
A (Test): Cycle 1 Day 15	C_{max}, AUC_{tau}	C_{max}, AUC_{tau}	A, D
	T_{max}, C_{min}, CL/F	T_{max}, C_{min}, MRC_{max}, $MRAUC_{tau}$	D
B (Reference): Cycle 2 Day 1	C_{max}, AUC_{tau}	C_{max}, AUC_{tau}	A, D
	T_{max}, C_{min}, CL/F	T_{max}, C_{min}, MRC_{max}, $MRAUC_{tau}$	D

A=analyzed using statistical model, D=displayed with descriptive statistics
[*] If data permit.

Table 9. PK Parameter Ctrough and Types of Analysis for PF-02341066, PF-06260812, Itraconazole and its Metabolites

Treatment Period: Visit	PF-02341066 and PF-06261082	Itraconazole and its metabolites	Analysis Type
A (Test):			
Cycle 1 Day 11	C_{trough}		D
Cycle 1 Day 13	C_{trough}		D
Cycle 1 Day 15	C_{trough}	C_{trough}	D
Cycle 1 Day 16	C_{trough}	C_{trough}	D
B (Reference):			
Cycle 1 Day 25	C_{trough}	Not applicable	D
Cycle 1 Day 27	C_{trough}		D
Cycle 2 Day 1	C_{trough}		D
Cycle 2 Day 2	C_{trough}		D

D=displayed with descriptive statistics

Appendix 5.6. Summary and Analysis

Tables and figures that will be provided include those identified below. Listings supporting the tables will be included. Data up to but not including the first day of PF-02341066 BID dosing (that is, data from the DDI evaluation period) will be summarized. BID dosing is scheduled to start on Cycle 2 Day 2. Data not included in the DDI sub-study report will be reported separately.

The number and percentage of patients enrolled in the itraconazole DDI sub-study who are in the following populations will be summarized.

Demographics and Baseline Characteristics

In addition to the standard demographic and baseline characteristics described in Section 8.2.1 (ie, sex, age, age category [<65, >=65], race, height, weight, ECOG performance status, primary diagnosis, current disease stage), the following additional baseline characteristics will be summarized for this study: body surface area (m^2), body mass index (kg/m^2), creatinine clearance, and renal impairment category (normal, mild, moderate, or severe). For renal impairment, the categories are as follows: normal (CLcr $\geq$ 90mL/min), mild (60mL/min $\leq$ CLcr < 90mL/min), moderate (30mL/min $\leq$ CLcr < 60mL/min), and (if applicable) severe (CLcr < 30mL/min. Creatinine clearance is calculated as follows: if sex = Male: (140 - age) × weight / (72 × serum creatinine); if sex = Female: (140 - age) × weight × 0.85 / (72 × serum creatinine). Summaries will be provided separately for each of the following populations: Safety, PK Concentration, PK Parameter, and PK Parameter Evaluable Analysis. The primary diagnosis will also be summarized on the Safety Population.

Medical History

Medical history data will be listed.

Prior and Concomitant Medications

Concomitant medications starting on or after C1D1 and before the first day of BID dosing for patients in the Safety Population will be summarized as described in Section 8.2.2; prior medications will be listed with the concomitant medications. In the listings, the medication will be considered ongoing if the stop date was on or after the first day of BID dosing.

Concomitant Nondrug Treatments

Concomitant nondrug treatments and procedure will be listed.

Conduct of the Study

The number and percentage of patients in each analysis population will be summarized. Additional standard summaries presented for the Safety Population will include patient disposition and study drug administration. Study drug administration (PF-02341066 only) will be described in terms of the following items:

1. The total number of days of 250 mg QD dosing, summed over all patients.
2. Summary (median, minimum, and maximum) of patients' days of exposure (actual days of dosing). A footnote will explain the circumstances relevant to the minimum value: days of missed doses due to temporary discontinuation, permanent discontinuation, or both for the patient(s) associated with the lowest value.
3. The number (%) of patients having at least one dose interruption of PF-2341066 while on 250 mg QD dosing.

Patient evaluability will be summarized for the each population.

Statistical Methods (PK)

Each PK parameter analyzed with statistical methods will be log-transformed (natural log) prior to analysis. After transformation, data for Test and Reference treatments will be analyzed using a mixed effects model with treatment as the fixed effect and patient as the random effect, implemented using SAS PROC MIXED with REML estimation method and Kenward-Roger degrees of freedom algorithm. In each case, the estimate of adjusted mean difference (Test-Reference) and corresponding 90% CI for the parameter obtained from the model will be exponentiated to provide the ratio (Test/Reference) of adjusted geometric means and 90% CIs for the ratio.

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

Primary PK Analysis

The primary PK parameters, AUC_{tau} and C_{max}, of PF-02341066 for Treatment Periods A and B from the PK Parameter Evaluable Analysis Population will be utilized to estimate the effect of multiple-dose itraconazole on the multiple-dose PK of PF-02341066. Each PK parameter will be log transformed and analyzed as described above. PF-02341066 alone (Treatment Period B) will be the Reference and PF-02341066 in combination with itraconazole (Treatment Period A) will be the Test.

Exploratory PK Analysis

The PK parameters, AUC_{tau} and C_{max}, of PF-06260182 for Treatment Periods A and B from the PK Parameter Evaluable Analysis Population will be utilized to estimate the effect of multiple-dose itraconazole on the PK of PF-06260182. Each PK parameter will be log transformed and analyzed as described above

PK Summary

Summary statistics will include a standard set of descriptive statistics, as follows: n, mean, median, standard deviation (SD), coefficient of variation (CV), minimum, maximum, and the number of concentrations above the lower limit of quantitation.

The statistics as shown in Table 10 will be presented for PK parameters by visit/treatment period for PF-02341066 and PF-06260182 as well as itraconazole and its metabolites, as applicable.

Table 10. Descriptive Statistics Used to Summarize Each PK Parameter

Parameter	Summary statistics
AUC_{tau} C_{max} C_{min} C_{trough} CL/F	N, arithmetic mean, median, CV%, SD, minimum, maximum, geometric mean, and geometric CV%
T_{max}	N, median, minimum, maximum
$MRAUC_{tau}$[a] MRC_{max}[a] MRC_{trough}[a]	N, arithmetic mean, median, CV%, SD, minimum, maximum

[a] calculated as follows:

([(AUC_{tau} or C_{max} or C_{trough}) of PF-06260182] / [(AUC_{tau} or C_{max} or C_{trough}) of PF-02341066]) × ([molecular weight of PF-02341066 {450.34 g/mol}/molecular weight of PF-06260182 {464.33 g/mol}]).

For AUC_{tau} and C_{max} of PF-02341066 and PF-06260182, a listing of the individual patient ratios (Test/Reference) will be provided. Box and whisker plots (median, and first and third quartiles [25^{th} and 75^{th} percentiles] with whiskers to the last data point within 1.5 × interquartile range) for individual patient parameters (AUC_{inf} and C_{max}) will be presented by treatment, overlaid with geometric means and individual values.

In addition, descriptive statistics and listings of all available PK parameters of PF-02341066 and PF-06260182, as well as itraconazole and its metabolites, sorted by patient ID and visit, will be presented in tabular form.

For summary statistics, median and mean plots of PK concentrations of PF-02341066 and PF-06260182 by sampling time, the nominal PK sampling time will be used. For individual patient plots by time, the actual PK sampling time will be used except the predose time is set to zero.

Presentations for the PK Concentration Population include, but are not limited to, the following:

For PF-02341066 and PF-06260182:

- A listing of all plasma concentrations of PF-02341066 and its metabolite PF-06260182 (including metabolite-to-parent ratios) sorted by patient ID, visit and nominal time postdose. The listing of plasma concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of plasma concentrations of PF-02341066 and PF-06260182 (including metabolite-to-parent ratios) by visit and nominal time postdose, using the standard set of summary statistics.

- Median plasma concentrations of PF-02341066 and PF-06260182 vs time plots (on both linear and semi-log scales) against nominal time postdose by visit.

- Mean plasma concentrations of PF-02341066 and PF-06260182 time plots (on both linear and semi-log scales) against nominal time postdose by visit.

- Individual plasma concentration of PF-02341066 and PF-06260182 vs time plots by visit (on both linear and semi-log scales) against actual time postdose.

For itraconazole and its metabolites:

- A listing of all plasma concentrations of itraconazole and its metabolites sorted by patient ID, visit and nominal time postdose. The listing of plasma concentrations will include the actual times.

- A summary of plasma concentrations of itraconazole and its metabolites by visit and nominal time postdose, using the standard set of summary statistics. Deviations from the nominal time will be given in a separate listing.

Presentations for the PK Parameter Population include, but are not limited to, the following:

For PF-02341066 and its metabolite PF-06260182:

- A summary of plasma concentrations of PF-02341066 and PF-06260182 by visit and nominal time postdose, using the standard set of summary statistics.

- Median plasma concentrations of PF-02341066 and PF-06260182 vs time plots (on both linear and semi-log scales) against nominal time postdose by visit.

- Mean plasma concentrations of PF-02341066 and PF-06260182 vs time plots (on both linear and semi-log scales) against nominal time postdose by visit.

- Descriptive statistics and listing of all PK parameters of PF-02341066 and of PF-06260182, by patient ID and visit.

For itraconazole and its metabolites:

- A summary of plasma concentrations of itraconazole and its metabolites by visit and nominal time postdose, using the standard set of summary statistics.

- Descriptive statistics and listing of all PK parameters of itraconazole and of its metabolites, by patient ID and visit; in this report, the only PK parameter reported for itraconazole and for its metabolites is C_{trough}.

Presentations for the PK Parameter Evaluable Analysis Population include, but are not limited to, the following:

For PF-02341066 and its metabolite PF-06260182:

- A summary of plasma concentrations of PF-02341066 and PF-06260182 by treatment (Treatment Periods A and B) and nominal time postdose, using the standard set of summary statistics.
- Median plasma concentrations of PF-02341066 and PF-06260182 vs time plots (on both linear and semi-log scales) against nominal time postdose by treatment (Treatment Periods A and B).
- Mean plasma concentrations of PF-02341066 and PF-06260182 vs time plots (on both linear and semi-log scales) against nominal time postdose by treatment (Treatment Periods A and B).
- Summary statistics of PK parameters of PF-02341066 and of PF-06260182, by treatment (Treatment Periods A and B).
- Box and whisker plots for individual patient parameters, AUC_{tau} and C_{max} of PF-02341066 and of PF-06260182 by treatment (Treatment Periods A and B) and overlaid with geometric means.

For itraconazole and its metabolites:

- A summary of plasma concentrations of itraconazole and its metabolites by visit and nominal time postdose, using the standard set of summary statistics.

- Descriptive statistics and listing of all PK parameters of itraconazole and of its metabolites, by patient ID and visit; in this report, the only PK parameter reported for itraconazole and for its metabolites is C_{trough}.

Safety

Adverse Events

All AEs with a start date before the first day of BID dosing will be listed but only TEAEs will be summarized. A TEAE is any AE that starts after the first dose of study drug (Cycle 1 Day 1) or is a pre-existing condition that worsens after the initiation of PF-02341066 treatment. In the listings, the AE will be considered "ongoing" if the stop date was on or after the first day of BID dosing. In particular, although not expected, should there be a grade 5 AE with a recorded start date before the BID dosing and a recorded stop date after BID dosing, for programming purposes, this will be considered "ongoing" in listings. Deaths within 28 days of the last day of QD dosing will be separately reported and, if any, listed.

The standard overall summary tables of TEAEs will be provided by relationship to study drug, based on the Safety Population: (1) all causality, (2) PF-02341066-related only, (3) itraconazole-related only, and (4) both PF-02341066 and itraconazole-related. These tables include the number of patients evaluable for AEs, the number of AEs, and the number and percentage of patients having: AEs, SAEs, grade 3 or 4 AEs, grade 5 AEs, AEs associated with permanent discontinuation from treatment that occurred prior to BID dosing, and AEs associated with temporary discontinuation of treatment that occurred prior to BID dosing. Note that a dose reduction prior to BID dosing was not allowed.

TEAEs (by system organ class and preferred term in descending order) associated with permanent discontinuation of (1) PF-02341066 (only PF-2341066), (2) of itraconazole (only itraconazole), or (3) of both PF-02341066 and itraconazole will be provided based on the Safety Population separately for all causality and for treatment related TEAEs; a listing of all TEAEs associated with permanent discontinuation will also be shown. Also, TEAEs (by system organ class and preferred term in descending order) associated with temporary discontinuation of PF-02341066 (with or without the simultaneous permanent discontinuation of itraconazole) will be provided based on the Safety Population separately for all causality and for treatment related TEAEs. All TEAEs associated with temporary discontinuation or dose reduction will also be provided in a standard listing. However, the listing will footnote the fact that dose reductions of PF-02341066 prior to BID dosing were not allowed in the protocol and dose reductions of itraconazole are not allowed; accordingly tables of TEAEs associated with dose reductions will not be presented in this report, which addresses results up until the start of BID dosing.

