A PHASE 1 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF PF-04449913, AN ORAL HEDGEHOG INHIBITOR, ADMINISTERED AS SINGLE AGENT IN SELECT HEMATOLOGIC MALIGNANCIES

Compound: PF-04449913
Compound Name (if applicable): Not Applicable
EudraCT Number 2009-011285-29
US IND Number (if applicable): 105453
Protocol Number: B1371001
Phase: 1

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## Document History

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<td>Amendment 3*</td>
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*Note: The table contains redacted text.*
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<td>This amendment incorporates all revisions to date except those in the amendment(s) indicated with an (<em>). The sites following the amendment(s) marked with an (</em>) above must use the specific region/country/site amendments as well as the current amendment.</td>
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PROTOCOL SUMMARY

Indication:

PF-04449913 will be administered as a single agent to adults with select advanced hematologic malignancies. Patients are eligible if they are refractory, resistant or intolerant to prior therapies. They may also be newly diagnosed and previously untreated (for all diseases with the exception of non-T315I CML) but not eligible for standard treatment options, or for whom standard therapies are not anticipated to result in a durable response.

Objectives:

Primary Objectives

1. To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of PF-04449913 when administered alone to adults with select advanced hematologic malignancies.

Secondary Objectives

1. To determine the safety and tolerability of PF-04449913 when administered alone to adults with select advanced hematologic malignancies.

2. To evaluate the pharmacodynamics of PF-04449913 alone in adults with select advanced hematologic malignancies.

3. To evaluate the pharmacokinetics of PF-04449913 alone in adults with select advanced hematologic malignancies including an evaluation of the effect of food.


5. To characterize the effects of PF-04449913 alone on QTc in adults with select advanced hematologic malignancies.

Endpoints:

Primary Endpoint

1. First cycle dose limiting toxicities (DLTs) (Section 3.1.2).

Secondary Endpoints

1. Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

2. Pharmacodynamic biomarker modulation.
3. Pharmacokinetic parameters of PF-04449913.

4. Overall response, time to progression (TTP), duration of response and progression-free survival (PFS) as defined by disease specific clinical practice guidelines (Appendix 4 through Appendix 8).

5. QTc interval.

**Trial Design:**

This is an open-label, multi-center, Phase 1 study of PF-04449913 administered orally as single agent to adults with select advanced hematologic malignancies. Patients are eligible if they are refractory, resistant or intolerant to prior therapies. They may also be newly diagnosed and previously untreated (for all diseases with the exception of non-T315I CML and in compliance with national treatment guidelines for AML) but not eligible for standard treatment options, or for whom standard therapies are not anticipated to result in a durable response.

The study will assess PF-04449913 administered as single agent once daily in a continuous regimen to patients with select advanced hematologic malignancies. The later cohorts may be enriched for diseases which exhibit early signs of activity in the preceding dose escalation cohorts. A dose escalation design will be applied in 3-6 patient cohorts up to identification of the maximum tolerated dose (MTD) or attainment of the dosing cap. The starting dose will be 5 mg once daily. Dosing of PF-04449913 will be based on flat milligram increments without adjustment for body surface area. There will be a lead-in period on Day -6 for each dose escalation cohort in which the single-dose pharmacokinetics and pharmacodynamics of PF-04449913 will be characterized prior to initiation of continuous dosing in the first cycle of treatment. The lead-in period duration, PK time-points, doses and/or regimens used in subsequent cohorts may be modified based on the exposure (AUC) observed during the lead-in period (although the number of PK samples will not be increased).

Once the MTD is established or attainment of the dosing cap, a cohort will be expanded with at least 8 additional patients to further characterize safety and tolerability at the MTD/maximum administered dose (MAD) or a lower dose that has already been tested, to conduct a pharmacokinetic food effect assessment (Sections 3.1.3 and 5.2.4.2), and to collect blood and urine for metabolite profiling/urine PK.

