PROTOCOL A8081001

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

STATISTICAL ANALYSIS PLAN

(SAP)

Version: 10.0

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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 in version 10.0 from version 9.0 (dated June 30, 2016) described in the current document are as below.

- Updated SAP to incorporate changes reflected in protocol Amendment #23 and #24 and protocol administrative clarification letters.
- Specified the updated safety analyses for various cohorts in the final CSR reporting.
- Clarified the analyses details for the hypogonadism parameters and patients who were in RP2D Enriched Other cohort but not in any other defined RP2D cohorts.
- Editorial changes to enhance clarity.

The main changes in version 9.0 from version 8.0 (dated June 13, 2016) all pertained to the itraconazole sub-study, as summarized here:

- Clarified details regarding displays of the Treatment Emergent Adverse Events (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 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 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 6.0 (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 marker 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 "MET" to "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 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: 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 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, MET amplified NSCLC cohort, ALK-negative NSCLC Cohort #2).

The main changes (more minor changes in italics) 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 - #24 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, the ROS1 marker positive NSCLC patients, and the MET Exon 14 alterations 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 CCI 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 standard 3 + 3 design [1] for dose escalation component in patients with advanced, solid tumors refractory to standard therapy. Patients are enrolled in cohorts of three patients. 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

- MET amplified NSCLC cohort
- ROS1 marker positive NSCLC cohort
- Enriched Other cohort, including NSCLC patients with tumors harboring 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 and analyses of hypogonadism 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 MET kinase domain activating mutations; or having chromosomal translocations/ fusions that lead to altered transcriptional regulation of 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 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 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.

[redacted]

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

[redacted]

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 approximately 600 patients will be enrolled in this study including patients in the dose escalation, RP2D, and DDI cohorts (rifampin and itraconazole).

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)^5

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
  - MET-amplified NSCLC enriched cohort
  - ROS1 marker 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 marker 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, the ROS1 marker positive NSCLC patients, and the MET Exon 14 alterations NSCLC patients. The Supplemental SAP also includes detail regarding evaluation of response for RP2D cohorts that use RECIST 1.0[4] (ALK-positive NSCLC cohort, MET-amplified NSCLC cohort, and ROS1 marker positive NSCLC patients, and Enriched Other cohort) and separately for those that use RECIST 1.1[5] (ALK-negative NSCLC cohort #1 and ALK-negative NSCLC cohort #2).

4.2.1.1. MET-Amplified NSCLC Cohort

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

- High Level MET Gene Amplified Category (MET/CEP7 ratio ≥5.0): as documented in Amendment # 24 and based on the Protocol Administrative Clarification Letter (PACL) dated 15 May 2017, the MET/CEP7 ratio cutoff for this group was revised to ≥4.0. As per the PACL dated 11 September 2018, this group was closed to further enrollment. The remaining 14 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

- Medium Level MET Gene Amplified Category (MET/CEP7 ratio >2.2 to <5.0): as documented in Amendment # 24 and based on the PACL dated 15 May 2017, the MET/CEP7 ratio cutoff for this group was revised to >2.2 to <4.0; this

group was closed to further enrollment. The remaining 13 enrollment slots were transferred to the MET Exon 14 alterations subgroup within the Enriched Other cohort.

- Low Level MET Gene Amplified Category (MET/CEP7 ratio ≥1.8 to ≤2.2)

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 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 MET or ROS1 to occur prior to enrollment was removed. Thus, MET or ROS1 testing may have been performed prior to patient entry into this cohort. However, if the test result for either MET or ROS1 was positive, then the patient could not be enrolled into this cohort.

The ALK-negative cohort #2 was driven partly by the belief that patients whose tumors were negative by the Investigational Use Only (IUO) test, 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 MET kinase domain activating mutations; who have chromosomal translocations/ fusions that lead to altered transcriptional regulation of 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 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 171patients will be enrolled. RECIST version 1.0 is used to assess tumor activity in this cohort.