Additionally, summary tables based on the Safety Population will be presented separately for the following categories of TEAEs: (1) all causalities, (2) PF-02341066-only, (3) itraconazole-related only and (4) PF-02341066-related and itraconazole-related:

- TEAEs by PT (or clustered term) and maximum CTC grade in descending order of frequency

- Serious TEAEs by PT (or clustered term) and maximum CTC grade in descending order of frequency

Each of the tables presented by PT or clustered term will have a corresponding table in which the PTs within each cluster term are displayed by maximum CTC grade. The clustered terms will be sorted in descending order of frequency, and then the PTs within clustered term will be sorted in descending order of frequency.

Laboratory Data, ECG Data, and Vital Signs

These summaries will be provided for the Safety Population. All data with a measurement date before the first date of BID dosing will be listed.

Laboratory Data

For each laboratory value (hematology and chemistry), the maximum CTC grade shift from baseline to post-baseline value will be presented for 2 time intervals: Cycle 1 Day 1 through Cycle 1 Day 15, and Cycle 1 Day 1 through Cycle 2 Day 1. Scheduled and unscheduled data will be included in the appropriate interval(s). The summary tables will footnote that all data collected up to but not including the first day of BID dosing are included in the "Cycle 1 Day 1 through Cycle 2 Day 1" interval. CTCAE Version 3.0 criteria will be used. It will be noted that CTCAE grading criteria for hypercalcemia and hypocalcemia will be applied to serum calcium values without correction for albumin. Baseline is defined as Cycle 1 Day 1 (predose); if missing, then the measurement collected at screening will be used. If there are multiple baseline results, the result closest to Cycle 1 Day 1 (predose) will be used.

ECG Data

ECG data summaries based on the categories described in Appendix 4 will be presented for 2 post-baseline time intervals: Cycle 1 Day 1 through Cycle 1 Day 15, and Cycle 1 Day 1 through Cycle 2 Day 1. Scheduled and unscheduled data will be included in the appropriate interval(s). The summary tables will footnote that all data collected up to but not including the first day of BID dosing are included in the "Cycle 1 Day 1 through Cycle 2 Day 1" interval. Baseline is defined as the mean of predose measurements on Cycle 1 Day 1; if missing, then the mean of measurements collected at screening will be used.

In addition, each parameter will be summarized using descriptive statistics for the observed values and changes from baseline as described in Section 8.2.2.6 at each of the following scheduled timepoints (predosing at 0 hours, and 1 and 4 hours postdosing, as indicated):

Cycle 1 Day 1 0H
Cycle 1 Day 1 1H
Cycle 1 Day 1 4H
Cycle 1 Day 15 0H
Cycle 1 Day 15 1H
Cycle 1 Day 15 4H
Cycle 2 Day 1 0H
Cycle 2 Day 1 4H

Vital Sign Data

Vital sign data summaries based on the categories described in Appendix 4 will be presented for the time interval Cycle 1 Day 1 through Cycle 2 Day 1; the summary table will footnote that scheduled and unscheduled data collected up to but not including the first day of BID dosing are included. There is no summary through Cycle 1 Day 15 because vital signs are only scheduled to be collected on Day 1 of each cycle. In these summaries, baseline is defined as Cycle 1 Day 1 (predose); if missing, then the measurement collected at screening will be used.

Vital signs data for pulse rate, systolic blood pressure, diastolic blood pressure, temperature, and weight at baseline and each scheduled assessment time, will be summarized using descriptive statistics as described in Section 8.1.2; change from baseline summaries will be included.

PROTOCOL A8081001

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

SUPPLEMENTAL STATISTICAL ANALYSIS PLAN (SAP) FOR ALK-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC), ROS1-POSITIVE AND MET EXON 14 ALTERATIONS NSCLC PATIENTS

Version: 1.5

[redacted]

Date: 27 February 2018

[redacted]

[redacted]

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

The main change in this document from version 1.4 (dated May 4, 2016) is as follows:

- Updated document to also serve as a supplemental SAP for NSCLC patients with tumors harboring MET exon 14 alterations (hereafter referred to as MET exon 14 alterations NSCLC patients) given that similar analyses (eg, independent review--IRR) may be done for this cohort as for the ALK-positive NSCLC cohort and ROS1-positive NSCLC patients.

- Added biomarker analysis sets, biomarker endpoints and analysis methods for MET exon 14 alterations NSCLC patients.

The main changes in version 1.4 from version 1.3 (dated February 27, 2015) are as follows:

- Updated wording on missing date imputation and changed how missing dates are imputed for the ROS1 data.

- Added “abdominal pain” and “blood creatinine increase” to the list of AEs of special interest for the ROS1 patients.

- For ROS1 patients, specified in more detail both the calculation of time to progression for the most recent prior therapy and the analysis comparing the time to progression on crizotinib to the time to progression on the most recent prior therapy.

- Reworded the ROS1 analysis population definitions for clarity.

- Added computational details for the Kaplan-Meier results, the exact method based on the F-distribution, and the recurrent event analysis for TTP.

- Clarified how AEs that start in Follow-up are counted in the prevalence tables.

The main changes in version 1.3 from version 1.2 (dated April 29, 2013) were:

- Updated document to also serve as a supplemental SAP for the ROS1-positive NSCLC patients given that similar analyses (eg, independent review--IRR, clustered terms for related AEs) may be done for this cohort as for the ALK-positive NSCLC cohort.

- Updated sections as necessary to accommodate the inclusion in the analyses of the ROS1-positive patients the 3 ROS1-positive patients enrolled in the ALK-negative Cohort #2.

- Removed list of clustered adverse events (Appendix 1) and replaced with reference.

- Moved former Appendix 2 to Appendix 1, clarified that Appendix 1 pertained to the ALK-positive NSCLC cohort, and added Appendix 2 to describe the analyses of AEs and clustered AEs of special interest for the ROS1-positive NSCLC patients.

- Added note to clarify that confirmation of response is required when applying RECIST 1.1 to the ALK-negative NSCLC cohort given that this is a one-arm study with response as a key endpoint.
- For the definition of endpoints in weeks, updated to divide data in days by 7 (vs. 7.02).
- Updated Section 1 to include a cumulative list of amendments from prior versions.
- Added more detail to Appendix 5.
- Changed references to the ROS marker to ROS1.
- Corrected and clarified the analysis of IRR results.
- Slightly modified the OS definition to remove unnecessary limitations, allowing the protocol to determine the duration of follow-up.
- Corrected typographical errors and added minor clarifications.

The main changes in version 1.2 from version 1.1 (dated October 27, 2010) were:

- Update OS definition to include censoring of patients who completed the required per protocol 1 year follow-up with no further follow-up planned. Also clarified the use of the Subject Summary CRF page to censor OS for patients who withdraw from the study.
- Updated clustered terms to be consistent with the recently updated clustered terms used across PF-02341066 studies.
- Updated censoring definition for duration of AE in Appendix 3 for cases where date of death is the same as the date of resolution of the AE.
- Clarified the data available for subsequent anti-cancer treatment on Subject Survival page in Appendix 4.
- Removed statement in footnote of response table in Appendix 4 stating that patients must have measurable disease at baseline since this requirement was removed.
- Added Appendix 5 to describe evaluation of response for ALK-negative NSCLC patients.

Other more minor changes were made. Those made in version 1.2 include:

- Updated definition of last available on treatment visit date described in Appendix 3 to include additional PK pages for consistency across PF-02341066 studies.
- Clarified the acceptable time window for an adequate baseline tumor assessment in Appendix 4.

- Added more detail about the type of protocol deviations that may be summarized in Section 5.5.

- Clarified which patients are excluded from the waterfall plot described in Section 8.1.1.

- Clarified that the ALK- NSCLC Cohort referred to in Section 8.1.4 is the ALK- NSCLC Cohort #1.

The main changes in version 1.1 from version 1.0 (dated April 4, 2010) were:

- Analysis of time to response (TTR) updated to be performed by descriptive statistics for subgroup of responders versus Kaplan-Meier (KM) method. Time intervals for categorical summary of TTR also specified.

- Description of estimated KM curves updated to include display of 95% Hall-Wellner confidence bands.

- Duration of follow-up analyses for PFS and OS based on the reverse Kaplan-Meier method added.

- Description of waterfall plot added.

- Time to AE onset and time to Grade 3/4 AE onset updated to be performed by descriptive statistics for the subgroup of patients with the specified AE.

- Shift tables of AE prevalence by grade removed.

- Diagnostic concordance analyses (Section 8.1.5) updated.

- Appendix 4 added to include documentation of programmatic assessment of tumor data.

The other changes made in version 1.1 include:

- Clarification added that standard analyses (Section 8.2.1) will be performed using the safety population.

- 'Alanine aminotransferase' updated to be defined as a clustered AE. 'Orthostatic hypotension' removed from 'neuropathy' clustered term. 'Localized oedema' added to 'oedema' clustered term.

- Consideration of laboratory abnormalities associated with AEs in special AE analyses removed (ie, analyses will be based on AE data only).

- Definition of last available on treatment visit date used in censoring for duration of AE analyses was updated (Appendix 3 was added).

2. INTRODUCTION

This document is a supplemental SAP that describes the details of the statistical analyses and summaries for the following patients groups: ALK-positive non-small cell lung cancer (NSCLC) cohort, ROS1-positive NSCLC patients and MET exon 14 alterations NSCLC patients.

This analysis plan is meant to supplement the study protocol and main SAP. Any deviations from this supplemental analysis plan will be described in the Clinical Study Report.

2.1. Study Design

This is an open label, multi-center, Phase 1, dose escalation, safety, pharmacokinetic and exploratory study. A cohort of ALK-positive NSCLC patients were recruited in the RP2D enriched population cohorts. In addition, a cohort of ROS1-positive NSCLC patients and a cohort of MET exon 14 alteration NSCLC patients were also recruited into the RP2D enriched population. The ROS1-positive NSCLC patients include the patients enrolled in the ROS1-positive NSCLC cohort as well as 3 ROS1-positive patients enrolled in the ALK-negative NSCLC cohort #2; see Section 8.1.1 details. Note that "ROS" and "ROS1" are used interchangeable in study documentation.

The MET exon 14 alteration NSCLC patients will be selected considering:

- who are enrolled in "SUBGROUP 17" on the *Subject Randomization CRF;*
- AND "Result Classification" = "Positive" on the *Diagnostic Marker Test – cMET CRF (*UNPL_DIAG_CMET3*)*;
- AND primary diagnosis is NSCLC (code 10029664).

Further details about the study design can be found in the main SAP and protocol.

2.2. Study Objectives

The study objectives are documented in the main SAP (Section 2.2) and protocol (Section 2).

3. INTERIM ANALYSES, FINAL ANALYSES, AND UNBLINDING

This is an open label, single-arm trial for which no formal interim analysis is planned. The final analysis will be performed after the last patient last visit; however, earlier analyses of the data may be performed for publication and regulatory reporting purposes.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No formal statistical hypothesis testing was planned for the ALK-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 were originally to 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 were to be enrolled into this cohort to adjust for 10% loss of patients who are not evaluable for response.

As of 19 April 2012, 8 confirmed objective responses (complete response [CR], partial response [PR]) were observed in a total of 14 response evaluable patients enrolled in the ROS1-positive NSCLC cohort. Based on the number of confirmed objective responses observed, the null hypothesis was rejected. As recorded in the Note to File dated 12 November 2012, and in Protocol Amendment 20 (Appendix 16.1.1), the sample size of the ROS1-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.

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 $\geq$7 objective responses are observed among the first 33 evaluable patients.

As of 01 August 2016, 11 confirmed objective responses (CR, PR) were observed in a total of 28 response evaluable patients with MET exon 14 alterations NSCLC. Based on the number of confirmed objective responses observed, the null hypothesis was rejected and with Protocol Amendment 23 the sample size for NSCLC patients with tumors harboring MET exon 14 alterations was increased to approximately 50 patients and a separate group of approximately 5 NSCLC patients with tumors harboring MET exon 14 alterations to be enrolled at clinical sites in Japan was added.

With a Protocol Administrative Clarification Letter (PACL) (dated 15 May, 2017), 13 enrollment slots in the MET intermediate amplification group were transferred to the Enriched Other cohort to facilitate further enrollment of NSCLC patients with tumors harboring MET Exon 14 alterations. As a result of this PACL, the total enrollment for NSCLC patients with tumors harboring MET Exon 14 alterations was increased to 68 patients (50 original patients + 13 transferred slots + 5 Japanese patients).