Treatment with PF-04449913 may continue for up to 12 cycles or until disease progression, patient withdrawal or unacceptable toxicity occurs. Patients who complete 12-cycles of treatment will be considered to have completed the trial. Patients who are still on trial after 12-cycles and who continue to benefit from treatment may have the option to continue treatment upon agreement between the investigator and sponsor, and pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed at the same frequency listed in Table 1 (Schedule of Activities).
The RP2D will be determined after review and discussion of the study data by the sponsor and investigators. Consideration will be given to the PK profile, type and severity of drug related toxicity and clinical suitability for long-term administration.

Pre- and post- PF-04449913 dose blood, bone marrow biopsies and normal skin may be obtained for biomarker assessments and evaluating potential genetic changes that could correlate to clinical outcome. These assessments will include pharmacodynamic analyses of Hedgehog target genes, proteins and other signaling pathways which may interact with the Hedgehog pathway.

**Statistical Methods:**

**Sample Size Determination**

No formal sample size determinations were performed for the dose escalations. The sample sizes for assessing the food effect and pharmacodynamic biomarker analysis were chosen empirically.

The number of patients to be enrolled in the study will depend on the observed safety profile, and the number of dose escalations.

The expected number of patients is estimated to be 52.

**Analysis:**

As the primary purpose of this study is to define the MTD and RP2D, no confirmatory inferential analyses are planned. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, pharmacokinetic and pharmacodynamic parameters. Data will also be displayed graphically where appropriate.
## SCHEDULE OF ACTIVITIES

**Table 1.** PF 04449913 Single Agent Escalation in Select Hematologic Malignancies

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<tr>
<th>Protocol Activity</th>
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<th>Lead-in PK period&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Cycle 1 (28-day cycle)</th>
<th>Even Cycles&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Odd Cycles&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Even Cycles&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Odd Cycles&lt;sup&gt;*&lt;/sup&gt;</th>
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<td>PF-04449913 Blood for Metabolite profiling&lt;sup&gt;17&lt;/sup&gt;</td>
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<sup>1</sup> Informed Consent: Obtain informed consent of the subject and sign the informed consent document.
<sup>2</sup> Medical/Oncologic History: Obtain a medical history and review relevant prior medical records.
<sup>3</sup> ECOG Performance Status: Assess ECOG performance status.
<sup>4</sup> Physical Examination: Conduct a complete physical examination.
<sup>5</sup> CBC: Complete blood count.
<sup>6</sup> Blood Chemistry: Conduct a comprehensive blood chemistry panel.
<sup>7</sup> Urinalysis: Perform a urinalysis.
<sup>8</sup> Pregnancy test: Conduct a pregnancy test.
<sup>9</sup> 12-lead ECG: Perform a 12-lead electrocardiogram.
<sup>10</sup> Adverse Event Monitoring: Monitor for adverse events.
<sup>11</sup> Review Prior/Concomitant Medication: Review prior and concomitant medications.
<sup>12</sup> Drug Compliance: Monitor drug compliance.
<sup>13</sup> PF-04449913: Commence treatment with PF-04449913.
<sup>14</sup> Lead-in PK period: Collect lead-in pharmacokinetic samples.
<sup>15</sup> Blood for PK: Collect blood samples for pharmacokinetic analysis.
<sup>16</sup> Blood for Metabolite profiling: Collect blood samples for metabolite profiling.

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<tr>
<th>Protocol Activity</th>
<th>Screen</th>
<th>Lead-in PK period(^{14})</th>
<th>Cycle 1 (28-day cycle)</th>
<th>Even Cycles(^{*})</th>
<th>Odd Cycles(^{*})</th>
<th>End of Tx Withdrawal</th>
<th>Post Tx Follow Up(^{22})</th>
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<td>PF-04449913 Urine collection for PK(^{18})</td>
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<td>Bone marrow aspirate and/or biopsy for clinical staging (biopsy may also be used for pharmacodynamic (PD) biomarker analysis)(^{19}) (±5 days)</td>
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<td>Immunophenotyping and Cytogenetics(^{20})</td>
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<td>For CML Patients: mutation status and PCR for BCR-ABL(^{24})</td>
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<td>For Non-CML patients: mutation status(^{22})</td>
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<td>Blood samples for PD biomarkers(^{21})</td>
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<td>Normal Skin Punch Biopsy(^{23}) (±2 day)</td>
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\(^{*}\) For Cycle 7 and above only a Day 1 assessment is required.