In NSCLC patients with tumors harboring 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. As of data cutoff date 01 August 2016, 11 confirmed objective responses (CR, PR) were observed in a total of 28 response-evaluable patients with MET Exon 14-positive NSCLC. Based on the number of confirmed objective responses observed, the null hypothesis was rejected. The proportion of responders will be estimated with better precision if the number of evaluable patients exceeds 33 patients.

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

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

3. As of the PACL issued 07 December 2017, sites were allowed to enroll an additional 13 patients with MET Exon 14-positive NSCLC into the Enriched Other cohort. These patients were originally slotted for the broader Enriched Other cohort and

were now assigned specifically to patients with MET Exon 14-positive NSCLC. As a result, the total enrollment of the Enriched Other cohort subset of patients with MET Exon 14-positive NSCLC increased to 81 patients (68 [defined in point 2 above] + 13 patients).

4. As of the PACL issued 11 September 2018, further enrollment of NSCLC patients into the MET high amplification group was closed and the remaining 14 enrollment slots were transferred to the MET Exon 14-positive NSCLC subgroup within the Enriched Other cohort. As a result, the total enrollment for patients with MET Exon 14-positive NSCLC was increased to 103 patients (81 [defined in point 3 above] +14+8 [additional slots that were allowed without exceeding the total overall study enrollment of approximately 600 patients]).

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

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. CCI [redacted] 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 marker positive NSCLC cohort, the ALK-positive NSCLC cohort, and the MET Exon 14 alterations NSCLC patients. 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, MET, and Enriched Other. See the Supplemental SAP for details regarding the ROS1 marker positive and MET exon 14 alterations NSCLC patients.

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 marker positive NSCLC Patients and MET Exon 14 alteration NSCLC patients

Additional details regarding the PK and other analyses planned for the ROS1 marker positive NSCLC patients and for MET Exon 14 alteration 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.

Ophthalmologic Exam Evaluable Set definitions has been updated to "NSCLC Detailed Ophthalmologic Exam - ITT Population" and "NSCLC Detailed Ophthalmologic Exam 10 Tests – Evaluable Population" in section 5.6 below.

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 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 parameters was to be performed at the next clinic visit to confirm hypogonadism.

Hypogonadism Test Evaluable Population

The Hypogonadism Test Evaluable Population is defined as patients included in the Safety Population who have complete screening and at least one post baseline visit data for at least the key parameters of total testosterone, free testosterone, sex hormone binding globulin (SHBG).

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. As of IRB/EC approval of Protocol Amendment #23, tumor scans from ROS1 marker positive NSCLC patients will no longer be collected for and submitted to an independent radiology laboratory for review. In addition, all tumor scans from NSCLC patients with tumors harboring MET Exon 14 alterations will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As per PACL dated 9 March 2018, all tumor scans for patients enrolled in the MET-amplified NSCLC cohort will be collected and submitted to an independent radiology laboratory for review until notification is received from the Sponsor. As of IRB/EC approval of Amendment #24, tumor scans from patients with MET-amplified NSCLC will no longer be collected and submitted to an independent radiology review laboratory.

- 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, 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)].

C
C
I

[redacted]

- 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.

C
C
I

[redacted]

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. CCI /Pharmacogenomic Parameters

Missing data for the CCI 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 CCI 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 binary 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).[2] 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, ROS1 marker positive NSCLC and MET Exon 14 alteration 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: MET-amplified NSCLC cohort
6. RP2D: ROS1 marker positive NSCLC cohort *, +
7. RP2D: MET Exon 14 alteration NSCLC
8. RP2D: Rifampin Drug Drug Interaction
9. RP2D: Itraconazole Drug Drug Interaction
10. RP2D: MDZ Drug Drug Interaction
11. 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 marker 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 marker 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 purpose, 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 marker positive NSCLC or 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.

For the High Dose Escalation, MET amplified NSCLC, MET Exon 14 NSCLC, Enriched Other cohorts, all efficacy and safety analyses will be conducted separately

within each cohort according to the previous sections in this SAP and supplemental SAP.