With a second PACL dated 7 December, 2017 an additional 13 NSCLC patients with tumors harboring MET Exon 14 alterations were allowed to be enrolled into the Enriched Other cohort. The additional 13 enrollment slots were originally slotted for the Enriched Other cohort and were then assigned specifically to NSCLC patients with tumors harboring MET Exon 14 alterations rather than the broader Enriched Other cohort. The additional 13 patients brought the total enrollment of the Enriched Other cohort subset of MET Exon 14 NSCLC patients to 81 (68 + 13 slots).

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS POPULATIONS

The following analysis populations will be used for the subset of ALK-positive NSCLC patients, for the subset of ROS1-positive NSCLC patients and also for the subset of MET exon 14 alterations NSCLC patients. Of note, three patients enrolled in the ALK-negative NSCLC cohort #2 were retrospectively determined to be ROS1-positive, and these patients will be included with the ROS1-positive NSCLC patients (see Section 8 for details).

5.1. Safety Analysis Set

The safety analysis (SA) set will include all enrolled patients who receive at least one dose of PF-02341066 on Cycle 1, Day 1. This is the primary population for all standard analyses (Section 8.2.1 of the main SAP) and safety analyses (Section 8.2.2 of the main SAP and Section 8.1.2 of the supplemental SAP).

5.2. Response – Evaluable (RE) Population

The response-evaluable population is defined as all patients in the safety analysis set who have an adequate baseline disease assessment (definition for adequate baseline tumor assessment is reported in Appendix 5 and Appendix 6).

In addition, for any interim reporting of the data, patients also need to meet at least 1 of the following 2 criteria:

- had at least one post-baseline disease assessment at least 6 weeks from first dose.
- withdrew from the trial or experienced progressive disease/death at any time on study.

5.3. Evaluable Sets for PK Analyses

ALK-Positive NSCLC Cohort

The following PK populations will be used for the ALK-positive NSCLC cohort:

5.3.1. PK Concentration Analysis Set

The PK concentration population of PF-02341066 is defined as all patients in the safety population who have at least 1 concentration of PF-02341066 (including its active moieties, if appropriate).

5.3.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all patients in the safety population who have at least 1 of the PK parameters of interest for PF-02341066 (including its active moieties, if appropriate).

ROS1-Positive NSCLC and MET Exon 14 alterations NSCLC

The following PK populations will be used for the ROS1-positive and for the MET exon 14 alterations NSCLC patients:

PK Concentration Evaluable population (PKP_C): All patients in (SA) population who have at least 1 concentration of PF-02341066 following treatment.

PK Predose (0 H) Concentration Evaluable population (PKP_Ctrough): All patients in the PK Concentration Evaluable population who have at least one predose (0 H) concentration of PF-02341066, of which sample is collected between -1.2 H to 0 H of a.m. dosing on the PK collection day, or if the a.m. dose is not done on the PK collection day, 10.8 H to 13.2 H of p.m. dosing on the prior day.

PK Steady State Predose (0 H) Concentration Evaluable population (PKP_Ctrough,ss): All patients in the PK Predose Concentration Evaluable population who have 14 consecutive days of 500 mg daily dose prior to the PK sample collection and who have at least one predose (0 H) concentration on C1D15 or later, and of which sample is collected between -1.2 H to 0 H of a.m. dosing on the PK collection day, or if the a.m. dose is not done on the PK collection day, 10.8 H to 13.2 H of p.m. dosing on the prior day.

- In this study, the 500 mg daily dose was administered as 250 mg BID. Also, for clarification "and later" refers to "and later visits."

5.4. Biomarker Analysis Sets

MET Exon 14 alterations NSCLC

For the MET exon 14 alterations NSCLC patients, archival tumor tissue and baseline/end of treatment plasma samples were collected from consented patients. Tumor tissue biomarker analysis using Next Generation Sequencing (NGS) will be performed on all subjects with available tissue at the central laboratory Foundation Medicine, Inc. (FMI) and may also be performed at Cancer Genetics, Inc. (CGI) . Multiple site tumor testing is attributed to Companion Diagnostic (CDx) strategy changes with the central laboratory test at FMI being the test of reference supporting the CDx analyses. Plasma (ctDNA) biomarker analysis using NGS will be performed at Personal Genome Diagnostics (PGDx) . Biomarker analysis sets are defined as follows:

- Tumor tissue NGS biomarker analysis set (FMI): consists of patients with tumor tissue available for central testing at FMI.
- Tumor tissue NGS biomarker analysis set (CGI): consists of patients with tumor tissue that was sent for analysis at CGI.
- Plasma ctDNA NGS biomarker analysis set: consists of patients with plasma (ctDNA) samples that were sent for analysis at PGDx.

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

All deviations will be described when they appear and relate to the statistical analyses or analysis populations. Deviations will be summarized separately from the database and may include, but are not limited to: eligibility violations, deviations from the conduct of the study after start of study treatment, or cases where study evaluations were not performed as required by the protocol.

5.7. Sub-Populations

The patients in the safety population and response-evaluable population may be further divided into sub-populations according to baseline demographics and disease characteristics (eg, lines of previous anti-tumor treatments, ethnicity, gender, and ECOG performance status). Analyses of sub-populations are further described in Section 8.1.7

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

The following endpoints will be used to evaluate the anti-tumor activity of PF-02341066 for the subgroups of ALK-positive NSCLC patients, of ROS1-positive NSCLC patients and of MET exon 14 alterations NSCLC patients.

All efficacy analyses for CSR reporting dependent on disease assessments (objective response rate - ORR, disease control rate - DCR, duration of response - DR, time to response - TTR, progression-free survival-PFS, and time to progression - TTP) will be based on the derived investigator assessment of tumor data as further described in Appendix 5 and Appendix 6. Additional efficacy analyses based on the independent radiology review (IRR) of tumor data are described in Section 8.1.4.

For the purposes of the definitions of efficacy endpoints, the term “on study” includes the period from the date of the first dose until 35 days after the last dose of study medication (28 days + 1 week allowance). However, deaths will be included in the PFS analysis if they occur within 16 weeks (14 weeks for patients in the ALK-negative cohort #2) from the last tumor assessment on study and will be included in the overall survival (OS) analysis irrespective from their timing of occurrence. In the following definitions, ‘first dose’ refers to the Cycle 1, Day 1 dose (ie, the single Day -7 dose that was administered to patients enrolling prior to Amendment 16 is not included.)

Note that scheduled, post-baseline tumor assessments for the subgroup of ALK-positive NSCLC, ROS1-positive NSCLC and MET exon 14 alterations NSCLC patients were to be performed every other cycle (cycle length is 4 weeks; 3 weeks for the ALK-negative NSCLC cohort #2), 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. As of protocol Amendment 20, once a patient has completed 15 cycles, tumor imaging may be performed every fourth cycle (every 12 or 16 weeks, depending on the cycle length). For patients on 4-week cycles, once a patient has completed 24 cycles, tumor imaging may be performed every sixth cycle (every 24 weeks). For patients on 3-week cycles, once a patients 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.

- **Objective Response Rate (ORR)** is defined as the percent of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST (1.0)[1] or RECSIT 1.1[2] (ALK-negative cohorts only) relative to the RE population. Confirmed responses are those that persist on repeat imaging study at least 4 weeks after the initial documentation of response.

Patients will be considered non-responders until proven otherwise. Thus, patients will be counted as non-responders in the assessment of ORR if they:

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

- **Duration of Response (DR)** is defined as the time (in weeks or months) from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed, to the first documentation of objective tumor progression or death on study due to any cause, whichever occurs first. If tumor progression data include more than 1 date, the first date that tumor progression is documented will be used. For those with confirmed CR or PR, DR (in weeks or months) will be calculated as (first date of PD or death − first date of CR or PR +1)/7 (30.44 for months). Censoring for DR is identical to the censoring rules presented for PFS when patients have at least 1 on study disease assessment. DR will be calculated based on RE population for the subgroup of patients with a confirmed objective tumor response.

- **Time to Response (TTR**) is defined as the time (in weeks) from the date of first dose to first documentation of objective tumor response (CR or PR) that is subsequently confirmed. For patients proceeding from PR to CR, the onset of PR is taken as the onset of response. If lesion assessment data include more than 1 date, the date of the last assessment that confirmed lack of progression will be used. TTR will be calculated as (first response date − first dose date +1)/7. Time to response will be calculated for the RE population for the subgroup of patients with a confirmed objective tumor response.

- **Disease Control Rate (DCR) at weeks 8 and 16** is defined as the percent of patients with a confirmed CR, confirmed PR or stable disease (SD) according to RECIST 1.0 (or 1.1 for ALK-negative patients) based on the response at weeks 8 and 16, relative to the RE population. The best response of stable disease (SD) can be assigned if SD criteria were met at least once after the date of the first dose at a minimum interval of 6 weeks. If the response is observed prior to the indicated time (prior to 56 days for 8 weeks or prior to 112 days for 16 weeks) but progression is recorded at the next subsequent assessment time, then the disease is not considered controlled at the indicated time.

- **Progression Free Survival (PFS)** is defined as the time from the date of first dose to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurs first. PFS (in months) will be calculated as (first event date − first dose date +1)/30.44. PFS will be summarized for the SA population.

  Patients with inadequate baseline assessments will have their event time censored on the date of first dose. Patients lacking an evaluation of tumor response after the date of the first dose or for whom the first on study tumor assessment occurs after 16 weeks, will also have their event time censored on the date of the first dose unless death occurs within (and including) 16 weeks (in which case the death is an event). For the ALK-negative NSCLC cohort #2 patients evaluated using RECIST 1.1, 14 weeks was used in lieu of 16 weeks in these assessments.

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

  - Who are alive, on study and progression free at the time of the analysis;
  - Who discontinue treatment without documented disease progression and who do not die on study;
  - Who have documentation of disease progression more than 35 days after treatment end date or died more than 16 weeks (14 weeks for ALK-negative patients) after the last on study tumor assessment;
  - Who have documentation of disease progression or death on study after > 16 weeks after the last on-study tumor assessment (>14 weeks for ALK-negative patients). The 16 weeks duration is derived from 8-weeks assessment intervals, which in turn are based on two 4-weeks dosing cycles. The 14 weeks duration for ALK-negative patients is derived from two, 7-week assessment intervals (6 weeks + 1 week allowance per protocol based on 3-weeks-dosing cycle). The 16-week gap (14 week gap for ALK-negative patients) is maintained even if the assessment intervals are extended once patients are enrolled for an extended period. Note: if disease progression is documented after >16 weeks (>14 weeks for ALK-negative patients) for patients under Protocol Amendment 20 allowing for tumor assessments every 24 weeks, once a patient has completed 24 cycles (35 cycles for ALK-negative patients), additional censoring rules may be considered (eg, considering PD when it occurs).
  - Who are given anti-tumor treatment other than the study medication while on study and prior to documented disease progression or death on study. In this case, the last evaluable assessment prior to start of the anti-tumor treatment will be used. One exception to this rule is for patients who have documented PD or death within (and including) 14 days of anti-cancer systemic therapy, the PD or death will be considered an event.

- **Probability of PFS at 6-months** is defined as the probability of being alive and progression-free at six-months after the date of first dose based on the Kaplan-Meier estimate.[3]

- **Time to Progression (TTP)** is defined as the time (in months) from the date of first dose to the date of the first documentation of objective tumor progression. If tumor progression data include more than 1 date, the first date will be used. TTP (in months) will be calculated as (first event date − first dose date +1)/30.44. TTP will be calculated for ROS1-positive NSCLC and MET exon 14 alterations NSCLC patients in the SA population.

  Patients with inadequate baseline assessments will have their event time censored on the date of first dose. Patients lacking an evaluation of tumor response after the date of the first dose or for whom the first on study tumor assessment occurs after 16 weeks will also have their event time censored on the date of the first dose. For patients in the ALK-negative NSCLC cohort, 14 weeks will be used in lieu of 16 weeks in these assessments.

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

  - Who are alive, on study and progression free at the time of the analysis;
  - Who died without documented disease progression;
  - Who had documentation of disease progression more than 35 days after treatment end date;
  - Who have documentation of disease progression on study after ≥2, consecutive missed tumor assessments (ie, >16 weeks [or >14 weeks for patients in the ALK-negative NSCLC cohort] after last on-study tumor assessment). Note: if disease progression was documented after >16 weeks (>14 weeks for the ALK-negative NSCLC cohort) for patients under Protocol Amendment 20 allowing for tumor assessments every 24 weeks, once a patient had completed 24 cycles (35 cycles for the ALK-negative NSCLC cohort), additional censoring rules could be considered (eg, considering PD when it occurred);
  - Who are given anti-tumor treatment other than the study medication prior to documented disease progression on study. In this case, the last evaluable assessment prior to start of the anti-tumor treatment will be used. One exception to this rule is for patients who have documented PD within (and including) 14 days of anti-tumor treatment, in which case, the PD will be considered an event.