\(^{**}\) Days -6 should be considered Baseline for all assessments (except when the assessments are required only at screening). There is no Day 0 in the study.
Footnotes for Schedule of Activities – Phase 1 (PF-04449913 Single Agent Dose-escalation in Select Hematologic Malignancies)

1. Informed Consent: Must be obtained prior to undergoing any study procedure and may occur prior to the 28-day screening period.

2. Medical History: To be collected within 28 days prior to first dose of PF-04449913. Includes oncology history, history of other diseases (active or resolved), and concomitant illnesses. During trial treatment any new or worsened conditions since baseline should be reported on the Adverse Event CRF. Include information on prior regimens, including dosing and duration of administration plus description of best response observed and treatment failure based on Disease Specific Guidelines.

3. ECOG performance scale is available in Appendix 1 of the protocol.

4. Physical examination includes major body systems as well as measurement of spleen and liver size to assess extramedullary disease (EMD) (if PE obtained within 48 hrs of previous assessment, the evaluation need not be repeated). Weight must be recorded at Screening and Cycle 1/Day 1 of each cycle. Height need not be recorded after first measurement.

5. CBC: WBC with differential, hemoglobin and platelet count. Additional hematology tests may be performed as clinically indicated. If CBC was obtained within 48 hours of scheduled blood draw, the collection need not be repeated.

6. Blood Chemistry: Total bilirubin, indirect and direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, magnesium, chloride, calcium, phosphorus, BUN, creatinine, uric acid, glucose. Additional chemistry tests may be performed as clinically indicated (eg, amylase, lipase, creatinine kinase, GGT). If blood chemistry was obtained within 48 hours of scheduled blood draw, the collection need not be repeated.

7. Urinalysis: For pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite (microscopic urinalysis). Additional urinalysis may be performed as clinically indicated.

8. Pregnancy tests (serum/urine) for women of childbearing potential only, which must be performed within 72 hours prior to initiation of treatment. It may also be repeated as per request of IRB/IECs or if required by local regulations.

9. 12-lead ECG: At each time point, three consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. ECGs will be collected as follows: a) at Screening; b) On Day -6, at pre-dose and 1, 4, and 24 hr post-dose; c) On Cycle 1/Day 1, at pre-dose and 1 hr post-dose; d) On Cycle 1/Day 5 pre-dose and Day 8, at pre-dose, 1hr (matched with the ECG) and 4hr post-dose; e) On Cycle 1/Day 15, at pre-dose and 1 hr post-dose (matched with the ECG); f) On Cycle 1/Day 21, at pre-dose and 1, 2, 4, and 24 hours following the dose of PF-04449913.

10. Adverse Events: Patients will be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable,” whichever is later. Serious Adverse Events should be monitored and reported from the time the patient provides informed consent as described in Section 8 of the protocol.

11. Concomitant Medications: Concomitant medications will be recorded from 28 days prior to the start of study treatment, at study entry, and during the study. Once the patient has withdrawn from the study, concomitant medications and treatments should be recorded for 28 days post last on-study treatment administration or until initiation of another oncologic treatment and all study drug-related toxicities have resolved, whichever is later.

12. Drug compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability at Day 1 of each cycle.

13. PF-04449913 dosing: A single dose of PF-04449913 will be administered on Day –6 (lead-in period) for all patients.

14. The duration of the lead-in period may be modified based on pharmacokinetic data obtained. Based on this assessment, the timing of the PK and PD samples in the lead-in period may be modified, but the actual number of samples will not increase.