For the cohorts that were previously reported and with ongoing patients at the time of previous data cutoff including ALK Positive NSCLC, ALK negative NSCLC #1, ALK negative NSCLC #2, ROS 1 marker positive NSCLC, Rifampin DDI, Itraconazole DDI, all previously reported efficacy analyses were included in the CSRs associated with these cohorts. There will be no updated efficacy analyses for these cohorts. The safety analyses including patient disposition, demographic and baseline characteristics, treatment administration, protocol deviation, primary diagnosis, AE, SAE, permanent discontinuation, temporary discontinuation, dose reduction, death, e-DISH plots, lab shift summaries, vital sign and ECG summaries will be updated in the final CSR.

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, 3, 4, 5, 6
ALK-negative NSCLC #2 cohort:	items 1-6
ALK-positive NSCLC cohort:	items 1-4, 6-8
MET-amplified NSCLC cohort:	items 3, 4, 5, 6, 7
ROS1 marker positive NSCLC cohort:	items 3, 4, 5, 6, 7
MET Exon 14 alteration NSCLC patients:	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. Annual and unscheduled assessments are included in the evaluation of the worst change from baseline category; when the summary is across both eyes, then the worst scheduled or unscheduled post-baseline values for either eye is included in the summary. 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 marker positive NSCLC cohort, 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 pat Ophthalmologic Testing (Protocol Amendment

  ients 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 (without regard to simultaneous temporal occurrence).

The following are the definitions of abnormality:

- Best-corrected visual acuity (BCVA) : >= 2 line loss in either eye from baseline.
- 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 (IOP) >22 mm Hg

- Change in optical coherence tomography (OCT) center point thickness of >50 μm from baseline
- refractive error associated with BCVA (a change in spherical or cylindrical refraction power of ±1.25 diopters relative to baseline
- Pupillary diameters and symmetry: a change of greater than ±2 mm from baseline

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 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 compared to the laboratory-provided age-specific reference range for males. The 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 if there are sufficient 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 change from baseline on the hypogonadism parameters is of interest.

Observed values, including those below/above the age-specific reference ranges, and changes/shifts from baseline will be summarized at each timepoint, with as appropriate. Summaries will be presented for all patients regardless of their enrollment cohort. Additional summaries for each source of enrollment (ie, the 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 marker positive NSCLC patients and MET Exon 14 alterations NSCLC patients; PK analyses for the ROS1 marker positive NSCLC patients and MET Exon 14 alterations 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[3] "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, MET-amplified NSCLC cohort, ROS1 marker 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 MET amplified NSCLC cohort, (2) the ROS1 marker positive NSCLC cohort, and (3) patients in the Enriched Other cohort with NSCLC who have tumors harboring MET Exon 14 alterations. Within each patient group, survival follow-up will continue until 1 year after the last patient’s last dose. As of protocol Amendment #23, survival follow-up was extended for ROS1 marker positive NSCLC patients, NSCLC patients with tumors haboring MET gene amplification, and MET Exon 14 alterations to 2 years after the last patient in each of these cohorts has discontinued PF-02341066 treatment.

Response will be derived based on the investigator assessment according to the rules described in Appendices 5 and 6 of the Supplemental SAP for the following groups:

ALK-positive NSCLC cohort, ALK-negative NSCLC cohort #1, ALK-negative NSCLC cohort #2, MET-amplified NSCLC cohort, ROS1 marker 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 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 confirmed 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 marker positive NSCLC patients, and MET Exon 14 alterations 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.

For all patients in RP2D who are not in one of the other RP2D cohorts (Appendix 1), the best overall response per RECIST version 1.0 will be summarized. ORR, calculated as the number of evaluable patients with a best overall response of confirmed CR or confirmed 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. If numbers of patient in certain tumor type/molecular marker are sufficient, the summary will be provided by these tumor type/molecular markers, as appropriate.