- **Overall survival (OS)** is defined as the time from the date of the first dose to the date of death due to any cause. OS (in months) is calculated as (date of death − first dose date +1)/30.44. For patients still alive at the time of the analysis, for those lost to follow-up and those who indicate that the patients completed the protocol-required follow-up with no further follow-up planned, the OS will be censored on the last date that patients were known

to be alive. OS will be summarized for the SA population. Note that this study has only a Subject Summary CRF page that captures reason for End of Treatment (EOT) (ie, does not have an End of Study [EOS] CRF). For OS, patients who withdraw consent will have their OS censored on the date the patient withdrew consent. Patients lacking any data beyond the first dose will have their OS censored at the date of first dose.

- **Probability of survival at 6 months and 1 year** are defined as the probability of survival at six-months and one year, respectively, after the date of first dose based on the Kaplan-Meier[3] estimate.

Date of PD for Duration of Response, TTP (for ROS1-positive NSCLC patients and for MET Exon 14 alteration NSCLC patients), and PFS

In case of multiple radiographic assessments performed at different timing in the same visit the date of PD will be the earliest date of:

- Last assessment date for target lesions (in the same visit) if the sum of lesion dimensions (SLD) meets the criteria for progression;

- Last assessment date for non-target lesions (in the same visit) if PD is documented based on the non-target response;

- Earliest date of new lesion dates (in the same visit).

In addition, for the ROS1 and MET exon 14 alterations patients, the TTP (in months) of the last prior treatment regimen before crizotinib will be calculated from the first dose date of the last prior treatment regimen to the date of progression: (progression date − first dose date +1)/30.44. Patients without a progression date will be censored to the last dose date of the last prior treatment regimen. If there are multiple drugs in the prior regimen, the earliest start date and latest end date will be used. TTP will be calculated for patients with ROS1-positive NSCLC and for patients with MET exon 14 alterations in the SA population with at least 1 prior anticancer regimen for advanced/metastatic disease. The median event time (and other percentiles) and 2-sided 95% CI for the median will be provided.

6.2. Safety Endpoints

For the ALK-positive NSCLC, the ROS1-positive NSCLC and the MET exon 14 alterations patients in the enriched population cohorts, safety endpoints include those described in Section 6.1 of the main SAP and the following additional endpoints. The focus of these analyses is on treatment emergent adverse events (TEAE) with the first dose date considered the Day 1, Cycle 1 dose. These analyses will be performed for individual adverse events (AEs), AEs of special interest and/or clustered AEs as specified in Appendix 1 for the ALK-positive NSCLC patients and Appendix 2 for the ROS1-positive NSCLC patients. The list of clustered events along with the associated AE preferred terms within the cluster is provided in the product's Safety Review Plan maintained by the Sponsor. Additional programming details for the derivation of these endpoints are included in Appendix 4.

- **Time to AE onset** (in days) is defined as the time from the date of the first dose to the onset date of the AE, regardless of grade. If a patient has multiple episodes of an AE, the date of the first occurrence is used. Time to AE onset (in days) will be calculated as (AE start date – first dose date +1). **Time to Grade 3/4 AE onset** (in days) is defined similarly as time to AE onset for AEs.

  Time to onset is calculated for the subgroup of patients who had the specific AE.

- **Duration of AE** (in days) is defined as the cumulative duration across episodes of the AE, regardless of grade where duration for each episode is the time from the AE start date to the AE end date. For one episode, duration (in days) = (AE end date – AE start date + 1). If a patient has multiple episodes of an AE, cumulative duration across all episodes will be used adjusting for any overlap. If a patient has an AE that was ongoing at the time of analysis, the time is censored at the last available on treatment visit date.

  Duration is calculated for the subgroup of patients who had the specified AE.

- **Prevalence of AE** is defined as the number of patients with an AE in a particular time period (including both new cases with an onset date during the specified time period AND cases with an AE continued from a previous time period) divided by the number of patients at risk during the specified time period. The number of patients at risk includes all patients except those who either have discontinued or died prior to the specified time period.

6.3. PK Endpoints

ALK-Positive NSCLC Cohort

PK endpoints are identical to those described in Section 6.1 of the main SAP.

ROS1-Positive NSCLC and MET Exon 14 Alterations NSCLC Patients

The following PK endpoints are of interest:

- Plasma concentrations of PF-02341066

- Mean steady state predose concentration or mean steady state trough concentration ($C_{trough, ss, mean}$) for PF-02341066 and PF-06260182 calculated by using the arithmetic mean of all evaluable plasma predose concentrations (C_{trough}) for that patient

6.4. Biomarker Endpoints

MET Exon 14 Alterations NSCLC Patients

MET Exon 14 alteration status will be classified as: alteration detected, alteration not detected, or sample not analyzable. Alteration detected indicates that NGS analysis detects a MET exon 14 alteration (positive for MET exon 14 alterations); alteration not detected indicates that NGS analysis does not detect a MET exon 14 alteration (negative for MET exon 14 alterations);

sample not analyzable indicates that a valid result satisfying analytical and QC specifications is not generated.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, imputation methods apply to partial dates. If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing day. Similarly, if both the day and month are missing, the first day of the year is used. For stop dates, the last day of the month or the last day of the year is used if the day or both the day and month are missing, respectively. These rules are used unless the calculations result in negative time durations (eg, date of resolution cannot be prior to date of onset). In these cases, the dates resulting in 0 time duration will be used.

This standard will be modified for the computation of TTP of the last prior treatment regimen prior to crizotinib in the ROS1 patients and the MET exon 14 patients. In particular, if the day of the month for the progression is missing the 1st of the month will be used, as above. However, if both month and day are missing and the year is equal to the year of the end date for the last prior treatment regimen, the end date for the last prior treatment regimen will be used.

7.2. Missing Efficacy Endpoint Values

For primary and secondary efficacy analyses no values will be imputed for missing data, except as specified in Section 6.1, where for time-to-event endpoints, non-event observations will be censored and for ORR, patients with no post-baseline tumor evaluations will be counted as non-responders.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Analyses of ORR, DR, TTR, and DCR will be performed for the RE population. The SA population will be used for the analysis of PFS, TTP, and OS.

8.1.1. Analyses of Efficacy Endpoints

ALK-Positive NSCLC Cohort

The point estimate of the objective response rate (ORR) will be provided along with the corresponding exact 2-sided 95% confidence interval using the exact method based on the F-distribution. The best overall response will also be summarized. The best overall response of SD can be assigned if stable disease criteria are met at least once after the date of the first dose at a minimum interval of 6 weeks. SD duration will be summarized in several time intervals, specifically, 0 to < 3 months, 3 to < 6 months, 6 to < 9 months, 9 to <12 months, and ≥ 12 months.

DCR at weeks 8 and 16 will be analyzed similarly as described for ORR.

DR will be summarized using the Kaplan-Meier method.[3] The median event time (if appropriate) and 2-sided 95% CI for the median will be provided. A graph of the estimated KM

curve will be presented along with 95% Hall-Wellner confidence bands, as appropriate. Since the number of patients with CR or PR may be small, the use of Kaplan-Meier method may be limited and the DR will also be summarized using descriptive statistics.

TTR will be summarized using descriptive statistics. In addition, the number and percent of patients with TTR in the following time intervals may be provided: 0 to <8 weeks, 8 to < 16 weeks, 16 to < 24 weeks, and ≥ 24 weeks.

PFS in the SA population will be summarized using the Kaplan-Meier method. The median event time (and other quartiles) and 2-sided 95% confidence interval for the median will be provided (Brookmeyer R and Crowley JJ).[4] A graph of the estimated KM curve will be presented along with 95% Hall-Wellner confidence bands, as appropriate.

The probability of PFS at 6 months will be based on the Kaplan-Meier estimate. A 2-sided 95% CI for the log [-log(6-months PFS probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6-months PFS probability itself.

OS in the SA population will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. The median event time and 2-sided 95% confidence interval for the median will be provided. A graph of the estimated KM curve will be presented along with 95% Hall-Wellner confidence bands, as appropriate.

The probability of survival at 6 months will be based on the Kaplan-Meier estimate. A 2-sided 95% CI for the log [-log(6-months survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6-months survival probability itself. The probability of survival at 1 year and confidence limits will be estimated similarly.

Duration of follow-up for PFS, and similarly for OS, will be summarized using the reverse Kaplan-Meier method (Schemper and Smith).[5] The median event time (and other quartiles) and 2-sided 95% confidence interval for the median will be provided (Brookmeyer R and Crowley JJ).[4]

A waterfall plot displaying the best percentage change in target lesion tumor size by best overall response will also be presented. The plot will be based on the derived investigator's assessment of tumor data as described in Appendix 5 and will be based on the RE population excluding patients with Early Death, a best overall response of Indeterminate, and those with non-measurable disease only.

For ORR, PFS, and OS, additional covariate adjusted or subgroup analyses may be performed to explore the influence of various baseline characteristics.

ROS1-Positive NSCLC Patients

For the purposes of analysis, the following groups will be used, as appropriate:

1. ROS1-positive NSCLC: Includes all patients in the ROS1-positive NSCLC cohort plus the 3 patients in the ALK-negative NSCLC cohort #2 who were retrospectively found to be ROS1-positive

2. ROS1-positive NSCLC cohort: Includes the 50 patients who were enrolled into this cohort.

3. ROS1-positive NSCLC cohort (First 27 evaluable patients): Includes the first 27 evaluable patients enrolled into the ROS1-positive NSCLC cohort for the planned test of the hypothesis specified in Section 4.1 above.

For analyses using group #1, tumor assessments are based on RECIST 1.0 except for 3 patients from ALK-negative cohort #2 for whom RECIST 1.1 is used.

The analysis of efficacy endpoints for ROS1-positive NSCLC mirrors that described for the ALK-positive NSCLC cohort with the following differences:

- For the ROS1-positive NSCLC patients, the best overall response and objective response rate will be summarized for each of the 3 groups above.

- Additionally, TTP in the SA population will be summarized using the Kaplan-Meier method. The median event time (and other quartiles) and 2-sided 95% confidence interval for the median will be provided (Brookmeyer R and Crowley JJ).[4] A graph of the estimated KM curve will be presented along with 95% Hall-Wellner confidence bands, as appropriate.

- The following analyses will be summarized separately for ROS1-positive NSCLC patients (group #1 above) and the ROS1-positive NSCLC cohort (group #2 above):

    - DCR at weeks 8 and 16
    - DR
    - TTR
    - PFS
    - PFS at month 6
    - TTP (only group #1 above)
    - OS
    - OS at 6 and 12 months
    - Duration of follow-up for OS

- The summary of reasons for objective progression (new lesion, ≥ 20% increase in target lesions, progression of non-target lesions) will be summarized for the ROS1-positive NSCLC patients (group #1 above). Note that the reason for objective progression is determined by first evaluating new lesions, then increase in target lesions and then non-target lesions.

- Duration of follow-up for PFS will not be summarized.

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

Subgroups analyses of best overall response will be performed using ROS1-positive NSCLC patients (group #1 above) to explore the influence of baseline characteristics.

MET Exon 14 Alterations NSCLC Patients

For the purposes of analyses, the following groups will be used, as appropriate:

1 MET exon 14 alterations NSCLC: Includes all patients in the MET exon 14 alterations NSCLC cohort

2 MET exon 14 alterations NSCLC (First 33 evaluable patients): Includes the first 33 evaluable patients enrolled into the MET exon 14 alterations NSCLC cohort for the planned test of the hypothesis specified in Section 4.1 above.

The analysis of efficacy endpoints for MET exon 14 alterations NSCLC mirrors that described for the ROS1-positive NSCLC patients with the following differences:

- All efficacy endpoints will be evaluated in group #1 above and only ORR will also be evaluate in group #2;
- The reasons for objective progression (new lesion, $\geq$ 20% increase in target lesions, progression of non-target lesions) will not be summarized;
- In the waterfall plot the MET exon 14 alteration status (Detected/Not detected and Not analyzable) for central testing will be shown.

8.1.2. Analyses of Safety Endpoints

In addition to the analyses described in the main SAP, the following safety analyses will be performed for ALK-positive NSCLC patients, ROS1-NSCLC patients (group #1) and MET exon 14 alterations NSCLC patients (group #1) as described below.