15. PF-04449913 Blood for PK for all cohorts including the food effect expansion: a) Blood samples will be collected during the lead-in period (Day -6), at pre-dose and at 0.5, 1, 2, 4, 8, 24, 48, 96 and 120 hr post-dose; b) On Cycle 1/Day 1 at pre-dose and 1 hr post-dose (matched with the ECG); c) On Cycle 1/Day 5 pre-dose and Day 8, at pre-dose, 1hr (matched with the ECG) and 4hr post-dose; d) On Cycle 1/Day 15, at pre-dose and 1 hr post-dose (matched with the ECG); e) On Cycle 1/Day 21 at pre-dose and at 0.5, 1, 2, 4, 8 and 24 hr post dose; f) For Cycles 2, 3, 4 and 5 on Day 1 at pre-dose and 1 hr post-dose (matched with the ECGs); g) For Cycles 6 and above, on Day 1 at 1 hr post-dose (matched with the ECG). If a patient undergoes a lumbar puncture a sample of CSF should be collected for exploratory analysis of PF-04449913 concentrations if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample.
16. For patients in the food effect study (first 8 patients): PK samples will be collected on Day -6 as described in footnote 15 (at pre-dose and 0.5, 1, 2, 4, 8, 24, 48, 96 and 120 hr) and modified for Cycle 1/Day 1 to the following: pre-dose and 0.5, 1, 2, 4, 8, and 24 hours post-dose. Each patient will serve as their own control in which PF-04449913 will be administered in the morning under either “fed” or “fasted” conditions on Day (-6) and Day 1 of Cycle 1. The testing order for fed versus fasted conditions will be as follows: The first 4 patients to participate in this sub-study will be tested under fed followed by fasted conditions, the next 4 patients will be tested under fasted followed by fed conditions.

17. PF-04449913 blood for metabolite profiling: Metabolite profiling will be conducted only in the food effect expansion cohort (first 8 patients). Blood samples will be collected at screening and on Cycle 1/Day 21, at pre-dose and at 0.5, 1, 2, 4, 8 and 24 hours following PF-04449913 dosing.

18. PF-04449913 Urine collection for PK/metabolite ID: Urine will be collected in all cohorts for PK and metabolite ID, but urine may only be analyzed for metabolite ID from the food effect expansion cohort. Patients will empty their bladders just prior to dosing on Cycle 1/Day 21 and urine collected over 24 hr post-dose.

19. A bone marrow aspirate and/or biopsy (±5 days of nominal date) will be collected for clinical staging (footnote 20; BM only). If a bone marrow biopsy is collected it may also be used for PD biomarker assessments, if feasible. For AML and CML AP/BC patients these will be collected at a) screening, b) every even cycle on Day 1 and c) at End of Treatment and at investigators discretion. For all other diseases these will be collected at screening and Day 1 of Cycle 2, 6 and 10 (and every 4 cycles), End of Treatment and at investigators discretion. If a bone marrow aspirate and/or biopsy has been collected within 28-days (excluding the screening sample) it need not be repeated. With sponsor approval, the screening bone marrow need not be performed based on the patient characteristics (eg, dry tap or inevaluable) or a bone marrow performed prior to the screening period may be used for study inclusion.

20. Quantitative immunophenotyping and cytogenetics on blood and/or bone marrow will be conducted for all patients at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy as well as at screening (if a bone marrow is not performed the assessments should be performed using blood), End of treatment, and at investigators discretion.

21. PF-04449913 blood for PD biomarkers: Blood will be collected a) at screening; b) On Day -6 at pre-dose, 1 hr, a 4 hr and 24 hr post PF-0449913 dosing; c) on Cycle 1/Day 21 at pre-dose.

22. Follow-up Visit: At least 28 days, and no more than 35 days, after discontinuation of treatment patients will return to undergo review of concomitant medications, CBC and blood chemistry, physical exam and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

23. A normal skin punch biopsy will be collected at screening and on Cycle 1/Day 21 (±2 day of nominal date). Both biopsies should be obtained from approximately the same body location. Sample handling details will be provided in the lab manual.

24. For all CML patients mutation analyses will be conducted on blood and/or bone marrow samples at screening only. Quantitative PCR for BCR-ABL will be conducted on blood and/or bone marrow samples at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy as well as at screening (if a bone marrow is not performed the assessments should be performed using blood), End of Treatment, and at investigators discretion.