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 MET-Amplified NSCLC Categories

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

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10. APPENDICES

Appendix 1. COHORT and OTHER SUBGROUP DEFINITIONS

The following describes how cohorts that will be used for analyses will be identified based on the data (note that the cohorts are defined for enrollment purpose, but the cohorts are not necessarily mutually exclusive for purposes of analysis):

Dose-escalation cohort

BID: Patient has a subject randomization 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:

- Subject randomization 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 primary diagnosis is non-small cell lung cancer AND laboratory (Abbott Lab, US Labs, or Esoterix) test for ALK was negative.

b. **RP2D: ALK-Positive NSCLC Cohort -** Patients in the RP2D cohort with "Result Classification" = "POSITIVE" on the *Diagnostic Marker Test – ALK CRF* AND primary diagnosis is non-small cell lung cancer. All ALK-Positive patients with Randomization Subgroup= "SUBGROUP 8" or "SUBGROUP 6" (Asian subjects who are ALK-Positive Day -7 exempt).

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. **MET-Amplified NSCLC Cohort** – Patients in the RP2D cohort with "Result Classification" = "POSITIVE" on the *Diagnostic Marker Test – cMET/Gene Amplification CRF* AND primary diagnosis is NSCLC. Subgroups of this cohort were identified in the protocol:

- High Level MET: MET/CEP7 Ratio ≥5: as documented in Amendment # 24, and based on the PACL dated 15 May 2017, the MET/CEP7 ratio cutoff for this group was revised to ≥4.0.
- Medium Level MET: MET/CEP7 ratio >2.2 to <5: as documented in Amendment # 24 and based the PACL dated 15 May 2017, the MET/CEP7 ratio cutoff for this group was revised to >2.2 to <4.0.
- Low Level MET: MET/CEP7 ratio ≥1.8 to ≤2.2

e. **ROS1 marker 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 MET Exon 14 subgroup of this cohort. For these patients, Subgroup = "SUBGROUP 17 (Enriched other (other cancers) cohort)" on the *Subject Randomization* CRF.

g. **RP2D: Enriched Other Cohort, MET Exon 14 Alteration Patients with NSCLC** – Enrolled in Randomization Subgroup = "SUBGROUP 17" on the Subject Randomization CRF and have a "Positive" finding on the *Diagnostic Marker Test –- CMET EXON 14 DELETION* CRFAND primary diagnosis is non-small cell lung cancer.

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 marker 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 marker positive NSCLC, MET-amplified NSCLC, ALK-negative NSCLC cohort #2, Rifampin cohort (if NSCLC) as well as the Enriched Other cohort. Additional summaries may be presented for separate cohorts.

- The patients used to analyze hypogonadism data are drawn from the patients in MET-amplified NSCLC and the Enriched Other cohort.

Appendix 2. SUMMARY OF ANALYSES BY COHORTS

The analyses of DDI cohorts (rifampin and itraconazole) are discussed in subsequent Appendix 4 and Appendix 5.

Analyses	COHORTS							
	Dose-Escalation	RP2D Cohort						
	Total and By Dose*	ALK-Positive NSCLC	ALK-Negative NSCLC #1	ALK-Negative NSCLC #2	MET amplified NSCLC §	ROS1 marker positive NSCLC §	MET Exon 14 NSCLC §	Enriched Other**, §
Standard Analyses								
Patient disposition	X	X	X	X	X	X	X	X
Patient disposition by Cycle		X		X				X
Demographic and Baseline Characteristics (including Prior Therapies)	X	X	X	X	X	X	X	X
Diagnostic Biomarker Results		X	X	X	X	X	X	X
Treatment Administration	X	X	X	X	X	X	X	X
Safety Analyses								
DLTs	X							
AE summaries	X	X	X	X	X	X	X	X
AEs (Cycle 1, Cycle >1)	X	X						~~X~~
Lab summaries	X	X		X	X	X	X	X
Labs (Cycle 1, Cycle 2, Cycle >2)	X	X						~~X~~
Time to AE, duration, etc.		X				X	X	
Efficacy Analyses								
Best overall response	Listings only	X	X***	X***	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	MET amplified NSCLC §	ROS1 marker positive NSCLC §	MET Exon 14 NSCLC §	Enriched Other**, §
Objective response rate		X	X	X	X	X	X	X
Duration of response		X	X	X	X****	X	X	(Listed)
Duration of SD		X	X	X	X	X	X	X
Time to response		X	(Listed)	(Listed)	X****	X	X	(Listed)
Disease control rate at 8 and 16 weeks (6 and 12 for ALK-negative NSCLC)		X		X	X****	X	X	
PFS, 6 month PFS		X			X****	X	X	(Listed)
OS, 6 and 12 month OS		X			X****	X	X	(Listed)
PK Analyses	X	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, 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 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 MET amplified NSCLC cohort.