8.1.2.1. Summary Tables for Clustered AEs

For the ALK-positive NSCLC cohort, summary tables of clustered treatment emergent AEs (preferred terms) will be presented for all causality and treatment-related AEs.

For the ROS1-positive NSCLC and MET exon 14 alterations NSCLC patients, all of the standard AE summary tables described in Section 8.2.2 of the main SAP will also include the clustered AE terms. In addition, summary tables of clustered AEs (and the preferred terms within cluster) will be presented for all causality AEs and separately for treatment-related AEs. Similar summaries will be presented for SAEs.

Clustered AE terms are listed in the product's Safety Review Plan maintained by the Sponsor.

8.1.2.2. Analyses of AEs and Clustered AEs of Special Interest

ALK-Positive NSCLC Cohort

The following analyses will be performed for AEs of special interest and clustered AEs of special interest as outlined in Appendix 1 for the ALK-positive NSCLC cohort.

Duration of AE (days) will be summarized for the SA population using the Kaplan-Meier method. The median and other quartiles, as appropriate, will be presented along with associated 95% confidence intervals. Duration of AE will be calculated only for the subgroup of patients with the AE. Treatment-related tables will be generated for both individual AEs of interest and clustered AE terms as specified in Appendix 1.

Descriptive statistics will be presented for time to AE onset (days), time to Grade 3/4 AE onset, and duration of AEs for the subgroup of patients with the AE.

The prevalence of AEs will be summarized for the SA population by preferred term and maximum CTC severity grade. Summaries will be presented for the following time periods separately: Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, and Cycle ≥7. AEs will include both individual AEs of special interest and clustered AE terms as specified in Appendix 1. Both treatment-related and all causality tables will be presented.

The by-cycle and grade AE prevalence tables mentioned above will provide information regarding the overall trend of the change in severity across time.

ROS1-Positive NSCLC Patients

The analyses of AEs and clustered AEs of special interest are outlined in Appendix 2 for ROS1-positive NSCLC patients.

Analyses for ROS1-positive NSCLC patients will be conducted similarly as described above for the ALK-positive NSCLC cohort with the following exceptions:

- All tables will be generated for all causality and treatment-related events.
- Due to the different cycle lengths for the 50 patients in the ROS1-positive NSCLC cohort and the 3 patients in the ALK-negative NSCLC cohort, prevalence of AEs for individual and clustered terms will be presented by the following time periods: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24, and Weeks ≥ 25.

MET Exon 14 Alterations NSCLC Patients

The analyses of AEs and clustered AEs of special interest are outlined in Appendix 3 for MET exon 14 alterations NSCLC patients.

Analyses for MET exon 14 alterations NSCLC patients will be conducted similarly as described above for the ALK-positive NSCLC cohort with the following exceptions:

- All tables will be generated for treatment-related events;
- Duration of AE (days) will be summarized using descriptive statistics only.

8.1.3. Pooled Safety Analyses

For ALK-positive NSCLC patients, data from studies A8081001, A8081005 and others as appropriate will be pooled as applicable to allow for an integrated review of safety data. Select demographic and safety tables that will be generated include, but are not limited to: patient disposition, demographic characteristics, dose administration, AEs (by age, gender and race), SAEs, lab shift summaries, vital signs, and ECGs.

Similarly safety data for ROS1-positive NSCLC patients and for MET exon 14 alterations NSCLC patients may be pooled with safety data for ALK-positive NSCLC patients from studies A8081001, A8081005 and others as appropriate.

8.1.4. Independent Radiology Review Analysis

An independent radiology review (IRR) of tumor data was to be performed for all ALK-positive NSCLC patients, for ROS1-positive NSCLC cohort and for MET exon 14 alterations NSCLC patients with available scans based on RECIST 1.0. The scans for the 3 patients enrolled in ALK-negative cohort #2 who were retrospectively found to be ROS1-positive (evaluated based on RECIST 1.1) will be collected but will not be included in the IRR. The IRR will be performed by an independent third-party core imaging laboratory in accordance with a review charter and will consist of sequential locked reads by two radiologists blinded to outside radiology reports, investigator assessments, adverse events, and assessing images independently of Pfizer and of each other. Adjudication of the best response and date of progression (only for MET exon 14 alterations NSCLC patients) will be performed. Discrepancies in this variable between the two radiologists will be adjudicated by a third radiologist who will determine which interpretation (Reader 1, Reader 2, or a third interpretation) will be used in the analyses. While all scans will be reviewed by at least 2 readers, a total of approximately 10 or more radiologists may participate in the reviewing process.

Note that as of a note to file (dated October 22, 2012), a decision was made to stop collection of scans for centralized independent imaging review for patients enrolled in ALK- marker negative cohort #1. In Amendment 17, an additional cohort of ALK- marker negative patients [ALK marker negative NSCLC cohort #2] was introduced in order to satisfy a FDA post-marketing commitment. With the addition of this cohort, the usefulness of the independent imaging review in Cohort #1 was considered limited. Retrospective collection of tumor scans was introduced for ROS1-positive NSCLC cohort as of Amendment 20 and for MET exon 14 alterations NSCLC patients as of Amendment 22.

The following analyses will be performed for the ALK-positive NSCLC cohort, for the ROS1-positive NSCLC cohort (group #2) and for MET exon 14 alterations NSCLC patients (group #1).

8.1.4.1. Analysis of Objective Response Rate

Two separate analyses of ORR will be performed. The first analysis of ORR, based on the RE population, will be based upon the derived investigator assessment of best overall response based on rules (described in Appendix 5). The second analysis will be based upon the IRR assessment of best overall response. For IRR analysis of ORR, the IRR RE population will be used; the IRR RE population is defined identically to the RE population (Section 5.2) with assessments based on the IRR rather than the investigator's assessment. The former analysis will be described in the CSR while the latter may be described in a separate IRR report.

A cross-tabulation of best overall response by type of assessment (ie, IRR or investigator) will be presented. The categories to be presented will include: (1) complete response, (2) partial response, (3) stable disease, (4) progressive disease, (5) early death, (6) indeterminate, and (7) not included in IRR RE (eg, due to unavailability of scans). This shift table will include all patients who are either in the IRR RE Population or the RE population.

Tumor measurements and assessments based on the IRR will be listed in displays that accompany the IRR report.

8.1.4.2. Analysis of Agreement and Disagreement Rates

The total event disagreement rate for response will be presented for group #2 of ROS1-positive NSCLC patients and for groups #1 and #2 of MET exon 14 alterations NSCLC patients.

Definition of Agreement Used to Determine Total Event Agreement and Disagreement Rates in Response

	Investigator	IRR	Variable Name
Agreement	No response	No response	a
	Response	Response	b
Disagreement	No response	Response	c
	Response	No response	d

N = (a + b + c + d)

The total event disagreement rate measures the proportion of patients for whom there is a discrepancy between the IRR and investigator as to whether the patient was a responder with either the IRR or the investigator, but not both, indicating the patient had achieved a response, among all patients who are in both the IRR RE and RE populations.

Total Event Disagreement Rate = [(c+d) / N] x 100%.

The total event agreement rate measures the proportion of patients for whom there is a concordance between the IRR and investigator as to whether the patient was a responder or a non-responder with both the IRR and the investigator, among all patients who are in both the IRR RE and RE populations.

Total Event Agreement Rate = [(a+b) / N] × 100%.

8.1.5. Diagnostic Analysis

8.1.5.1. ALK-Positive NSCLC Cohort

Several clinical trial assays (CTAs) have been used to identify ALK status for entry in this study. The following diagnostic summaries will be presented for ALK-positive NSCLC patients.

8.1.5.1.1. Overall Summary of ALK Marker Testing

An overall summary of type of test by test result will be presented based on the total patients in the safety population with a local test performed. This summary will include the number and percentage of patients tested by CTA (local CTA-Massachusetts General Hospital [MGH], CTA-Local [non-MGH]) or tested by an 'Other' Test. The table will also display the number of patients tested by a CTA-Local (non-MGH) that were retested by CTA-MGH.

A summary of the local testing sites will also be provided.

Summaries will be presented for the local test characteristics (evaluation method, collection method, tissue site) by type of local test. This summary will also be presented separately for the subgroup of patients who are ALK-positive as determined by CTA-MGH and for the subgroup of patients not determined ALK-positive by CTA-MGH.

Descriptive statistics for ALK percentage of positive cells will be provided for patients tested by MGH. This table will be further displayed by test characteristics (collection method, tissue site).

8.1.5.1.2. ALK Marker Status by Type of Test

A table of ALK marker status (positive, negative, or uninformative) by type of marker test (CTA-MGH or CTA-Local [non-MGH]) will be presented for the total patients in the safety population who were retested.

8.1.5.1.3. Objective Response

Best overall response and ORR will be summarized using the RE population for ALK-positive NSCLC patients tested by MGH. Best overall response will also be presented by ALK percentage of positive cells for ALK-positive NSCLC patients tested by MGH.

A by-patient bar graph displaying ALK percentage positivity by best response may also be presented for each type of test. A bar graph by level of ALK percentage of positive cells category by best response for each type of test may also be further presented. The categories will include: 0 to <15%, 15% to <25%, 25% to <50%, 50% to <75%, and ≥ 75%.

A waterfall plot of best percentage change from baseline in target lesion tumor size based on the derived investigator assessment by ALK percentage positivity for patients tested by MGH will also be displayed.

8.1.5.2. ROS1-Positive NSCLC Patients

Molecular based testing have been used to identify ROS-1 marker status for entry in this study.

The following diagnostic summaries will be presented for ROS1-positive NSCLC patients.

8.1.5.2.1. Overall Summary of ROS1 Marker Testing

An overall summary of type of test by test result will be presented based on the total patients in the safety population with a local test performed. This summary will include the number and percentage of patients tested by MGH local FISH and non-MGH (including local FISH and other tests). The number of percentage of patients tested for each non-MGH test laboratory will be summarized separately within the table.

Summaries will be presented for the local test characteristics (evaluation method, collection method, tissue site) by type of local test (MGH vs. non-MGH).

Descriptive statistics for ROS1 percentage of positive cells will be provided by category of test (MGH vs. non-MGH) and overall. This table will be further displayed by test characteristics (collection method, tissue site).

8.1.5.2.2. Objective Response

Descriptive statistics for ROS1 percentage of positive cells will also be presented by best overall response.

A by-patient bar graph displaying ROS1 percentage positivity by best overall response may also be presented. A bar graph by level of ROS1 percentage of positive cells category (0% to <15%, 15% to <25%, 25% to <50%, 50% to <75%, and ≥ 75%, or other as appropriate for the distribution of the data) by best response for each type of test may also be further presented.

A waterfall plot of best percentage change from baseline in target lesion tumor size based on the derived investigator assesment by ROS1 percentage positivity will also be displayed. A box plot of ROS1 percentage positivity and BOR based on derived tumor assessment will be provided.

8.1.5.3. MET Exon 14 Alterations NSCLC Patients

8.1.5.3.1. Overall Summary of Biomarker Testing

Several clinical trial assays (CTAs) at local laboratories have been used to identify MET exon 14 marker status for entry in this study.

Summaries will be presented for the local test characteristics (evaluation method, collection method, tissue site) by type of local test (LDT-Local [laboratory developed test], Others).

Summary of patient demographic (age, sex, race, weight, height) and baseline characteristics (prior advance/metastatic therapy, smoking history, histology) will be provided for the safety analysis set, tumor tissue NGS biomarker analysis set (FMI), tumor tissue NGS biomarker analysis set (CGI), and plasma ctDNA NGS biomarker analysis set, respectively.

Summary of MET exon 14 alterations status will include the number and percentage of patients for each alterations status category. Results will be summarized separately for tumor tissues in the NGS biomarker (FMI) and (CGI) analysis sets, and for plasma ctDNA NGS biomarker analysis set.

A summary of concordance assessment of MET exon 14 alteration status in the NGS biomarker (FMI) set with analyzable samples vs local assessment will include the number and percentage of patients with alteration detected and not detected at FMI, given that patients were Met Exon 14 alteration positive by local tests.

Patient listings will be provided for MET exon 14 alterations based on NGS tumor tissue (FMI), NGS tumor tissue (CGI), and plasma ctDNA. A patient listing including all genomic mutations (MET, ALK, ROS1, etc.) from NGS tumor tissue (CGI) and plasma ctDNA will be provided. Diagnostic ALK, ROS1 and MET exon 14 alterations results based on central lab FMI will be listed.

8.1.5.3.2. Objective Response and Duration of Response

ORR and duration of response will be estimated as described in Section 8.1.1 for the patients in the NGS tumor tissue (FMI) set with and without confirmed MET exon 14 alterations positive NSCLC by FMI.