25. For all Non-CML patients mutation analysis is required within 6-months of start of the lead-in period. If not been performed within 6 months the mutation analysis will need to be performed on blood or bone marrow at screening.
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1. INTRODUCTION

This is the first-in-patient study of PF-04449913, a novel small molecule inhibitor of the Sonic Hedgehog (Hh) Pathway being developed for cancer therapy. The study is designed to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of PF-04449913 administered orally alone to adults with select advanced hematologic malignancies. The general clinical plan is development of PF-04449913 in both hematologic malignancies and solid tumors.

1.1. Indication

PF-04449913 will be administered as a single agent to adults with select advanced hematologic malignancies. Patients are eligible if they are refractory, resistant or intolerant to prior therapies. They may also be newly diagnosed and previously untreated (for all diseases with the exception of non-T315I CML) but not eligible for standard treatment options, or for whom standard therapies are not anticipated to result in a durable response.

1.2. Background and Rationale

1.2.1. Malignancy, Stem Cells and the Hedgehog (Hh) Signaling Pathway

A milestone in understanding cancer as a developmental problem is the identification of cancer stem cells that self-renew, reinitiate tumor development and give rise to the tumor bulk. Ultimately, this can contribute to resistance and metastatic spread, affecting overall survival. Standard chemotherapy, radiotherapies and some targeted therapies can greatly reduce tumor bulk but may be less effective on quiescent cancer stem cells. The key challenge has been in identifying the molecular mechanisms that maintain and support cancer stem cell self-renewal and survival.

Hedgehog and Gli signaling (Hh-GLI) are critical pathways in animal patterning during embryogenesis, and may play a key role in human malignancies when aberrantly activated. Post birth, the Hh pathway is normally repressed. Hh signaling is initiated when Hh binds to Patched (PTCH) and deactivates its function, which in the absence of Hh, negatively regulates signaling. After Hh deactivates PTCH, the seven-transmembrane protein Smoothened (SMO), which is normally held in an inactive state by PTCH, is released to activate a signaling cascade that ultimately regulates the Gli family of transcription factors (Figure 1). Gli family member genes encode proteins that act either as transcriptional repressors in the absence of Hh, or as transcriptional activators in the presence of Hh. Several proteins can modulate the ratio of Gli activator (GliA) to Gli repressor (GliR) activity and, in doing so; ultimately determine the level of Hh perceived by the cell (Figure 1).

Since its original description, the Hh pathway has received increasing attention as a pleiotropic oncogenic pathway that has been implicated in both hematopoietic and solid tumor malignancies by diverse mechanisms, including direct cell cycle and anti-angiogenic effects (Thomas BJ, 2005; Straface G, et al, 2008). As these cell types and mechanisms are unrelated in developmental origin, site, or function, a common dependence of cancer stem cells on Hh-GLI signaling for survival and self-renewal, paralleling its roles in normal
development and homeostasis, could underlie its widespread involvement in human cancers (Altaba AR, 2008). An important caveat is that the Hh signaling pathway is dispensible for adult hematoepotic stem cell function (Gao J. et al, 2009).

Figure 1. Mechanism of Hedgehog Signaling

1.2.2. Role of Hh in PTCH Mutant Tumors

Aberrant activation of the Hh pathway in cancers is caused either by mutations in the pathway (ligand independent) or through Hh overexpression (ligand dependent). Connections between Hh and cancer were established from observations that mutations in the negative regulator, PTCH1, led to Gorlin syndrome (Hahn, H et al, 1996; Johnson RL et al, 1996) a condition where patients develop numerous basal cell carcinomas (BCC) and are predisposed to medulloblastoma and rhabdomyosarcoma. In almost all BCC (and many medulloblastoma and rhabdomyosarcoma) cases, the Hh pathway is hyper-activated as indicated by up-regulation of Hh target genes (Dahmane N et al, 1997; Evangelista M et al, 2006). Thus, therapeutic agents which antagonize this pathway may be appropriate clinical interventions.
1.2.3. Role of Hh in PTCH Wildtype Tumors