§For patients in the 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 marker 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 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. As of Amendment #23 survival follow-up was extended for ROS marker positive NSCLC patients, NSCLC patients with tumors haboring MET gene amplification, and MET Exon 14 alterations to 2 years after the last patient in each of these cohorts has discontinued PF-02341066 treatment.

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 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 ≥ 90mL/min), mild (60mL/min ≤CLcr<90mL/min), moderate (30mL/min ≤ 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.

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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 marker positive nor 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 (BAZETT'S CORRECTION) (msec):
Change categories: <450, 450-<480, 480-<500, ≥500

Maximum QTcF (FRIDERICIA'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

Maximum QRS COMPLEX increase from baseline (msec)
Change≥25% and Baseline Value≥100 msec
Change≥50% and Baseline Value<100 msec
None of the above

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

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

For the vital sign, laboratory, and ECG data, both planned and unplanned post-baseline measuremnt 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

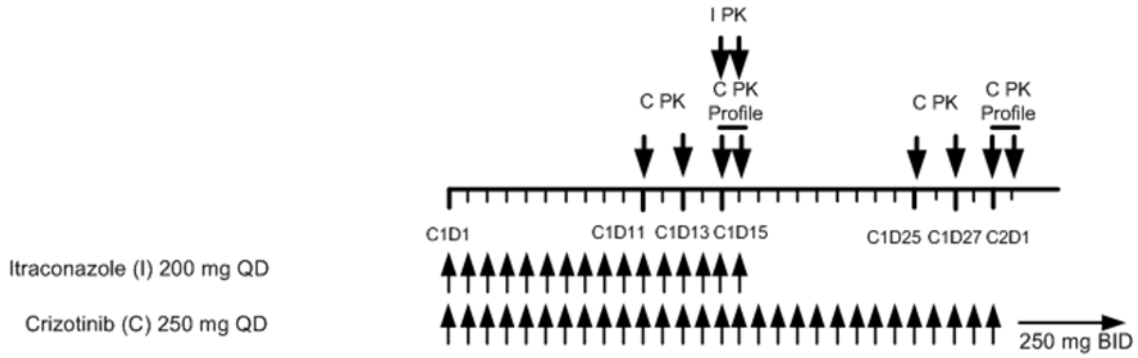
The details of the SAP as they pertain to the itraconazole DDI sub-study are included in this appendix.

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. If the patient never started BID dosing but did have PK analyses performed at the end of Treatment Period B, then the data for that patient would be included through the PK sampling scheduled for Cycle 2 Day 1, if available. If the patient never started BID dosing and withdrew before Cycle 2 Day 1, data would be included up through the withdrawal date. If the patient never started BID dosing and withdrew at or beyond Cycle 2 Day 1, data would be included up and through study day 29 (scheduled Cycle 2 Day 1). 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 ≥ 90mL/min), mild (60mL/min ≤ CLcr < 90mL/min), moderate (30mL/min ≤ 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%

$MRAUC_{tau}$ [a] MRC_{max} [a]	
T_{max}	N, median, 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. In the shift tables, individual grade shifts will be shown (ie, grade categories will not be collapsed.) 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 8.1.2.4;; change from baseline summaries will be included.