8.1.6. Analyses of PK Endpoints

ALK-Positive NSCLC Cohort

PK endpoints and the associated analyses are as described in the main SAP.

ROS1-Positive NSCLC Patients and MET Exon 14 Alterations NSCLC Patients

The following describes the analysis of the PK endpoints identified in Section 6.3:

- Listing of all concentrations sorted by patient identification number and nominal time postdose. The listing of concentrations includes the actual collection times. Deviations from the nominal time are given in a separate listing;
- Summary of predose (0H) concentrations by visit and ethnicity with descriptive statistics;
- Summary of $C_{trough,\ ss,\ mean}$ by ethnicity with descriptive statistics;
- Linear plots of median/mean predose (0H) concentrations against visit, by ethnicity.

8.1.7. Analyses of Sub-Populations

The following analyses are applicable for the ALK-positive NSCLC cohort, ROS1-positive NSCLC patients and MET exon 14 alterations NSCLC patients.

8.1.7.1. Efficacy Subgroup Analyses

As described in Section 5.7, efficacy analyses (described in Section 8.1) may also be conducted for sub-populations of the safety analysis and response-evaluable populations, for example, by dividing the populations according to: the number of previous anti-tumor treatments for metastatic disease (0, 1, 2, 3, and > 3; or 0 and ≥1), type of prior treatment for metastatic disease, ECOG performance status, age group (<65 years, ≥ 65 years), gender, race, race group (Asians, non-Asians).

Additional efficacy analyses may also be conducted for sub-groups defined by other baseline and disease characteristics such as disease histology, variants of the biomarkers, and others, as appropriate.

8.1.7.2. Adverse Event Subgroup Analyses

Treatment emergent adverse events will also be summarized by select baseline characteristics including age group (<65 years, ≥ 65 years), race group (Asians, non-Asians), gender, and others as appropriate.

8.1.7.3. PK Subgroup Analyses

The aforementioned analyses of PK parameters of interest may be performed by select baseline characteristics including age group, ethnicity, race group (such as Asian vs. non-Asian), gender, body weight, as appropriate. In this case, analyses will be repeated within each category and presented. If the sample size in a specific category is too small, listings may alternatively be presented.

8.2. COMPUTATIONAL METHODS

Kaplan-Meier Method.

Assume that the dataset *xx* has variables *duration* and *censor* for each patient, recording the time to event and censoring variable (0=not censored, 1=censored). Then the following SAS code will generate the median event time (and other quartiles) and the 2-sided Brookmeyer-Crowley 95% confidence interval for the median and an output dataset *yy*.

```
proc lifetest data = xx method =KM conftype = linear;
  time duration*censor_(1);
  survival out=yy  conftype = linear;
run;
```

Exact method based on the F-distribution

Assume that each observation has a binomial response recorded in variable *resp* in dataset *xx*. Then point estimate for a rate of response (eg, the ORR) along with the corresponding exact 2-sided 95% confidence interval using the exact method based on the F-distribution, along with an output dataset *yy*, can be computed in SAS as shown below.

```
proc freq data=xx;
  table  resp / binomial alpha = 0.05;
  output out= yy  binomial;
run;
```

The confidence interval will be given for the response category with the lower value (0 rather than 1, "N" rather than "Y"). To obtain the CI for the higher value, sort in descending order and use the ORDER=DATA option.

Recurrent event analysis within-patient TTP

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

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

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

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

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

9. REFERENCES

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

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10. APPENDICES

Appendix 1. Analyses of AEs and Clustered AEs of Special Interest for the ALK-Positive NSCLC Cohort

The following table presents the types of summaries that may be provided for AE and clustered AEs. Note that the list of AEs and clustered AEs reported below are only examples and may be further updated prior to final analysis.

A comprehensive list of clustered terms used in this study and MedDRA Preferred Terms associated with these clustered terms is archived in the Risk Management Committee central repository for the project.

	Time to AE onset		**Time to Grade 3/4 AE onset**		**Duration of AEs**		**AE prevalence**	
	Trt related	All Causality	Trt related	All Causality	Trt related	All Causality	Trt related	All Causality
INDIVIDUAL AES OF SPECIAL INTEREST								
Diarrhoea	X				X		X	X
Vomiting	X				X		X	X
Nausea	X				X		X	X
Pneumonitis	X		X		X		X	X
Dyspnoea	X				X		X	X
CLUSTERED AES OF SPECIAL INTEREST								
Alanine aminotransferase increased	X		X		X		X	X
Vision disorder	X				X		X	X
Oedema	X				X		X	X
Oesophageal related disorder	X		X		X		X	X
Neutropenia	X		X		X		X	X
Neuropathy	X				X		X	X

Note: Trt=Treatment; AE = Adverse Event

Appendix 2. Analyses of AEs and Clustered AEs of Special Interest for the ROS1-Positive NSCLC Patients

The following table presents the types of summaries that may be provided for AE and clustered AEs. Note that the list of AEs and clustered AEs reported below are only examples and may be further updated prior to final analysis.

A comprehensive list of clustered terms used in this study and MedDRA Preferred Terms associated with these clustered terms is archived in the Risk Management Committee central repository for the project.

	Time to AE onset	**Time to Grade 3/4 AE onset**	**Duration of AEs**	**AE prevalence**
	Treatment Related and/or All Causality	Treatment Related and/or All Causality	Treatment Related and/or All Causality	Treatment Related and/or All Causality
INDIVIDUAL AES OF SPECIAL INTEREST				
Diarrhoea	X		X	X
Vomiting	X		X	X
Nausea	X		X	X
Constipation	X		X	X
Dysgeusia	X		X	X
Hypokalaemia	X		X	X
Syncope	X		X	X
Electrocardiogram QT prolonged	X		X	X

	Time to Adverse Event Onset	**Time to Grade 3/4 Adverse Event Onset**	**Duration of Adverse Events**	**Adverse Event Prevalence**
	Treatment Related and/or All Causality	Treatment Related and/or All Causality	Treatment Related and/or All Causality	Treatment Related and/or All Causality
CLUSTERED AES OF SPECIAL INTEREST				
Elevated transaminases	X	X	X	X
Hepatotoxicity	X		X	X
Bradycardia	X		X	X
Vision disorder	X		X	X
Edema	X		X	X
Neutropenia	X	X	X	X
Leukopenia	**X**		**X**	**X**
Neuropathy	X		X	X
Dyspnoea	X		X	X
Interstitial lung disease	X	X	X	X
Dizziness	X		X	X
Pulmonary embolism	X		X	X
Upper respiratory infection	X		X	X
Abdominal pain	X		X	X
Blood creatinine increase	X		X	X

Appendix 3. Analyses of AEs and Clustered AEs of Special Interest for the MET Exon 14 Alterations NSCLC Patients

The following table presents the types of summaries that may be provided for AE and clustered AEs. Note that the list of AEs and clustered AEs reported below are only examples and may be further updated prior to final analysis.

A comprehensive list of clustered terms used in this study and MedDRA Preferred Terms associated with these clustered terms is archived in the Risk Management Committee central repository for the project.

	Time to Adverse Event Onset	**Time to Grade 3/4 Adverse Event Onset**	**Duration of Adverse Events**	**Adverse Event Prevalence**
	Treatment Related	Treatment Related	Treatment Related	Treatment Related
INDIVIDUAL AES OF SPECIAL INTEREST				
Diarrhoea	X	X	X	X
Vomiting	X	X	X	X
Nausea	X	X	X	X
Constipation	X	X	X	X
Syncope	X	X	X	X
Electrocardiogram QT prolonged	X	X	X	X
CLUSTERED AES OF SPECIAL INTEREST				
Elevated transaminases	X	X	X	X
Hepatotoxicity	X	X	X	X
Interstitial lung disease	X	X	X	X
Bradycardia	X	X	X	X
Vision disorder	X	X	X	X
Edema	X	X	X	X
Renal cyst	X	X	X	X
Blood creatinine increased	**X**	**X**	**X**	**X**
Back-ups (provide in source table but not in-text tables				
Neuropathy	X	X	X	X
Neutropenia	X	X	X	X
Leukopenia	X	X	X	X

Appendix 4. Programming Specifications for AE Analyses

a. Time to AE onset

1. Definition

Time to AE onset (days) will be calculated as first *AE start date – first dose date* +1. The definition and calculations are similar for time to Grade 3/4 AE onset. Time to AE onset is defined for patients with the AE.

AE start date
The Date of Onset for the first occurrence of the AE based on the Log AE CRF page.

First dose date
The date of the Cycle 1, Day 1 dose of PF-02341066. Patients who received the Day -7 dose only will be excluded from the time to AE onset calculation.

2. Clustered AEs

For clustered events, the aforementioned rules will be similarly applied considering each AE in a cluster. For example, the *AE start date* will be the Date of Onset of the AE in the cluster which occurs first.

b. Duration of AE

1. Definition

Duration of AE (days) is defined as the cumulative duration across episodes of the AE where duration for each episode is calculated as *AE end date – AE start date* +1 excluding any overlap. Duration of AE is defined for patients with the AE.

AE start date
The Date of Onset based on the Log AE CRF page.

AE end date
The Date Resolved based on the Log AE CRF page.

2. Censoring

AE resolution is considered an event (censoring variable=1). If a patient has an AE that was ongoing (even if it is not the last AE within a PT/cluster) at the time of analysis, the time is censored (censoring variable=0) at the last available on treatment visit date. Patients who die prior to resolution of the AE will be censored at the *date of death*. If the date of death is the same as the date of the resolution of the AE, the patient will be censored at that date (ie, resolution will not be considered an event) unless the AE is the AE that resulted in death.

Last available on treatment visit date (visits performed after treatment start and up to 28 days from last treatment dose)

This is defined as the latest date of assessment/onset associated with the following CRF pages (or if a date of assessment/onset is not available the 'Date of Visit' for the CRF page can be used). Only dates associated with non-missing assessments should be used for the calculation.

- AE Log [Date of onset for AEs with grade not equal to 5]
- Vital Signs [Actual date of collection]
- ECOG PS [Date of assessment]
- ECG [Actual date of ECG]
- Laboratory Data [Date of collection]
- Concomitant Drug Treatment [Start Date]
- Non-Drug Treatment/Procedure [Start Date]
- RECIST Tumor Lesion Measurement/Investigator Target Disease Lesions/ Investigator Non-Target Disease Lesions [Date]; RECIST (1.1 only) Lymph Node Lesions [Date]
- Physical Exam [Date of Visit at top of page]
- PK (including PK-sampling points, PK Point – PF-02341066, Pharmacokinetics (Point) – MDZ cohorts/ALL cohorts, Pharmacokinetics (Point) – MDZ/FE cohorts, Pharmacokinetics (Point) – ALL cohorts except for MDZ/FE cohort, PK Point – for MDZ study cohorts only, Pharmacokinetics (Point) – Morning spot urine, Pharmacokinetics (Point) – 24 hour urine collection – RP2D cohort only) [latest Start Date]
- Details of Today's AM/PM Dose [Dose date]
- Details of Yesterday's PM Dose [Dose date]
- Details of Tomorrow's AM Dose [Dose date]
- Lab Based Biomarker (Point) [Date]
- Pharmacodynamics (Point) [Date of Visit at top of page]
- Dosing Record – PF-02341066 [Start Date]
- Positron Emission Tomography [Date of Test]
- Fresh Tumor Biopsy [Actual Date]

- Ocular pages (including Fundoscopy Posterior Segment Right Eye/Left Eye, Biomicroscopy Anterior Segment Right Eye/Left Eye, Visual Acuity – Distance Right Eye/Left Eye; Ocular Characteristics Right Eye/Left Eye). Note also include additional Amendment 17 pages including: Intraocular Inflammation Anterior Segment Right Eye/Left Eye, Refractive Error Right Eye/Left Eye, Intraocular Pressure Right Eye/Left Eye, External Eye Examination Right Eye/Left Eye , Color Fundus Photographs Right Eye/Left Eye, Optical Coherence Tomography Right Eye/Left Eye [[Date of Exam]

- Diagnostic Marker Test – ALK, ROS, or MET, as available [Sample Date]

- Pharmacogenomic Sample Collection - P450 Genotyping [Sample Date]

If the derived last available on treatment visit date results in a negative duration of AE, then duration of AE will be censored at 1 day.

Date of death
Death date based on the Subject Survival Log CRF page.

3. Clustered AEs

For clustered events, a patient could have multiple overlapping events in the cluster. In this case, AE duration will be summed across all events in the cluster accounting for the overlap (ie, overlapping periods between events in the same cluster are not double-counted). Lags between events in the same cluster are not included in the duration.

The following scenarios provide examples of the calculation for 2 events in the same cluster. The extension to 3 or more events of the same cluster is similar to that described for 2 events.