The mechanism by which Hh acts in ligand-overexpressing cancers is still unclear. One model suggests that these tumors rely on autocrine signaling, where the Hh ligand produced by tumor cells acts on neighboring tumor cells to stimulate their growth or survival (Figure 1). This model is supported by in-vitro data showing that proliferation of tumor cell lines is accelerated by addition of Hh ligand (Berman DM et al, 2003) and inhibited by a Hh neutralizing antibody (Watkins DN et al, 2003) or by addition of the Hh antagonist cyclopamine. In this model, Hh ligand may directly affect the survival or proliferation of the majority of malignant cells in the tumor. In prostate cancer, Hh pathway activity seems to correlate with higher-grade tumors, and treatment of an aggressive prostate xenograft model with cyclopamine prevents metastasis to the lung. Furthermore, constitutive activation of the Hh pathway by overexpressing Gli1 in a rarely metastasizing clone, AT2.1, drove tumors to metastasize to the lung through induction of genes involved in epithelial/mesenchymal transition (Watkins DN et al, 2003; Berman DM, et al 2003; Thayer SP et al 2003; Karhadkar SS et al, 2004; Sanchez P et al, 2004). Thus, it has been suggested that overexpression of Hh ligand leading to pathway activation may be important for tumor proliferation, survival, and/or metastasis.

There are other tumor types where Hh may be acting not on the bulk of the tumor cells, but rather on the small fraction of cancer stem cells that are capable of self-renewal and differentiation among multiple lineages. Hh signaling from stem cells is required for the normal growth and regeneration of organs, including lung, gastrointestinal tract and prostate. Inappropriate and constitutive activation of Hh pathway during tissue repair and regeneration could promote tumorigenesis. Hh signaling has been indicated in proliferation of tissue stem cells from central nervous system (Palma V et al, 2005; Ahn S et al, 2005; Machold R et al 2003) mammary gland (Liu S et al 2005;) and hematopoietic stem cells (Bhardwaj G et al, 2001). Genetic inhibition of Hh signaling results in the loss of neural stem cell forming potential from the embryonic cortex (Palma V et al 2004) and activation of Hh signaling was shown to increase the number of mammary stem cells in vitro (Liu S et al, 2006). Expression of Hh pathway components have also been detected in mammary gland stem cells and in human breast cancer stem cells (CSC) characterized as CD44+/CD24-/LowLin- (Liu S et al 2006). Finally, Hh may act through a paracrine mechanism in ligand-dependent tumors. This model is more reminiscent of its role in development and organogenesis, where Hh ligand is secreted from the epithelium and signals to the underlying myofibroblast/mesenchyme/stroma compartment. The stromal compartment then signals back to the epithelium to regulate epithelial proliferation and differentiation through the production of factors, such as insulin-like growth factor (Lipinski RJ et al, 2005) platelet-derived growth factor (Xie J et al, 2001) fibroblast growth factor (Sun X et al, 2000) bone morphogenic protein (Yu J et al, 2002) Notch (Hallahan AR et al, 2004) and Wnt (Boras-Granick K et al, 2006; Madison BB et al, 2005) which have been identified as Hh target genes in various models.
1.2.4. Chronic Myeloid Leukemia and the Hh Signaling Pathway

Philadelphia-positive (Ph+) Chronic Myeloid leukemia (CML) arises owing to a translocation between the BCR serine/threonine kinase gene and the ABL1 tyrosine kinase. The American Cancer Society estimates that in 2008 there were 4,830 new cases of CML in the United States. Imatinib mesylate (a tyrosine kinase inhibitor or TKI) has been used as primary therapy to treat CML as it binds to the ABL1 kinase domain and inhibits phosphorylation of substrates (Martinelli G et al, 2009; Baccarani M et al, 2008; Baccarani M et al, 2006). Escape from this mechanism is both common and multifactorial, and stem cell transplantation (with its high morbidity and mortality rates) remains the only potential cure for the relatively few patients with this option. Thus, the identification of less toxic and potentially curative therapies which target this disease remains of great interest.