- **TWO EVENTS OF THE SAME CLUSTER WHERE ONE EVENT COMPLETELY CONTAINS THE OTHER EVENT**

```
event 1          [------------------------------]
                 startdate1                 enddate1
event 2              [----------------------]
                     startdate2         enddate2
```

duration = enddate1-startdate1+1

- **CERTAIN PORTIONS OF TWO EVENTS IN THE SAME CLUSTER OVERLAP**

```
event 1          [------------------------------]
                   startdate1               enddate1
event 2                        [----------------------]
                               startdate2         enddate2
```

duration = enddate2-startdate1+1

- **TWO EVENTS OF THE SAME CLUSTER ARE CONTIGUOUS TO EACH OTHER**

event 1 [----------]
startdate1 enddate1
event 2 [----------]
startdate2 enddate2

duration = enddate2-startdate1+1

- **TWO EVENTS OF THE SAME CLUSTER ARE NON-OVERLAPPING**

event 1 [----------]
startdate1 enddate1
event 2 [----------]
startdate2 enddate2

duration = (enddate1-startdate1+1) + (enddate2-startdate2+1)

c. AE prevalence

1. Definition

AE prevalence is defined as the number of patients with an AE in a particular time period (including both new cases with an onset date during the specified time period AND cases with an AE continued from a previous time period) divided by the number of patients at risk during the specified time period. The number of patients at risk includes all patients except those who either have discontinued or died prior to the specified time period. Only treatment-emergent AEs are summarized.

For the ALK-positive cohort and MET exon 14 alterations NSCLC patients, AE prevalence will be presented separately for Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, and Cycle ≥7. For ROS1-positive NSCLC patients, weeks will be used instead of cycles to accommodate the 3-week (ALK negative cohort) and 4-week cycles (ROS1 Cohort): Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24, and Weeks ≥ 25.

2. Assumptions

The assumptions are described in terms of the 7 cycle-related time periods being summarized for the ALK-positive NSCLC cohort and MET exon 14 alterations NSCLC patients, but the procedure is the same for the 7 sets of weeks for ROS1-positive NSCLC patients.

For an AE that resolves prior to the Follow-up period:

- Patients are counted for an AE in each cycle up until (and including) the cycle during which the AE resolved. Thus, the calculation conservatively assumes that if the AE resolved in a cycle, it resolved at the end of the cycle.

- For Cycle 1, a patient is counted in the numerator if the patient has an onset date of the AE during Cycle 1.

- For Cycle 2, a patient is counted in the numerator if the patient has an onset date of the AE during Cycle 2 OR an onset date in a previous cycle that is still ongoing in Cycle 2 (ie, did not have a resolution date prior to Cycle 2). The calculation for Cycles 3, 4, 5, and 6 is similar.

- For Cycles ≥7, a patient is counted in the numerator if the patient has an onset date in Cycle ≥7 OR an onset date in an earlier cycle that is still ongoing (did not have a resolution date in Cycle 6 or earlier cycle).

- If the patient is at risk during a particular time period, the patient will be included in the denominator for that time period. The number at risk includes all patients except those who either have discontinued (based on the 'Subject Summary' CRF) or died prior to the specified time period (ie, Death Date based on 'Subject Survival' CRF is prior to start of time period).

For an AE that starts before Follow-up and is ongoing/resolves in Follow-up:

- If the patient was exposed for ≥ the last cycle being summarized, then the AE will be counted in both the numerator and denominator of each cycle from the cycle of onset through the last cycle summary. Example: patient's last exposure to study drug was in the 8th cycle, AE that starts in Cycle 4: count the patient in the denominator for all cycles and count the AE in the numerator for Cycles 4, 5, 6 and ≥7.

- If the patient was exposed for < the last cycle being summarized, the AE will be excluded from all cycles exceeding the cycle of last exposure. Example: patient's last exposure to study drug was in the 5th cycle, AE starts in Cycle 4: count the patient in the denominator for Cycles 1, 2, 3, 4 and 5 only, and count the AE in numerator for Cycles 4 and 5 only.

For an AE that starts in Follow-up:

- If the patient was exposed for ≥ the last cycle being summarized, include in the numerator and denominator of the last cycle summarized. Example: patient's last exposure to study drug was in the 8th cycle, AE starts in Follow-up: count the patient in the denominator of all cycles and the AE in the numerator for Cycle ≥7.

- If the patient was exposed for < the last cycle being summarized, then do not count the AE in the prevalence tables. Example: patient's last exposure to study drug was in the 5th cycle, AE starts in Follow-up: count the patient in the denominator for Cycles 1, 2, 3, 4 and 5 but do not count in denominator for Cycles 6 or ≥7, and do not count the AE in the numerator of any cycle.

In general, in the text above, the last cycle includes the 28 days following the last dose, but the last cycle is truncated for anti-cancer therapy starting before the last dose + 28 days. Follow-up period is defined as starting the day after the end of the last cycle. However for the ROS1 report, the length of the last cycle of treatment was set at 28 days for the 50 patients in the ROS1 positive NSCLC cohort and 21 days for the 3 patients in the ALK negative NSCLC cohort; this strategy was used to align with the pre-specified cycle length in each of these cohorts (4 weeks for ROS1 positive NSCLC cohort and 3 weeks for ALK negative NSCLC cohort). Example: a ROS1 NSCLC patient started dosing for Cycle 5 (summarized as Weeks 17-20) on September 1. Follow-up would start September 29th, as long as the last day of dosing was on some date ≥ September 1 and ≤September 28. Initiation of anticancer treatment following the end of crizotinib treatment would not alter this designation for the ROS1 report.

Appendix 5. Evaluation of RECIST (version 1.0) Tumor Assessment Criteria

The following describes the rules used for derivation of tumor response and progression based on Investigator Assessment of tumor data collected in study A8081001 for cohorts using RECIST 1.0 including the ALK positive NSCLC cohort, MET amplified NSCLC cohort, MET exon 14 alterations NSCLC patients and ROS1-positive NSCLC cohort. The investigator assessments at each time are used to derived appropriate response category (CR, PR, SD, PD, IND) described below. Although the investigator provides response categories, the response categories derived using the RECIST criteria will be used in all summaries and analyses.

The primary efficacy analysis will be based on a programmatic approach to the investigator tumor assessment data recorded on the investigator target and non-target disease lesions pages of electronic case report forms (eCRFs).

A secondary efficacy analysis will be based on independent radiology review (by Bioclinica) and interpretation of tumor assessment scans from study sites. The details of this process are described in the study specific Bioclinica charter.

General Basis for the Rules

The tumor response criteria are based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.0).[1]

Study Specific Information

- **Baseline**: is defined as the last observation prior to the first dose of study drug. The first dose is referred to the Cycle 1, Day 1 dose. The length of a cycle is 28 days.
- **Adequate Baseline:**
    - The original definition of the acceptable time window for baseline evaluations specified that baseline tumor evaluations must be performed within 5 weeks (35 days) prior to the first dose of study drug. However, based on a case-by-case review of some patients with assessments outside the window but whose baseline lesions either remain unchanged at the first on-study evaluation or did not influence response outcome, the window for baseline evaluations was expanded to 365 days to prevent loss of important information contributing to the efficacy evaluation.
    - Presence of target and/or non-target disease at baseline (ie, patients will not be excluded if they only have non-target disease);
    - All lesions recorded at baseline must have an associated status recorded on the CRF (eg, measurements for target lesions and “present” for non-target lesions);
    - Baseline lesions must be assessed with an acceptable method that includes: Conventional CT Scan, Spiral CT Scan, X-ray, MRI, Physical Exam, Bone Scan (only for non-target lesions) and Other. Note: If based on data review “unacceptable” methods (eg, ultrasound) are noted under “Other”, then this category will not be considered acceptable (on a case by case basis). Note: eCRF

options of "Ultrasound", "Endoscopy", and "Cytologic Confirmation" are not acceptable methods.

- **"On-study" period for efficacy:** is defined as the time from the date of the first dose until 35 days after the last dose of study drug (28 days + 1 week allowance). However, deaths will be included in the PFS analysis if they occur within 16 weeks (2 tumor assessment timeframes) from the last tumor assessment.

- **Subsequent anti-tumor treatment:** include systemic anticancer therapy (other than study medication) as indicated on the Subject Survival CRF which collects 'Has the patient received any subsequent cancer therapy (yes/no)' and 'If yes, therapy start date'. Note that this study does not collect specific information regarding type of subsequent therapy.

Evaluation of Target Lesions for Each Visit:

Note:

- The sum of lesion dimensions (SLD) is only considered if the methods of assessments are consistent with baseline. The only exception is CT/MRI/Spiral CT as these are all considered "interchangeable" methods.

- PET/CT is not an acceptable modality unless only the CT part of the PET/CT is used for evaluation. In this case, the CRF page should only record CT not PET/CT as the modality. If PET/CT is recorded on the CRF as the modality, then the timepoint response becomes Indeterminate (IND). If PET/CT is the only modality used, then the best overall assessment becomes IND.

    - Complete Response (CR) is defined by the disappearance of all target lesions (where all target lesions are recorded with a length of 0 mm on the "Target Lesions" eCRF).

    - Partial Response (PR) is defined by a 30% or more decrease in the SLD of target lesions, taking as reference the baseline SLD.

    - Progressive Disease (PD) is defined by a 20% or more increase in the SLD of target lesions relative to baseline or the smallest sum (nadir) recorded since treatment started

    - Stable Disease (SD) is assigned when the measurement doesn't qualify for either a response (CR or PR) or PD.

    - Indeterminate (IND) is assigned if all target lesions are not assessed ("Not done" is checked on the "Target Lesions" eCRF) or any individual target lesion is evaluated as "Non-Measurable" ("Non-Measurable" is marked on the "Target Lesions" eCRF), or if inconsistent methods are used for post-baseline lesion assessment (see Note at the beginning of section) for any lesion, or an

unacceptable method is used for one or more target lesions, or if one or more target lesions are not assessed.

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

If a lesion was too small to measure, the site was to enter "Measureable" and enter "0.5 cm," equivalent to 5 mm.

Evaluation of Non-Target Lesions for Each Visit:

Note:

- The lesions assessed are only considered for CR, SD and PD if the methods of assessments are consistent with baseline. The only exception is CT/MRI/Spiral CT as these are all considered "interchangeable" methods.

- PET/CT is not an acceptable modality unless only the CT part of the PET/CT is used for evaluation. In this case, the CRF page should only record CT not PET/CT as the modality. If PET/CT is recorded on the CRF as the modality, then the timepoint response becomes Indeterminate (IND). If PET/CT is the only modality used, then the best overall assessment becomes IND.

    - Complete Response (CR) is assigned if all non-target lesions are assigned 'Absent' on the "log: Non-Target Disease Lesions" eCRF .

    - Stable is assigned if non-target lesions are marked 'Stable'' or 'Increase' or 'Decrease' and 'unequivocal progression' is not marked on the "log: Non-Target Disease Lesions" eCRF.

    - Progressive Disease (PD) is assigned if any non-target lesion is marked 'unequivocal progression' on the "log: Non-Target Disease Lesions" eCRF.

    - No Non-Target Lesion at Baseline (NB) is assigned if "No Non-Target Lesions" is checked on the "Non-Target Lesions Screening" eCRF.

    - Indeterminate (IND) is assigned if all non-target lesions are not assessed ("Not done" is checked on the "log: Non-Target Disease Lesions" eCRF) or if inconsistent methods are used for post-baseline lesion assessment (see Note at the beginning of section) for any lesion, or if one or more non-target lesions are not assessed.

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

Overall Response Evaluation for Each Visit (Week):

- Overall response is determined from both target and non-target lesion data using conventions in the table below under the assumption that there are no new lesions identified at the visit.

- If there are any new lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.

- To group target, non-target lesion measurements and overall tumor assessments to the corresponding actual post-baseline scan visit, a clustering algorithm is applied. Each cluster represents an actual tumor assessment visit. For each patient, the number of clusters is equal to the maximum number of assessments available among all target, non-target lesions and overall tumor assessments. SAS® software procedure, PROC FASTCLUS, is applied to a variable that represents the days from the date of the first dose to the date of the scan for each target and non-target lesion (date of scan – date of the first dose + 1). Then the assessments of target and non-target lesion that occurred close to each other in time will be assigned to the same cluster.

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

Target Lesion Response	Non-Target Lesion Response	Overall Response
CR	CR	CR
CR	SD	PR
CR	PD	PD
CR	IND	PR
PR	CR	PR
PR	SD	PR
PR	PD	PD
PR	IND	PR
SD	CR	SD
SD	SD	SD
SD	PD	PD
SD	IND	SD
PD	Any Response	PD
IND	PD	PD
IND	CR/SD/IND	IND
Not Collected at Baseline	CR/SD/PD/IND	CR/SD/PD/IND
CR/PR/SD/PD/IND	Not Collected at Baseline	CR/PR/SD/PD/IND
CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, IND=Indeterminate —includes missing/not done response entries as well as unclear images. Note: If non-target (or target) lesions are not collected at baseline, then the overall response is equivalent to the target lesions (or non-target) response.		

Timing of Response

If there are multiple assessments within a cluster, then the following rules will be applied to derive the time of response for target, non-target and new lesions based on that cluster:

- If there are multiple new lesions in a cluster, then the first date that a new lesion was documented will be used as the actual date of PD;

- For target and non-target lesions the date of response (CR, PR, SD, PD, IND, as applicable) will be recorded as the date of the last radiographic evaluation included in the series for that assessment.

The date of best overall response is defined as the first date the response was documented.

The date of PD (for PFS and TTP) is the earliest date of:

1. Last assessment date for target lesions (in a cluster) if the SLD meets the criteria for progression;

2. Last assessment date for non-target lesions (in a cluster) if PD is documented based on the non-target response;

3. Earliest of new lesion dates (in a cluster).

The censoring date for PFS is the last date of an evaluable assessment that showed no PD.

Confirmed Objective Response Evaluation for Each Patient:

- Confirmed objective responses, including CR and PR, are defined as responses that persist on repeat imaging study for 2 assessments with a time period of at least 4 weeks (28 days) between 2 assessments. These 2 assessments need to evaluate all sites of disease that have been followed since baseline (ie, all target and non-target lesions).

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

Best Overall Response Evaluation for Each Patient:

- The best overall response is the best response (confirmed CR, confirmed PR, SD, Early Death, PD or IND) recorded during the "on-study" period.

- Best overall response is derived from the sequence of objective responses.

- Patients' best overall response will be Early Death if patient died within 42 days of the date of the first dose and prior to having sufficient evaluations for overall response.

- All assessments done after the PD or after "anti-tumor treatment" but prior to PD will not be considered for evaluation of best overall response, duration of response, or time to

response (with the exception of an assessment of PD obtained within 14 days from start of an anti-tumor treatment in which case PD is still considered in the evaluation of the best overall response).

- For a patient to qualify for a best response of SD, the overall response evaluation must have met the stable disease criteria at least once since the date of the first dose at a minimum interval of 6 weeks (42 days). For any unconfirmed CR and PR, the best response will be SD provided it meets the 42 days requirement.

- Indeterminate (IND) is assessed for a patient who has only a baseline assessment or a response assessment of CR/PR/SD at an interval less than 6 weeks (42 days) and has no subsequent disease evaluation, or has all overall response evaluations assessed as IND.

- If a patient's first overall response or first response other than IND is PD (documented within 16 weeks of first dose), then the patient's best overall response is PD. If the first response of CR/PR/SD at < 42 days is followed by a PD then the best overall response is PD.

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

Week 8	**Week 16**	**Week 24**	**Week 32**	**Best Overall Response**
Early Death				ED
CR	CR	PD		Confirmed CR
CR	IND	CR	PD	Confirmed CR
PR	CR	CR	PD	Confirmed CR
PR	CR	PD		Confirmed PR
PR	PR	PD		Confirmed PR
PR	SD/IND	PR	PD	Confirmed PR
PR	PR	CR	PD	Confirmed PR
CR	PR			If this is recorded despite data query then: SD if CR documented at 6 weeks; otherwise it is PD.
CR	PD/IND/missing			SD*
PR	PD/IND/missing			SD*
SD	PD/IND/missing			SD*
SD or IND	CR	PD		SD*
SD or IND	PR	PD		SD*
IND	PD			PD
IND	SD	PD		SD*
IND	IND	PD		IND

* The minimum assessment time from the date of the first dose to qualify as SD as the best overall response is 42 days.

Appendix 6. Evaluation of RECIST (version 1.1) Tumor Assessment Criteria (ALK-Negative NSCLC Patients Only)

The following describes the rules used for derivation of tumor response and progression based on Investigator Assessment of tumor data collected in study A8081001 for the cohort of ALK negative NSCLC patients recruited in the RP2D enriched population. The investigator assessments at each time are used to derived appropriate response category (CR, PR, SD, PD, IND) described below. Although the investigator provides response categories, the response categories derived using the RECIST criteria will be used in all summaries and analyses.

The analysis will be based on a programmatic approach to the investigator tumor assessment data recorded on the investigator target and non-target disease lesions pages of electronic case report forms (eCRFs).

Note that since this is a one-arm study with objective response as a key endpoint of interest, confirmation of response will be required when applying RECIST 1.1 to the ALK-negative NSCLC cohort. RECIST 1.0 requires confirmation in all cases while RECIST 1.1 requires confirmation for only one-armed studies.

General Basis for the Rules

The tumor response criteria are based on RECIST 1.1.[2]

Study Specific Information

- **Baseline**: is defined as the last observation prior to the first dose of study drug. The first dose is referred to the Cycle 1, Day 1 dose. The length of a cycle is 21 days.

- **Adequate Baseline:**

    - Baseline tumor evaluations must be performed within 5 weeks (35 days) prior to the first dose of study drug. Scans outside the time window will be considered protocol violations and will be evaluated on a case by case basis

    - Presence of target and/or non-target disease at baseline (ie, patients will not be excluded if they only have non-target disease);

    - All lesions recorded at baseline must have an associated status recorded on the CRF (eg, measurements for target lesions and “present” for non-target lesions);

    - Baseline lesions must be assessed with an acceptable method that includes: Conventional CT Scan, Spiral CT Scan, X-ray, MRI, Physical Exam, Bone Scan (only for non-target lesions), and Other. Note: If based on data review “unacceptable” methods (eg, ultrasound) are noted under “Other”, then this category will not be considered acceptable (on a case by case basis). Note: eCRF options of “Ultrasound”, “Endoscopy”, and “Cytologic Confirmation” are not acceptable methods for this cohort.

- **"On-study" period for efficacy:** is defined as the time from the date of the first dose until 35 days after the last dose of study drug. However, deaths will be included in the PFS analysis if they occur within 14 weeks (2 tumor assessment timeframes) from the last tumor assessment.

- **Subsequent anti-tumor treatment:** include systemic anticancer therapy (other than study medication) as indicated on the Subject Survival CRF which collects 'Has the patient received any subsequent cancer therapy (yes/no)' and 'If yes, therapy start date'. Note that this study does not collect specific information regarding type of subsequent therapy.

Methods of Tumor Assessment:

- The following are considered "interchangeable" methods: Conventional CT Scan, Spiral CT Scan and MRI.

Evaluation of Target Lesions for Each Visit:

Notes:

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

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

- Complete Response (CR) is defined by the disappearance of all non-lymph node target lesions (where all target lesions are recorded with a length of 0 mm on the "Target Lesions" eCRF). Any pathological lymph nodes (recorded as target lesion) must have reduction in short axis to < 10 mm. Note: the SLD may not be zero if lymph nodes are included as target lesions.

- Partial Response (PR) is defined by a 30% or more decrease in SLD of target lesions, taking as reference the baseline SLD.

- Progressive Disease (PD) is defined by a 20% or more increase in the SLD of target lesions relative to baseline or to the smallest SLD (nadir) recorded since treatment started. In addition to the relative increase of 20%, SLD must also demonstrate an absolute increase of at least 5 mm (≥ 5 mm) relative to baseline or to the smallest SLD (nadir) recorded since treatment started.

- Stable Disease (SD) is assigned when neither sufficient shrinkage to qualify for PR/CR nor sufficient increase to qualify for PD is observed, taking as reference the SLD post treatment.

- No Target Lesion at Baseline (NB) is assigned if "No Target Lesion" is checked, on the "Target Lesions" eCRF.

- Indeterminate (IND) is assigned if any or all target lesions are not assessed ("Not done" is checked on the "Target Lesions" eCRF) or any individual target lesion is evaluated as "Non-Measurable" ("Non-Measurable" is marked on the "Target Lesions" eCRF), or if inconsistent methods are used for post-baseline lesion assessment (see Note at the beginning of section) for any lesion, or an unacceptable method is used for one or more target lesions.

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

Evaluation of Non-Target Lesions for Each Visit:

Notes:

- The lesions assessed are only considered for CR, Non-CR / Non-PD and PD if the methods of assessments are consistent with baseline. The "interchangeable" methods noted above are all considered consistent methods.

  - CR is defined by the disappearance of all non-target lesions (where all non-target lesions are marked 'Absent' on the "Non-Target Lesion" eCRF). All lymph nodes must be non-pathological in size (< 10 mm in short axis).

  - Non-CR / Non-PD is defined if all non-target lesions are marked 'Stable' on the "Non-Target Disease Lesions" eCRF.

  - No Non-Target Lesion at Baseline (NB) is assigned if "No Non-Target Lesions" is marked on the "Non-Target Lesions" eCRF.

  - Indeterminate (IND) is assigned if any or all non-target lesions are not assessed ("Not done" is checked on the "log: Non-Target Disease Lesions" eCRF) or if inconsistent methods are used for post-baseline lesion assessment (see Note at the beginning of section) for any lesion.

  - Progressive Disease (PD) is assigned if any non-target lesion is marked 'unequivocal progression' on the "Non-Target Disease Lesions" eCRF. Any discrepancies between the non-target lesion assessment status and information on the IOTA page will be queried.

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

Overall Response Evaluation for Each Visit:

- Overall response is determined from the derived target and non-target lesion data using conventions in the table below under the assumption that there are no new lesions identified at the visit.

- If there are any new lesions at a time point, then the response is PD at that time point regardless of target or non-target lesion response.

- To group target and non-target lesion measurements and Investigator Overall Tumor Assessment (IOTA) eCRF to the corresponding actual post-baseline scan visit, a clustering algorithm is applied. Each cluster represents an actual visit. For each patient, the number of clusters is equal to the maximum number of assessments available among all target and non-target lesions. SAS software procedure, PROC FASTCLUS, is applied to a variable that represents the days from the date of first dose to the date of the scan for each target and non-target lesion (date of scan – date of first dose +1). Then the assessments of target and non-target lesions that occurred close to each other in time will be assigned to the same cluster.

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

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

Best Overall Response Evaluation for Each Patient:

- The best overall response is the best response (confirmed CR, confirmed PR, SD, Early Death, PD or IND) recorded during the “on-study” period.

- Best overall response is derived from the sequence of objective responses.

- A patient's best overall response will be Early Death if the patient died within 42 days of first dose and prior to having sufficient evaluations for overall response.

- Assessments done after PD or after "anti-tumor treatment" but prior to PD will not be considered for evaluation of best overall response, duration of response, or time to response (with the exception of an assessment of PD obtained within 14 days from start of an anti-tumor treatment in which case PD is still considered in the evaluation of the best overall response).

- For a patient to qualify for a best response of SD, the overall response evaluation must have met the stable disease criteria at least once since first dose at a minimum interval of 6 weeks (42 days). For any unconfirmed CR and PR, the best response will be SD provided it meets the 42 days requirement.

- Indeterminate (IND) is assigned for a patient who has only a baseline assessment, or a response assessment of CR/PR/SD at an interval less than 6 weeks and has no subsequent disease evaluation, or has all overall response evaluations assessed as IND.

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

Timing of Response

If there are multiple assessments within a cluster, then the following rules will be applied to derive the time of response for target, non-target and new lesions based on that cluster:

- If there are multiple new lesions in a cluster, then the first date that a new lesion was documented will be used as the actual date of PD;

- For target and non-target lesions the date of response (CR, PR, SD, PD, IND, as applicable) will be recorded as the date of the last radiographic evaluation included in the series for that assessment.

The date of best overall response is defined as the first date the response was documented.

The date of PD (for PFS and TTP) is the earliest date of:

1. Last assessment date for target lesions (in a cluster) if the SLD meets the criteria for progression;

2. Last assessment date for non-target lesions (in a cluster) if PD is documented based on the non-target response;

3. Earliest of new lesion dates (in a cluster).

The censoring date for PFS is the last date of an evaluable assessment that showed no PD.

Confirmed Objective Response Evaluation for Each Patient:

- Confirmed objective responses, including CR and PR, are defined as responses that persist on repeat imaging study for 2 assessments with a time period of at least 4 weeks (28 days) between 2 assessments. These 2 assessments need to evaluate all sites of disease that have been followed since baseline (ie, all target and non-target lesions).

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

Note: For consistency with RECIST 1.0 as described above, the term "IND" for indeterminate is used in lieu for "NE" for inevaluable, which is the designation used in the protocol.