Several studies (Zhao C et al, 2009; Dierks C et al, 2008; Sengupta A et al, 2007) have identified components of the Hh pathway as a potential drug targets in BCR-ABL-positive CML as it may play a key role in leukemic stem cells (LSC’s). Dierks et al described a 4-fold induction of GLI1 and PTCH1 in CD34+ chronic or blast crisis CML cells. BCR-ABL expression induced SMO, Gli-1 and PTCH levels within the stem cell compartment in a mouse model of CML (Dierks et al, 2008). The PTCH1 expression level is 20-fold higher in patient derived CD34+ blast-crisis CML cells compared to CD34+ chronic-phase CML cells (Sengupta A et al, 2007) Gli-2 expression increases progressively in chronic phase and blast crisis CML samples, and SMO is essential for expansion of the leukemic stem cell pool as compared to normal hematopoietic stem cells (HSC’s) (Radich et al, 2006). Zhao et al demonstrated that Hh signaling is activated in LSCs through up regulation of SMO. While SMO does not impact long-term reconstitution of regular hematopoiesis, the development of retransplantable BCR-ABL-positive leukemia was abolished in the absence of SMO expression. Furthermore, loss of SMO impairs LSC renewal and decreases induction of CML by the BCR–ABL oncoprotein and by depletion of the CML stem cell, whereas constitutively active SMO augments CML stem cell number to accelerate disease. The cell fate determinant Numb, which depletes CML stem cells, is increased in the absence of SMO activity. Pharmacological inhibition of Hh signaling impairs not only the propagation of CML driven by wild-type BCR–ABL, but also the growth of imatinib-resistant mouse and human CML by reducing the number of LSCs in-vivo (Zhao et al, 2009).

Collectively, these data indicate that Hh pathway activity is required for maintenance of leukemic stem cell populations in diseases which are driven by BCR-ABL including Ph+ CML. By targeting the Hh pathway, drug resistance and disease progression associated with imatinib or other TKI failures might be avoided.
1.2.5. Role of Hedgehog in Other Myeloid Malignancies

In addition to CML, aberrant Hh signaling has been described in a variety of human leukemia and leukemia stem cells. Patient derived acute myeloid leukemia (AML) samples expressed Gli-1 in proportion to the number of CD34+ blast cells (Jamieson et al, personal communication). Expression levels of PTCH, SMO and GLI1 were examined in several leukemic cell lines (Bai LY et al, 2008). PTCH and SMO were expressed in Jurkat T-ALL cells, and Shh and GLI1 were expressed in human promyelocytic leukemia (HL-60) and KG-1 cells. Hh signaling is up-regulated in several subtypes of human AML cells, including primary CD34+ leukemic cells and cytokine-responsive CD34+ cell lines such as Kasumi-1, Kasumi-3 and TF-1. These CD34+ cells express the downstream effectors glioma associated oncogene homolog (GLI) 1 or GLI2, indicative of active Hh signaling. Inhibition of Hh signaling induced apoptosis after 48 h of exposure, although these CD34+ cell lines exhibited resistance to cytarabine (Ara-C). This data was confirmed by reverse transcription–polymerase chain reaction (RT-PCR) for Hh pathway components and a GLI-responsive reporter assay (Kobune M et al, 2009).

Given the central role that Hh signaling plays in cell differentiation, Hh inhibition represents a mechanistically novel approach to eliminate the LSC population and thus abrogate tumor proliferation in at least a subset of CD34+ myeloid driven hematopoietic malignancies.

1.2.6. Properties of PF-04449913

PF-04449913 is a potent and selective inhibitor of the Hedgehog signaling pathway through binding to the target, SMO. PF-04449913 inhibited the binding of a known comparator inhibitor of SMO with an IC$_{50}$ of 4 nM. In addition, in a Shh-induced Gli-Luciferase reporter assay, PF-04449913 inhibited the Hh pathway activity with an IC$_{50}$ of 3 nM. Using human aortic adventitial fibroblasts, Shh stimulation for 48 hours induced a 300% increase in endogenous Gli1 levels, assessed using quantitative PCR; PF-04449913 at 100 nM inhibited 75% of the ligand-induced Gli1 levels. PF-04449913 was also evaluated in mouse 3T3-L1 preadipocytes, a cell line that forms triglycerides through a mechanism activated by insulin and antagonized by Shh. In this model, PF-04449913 (50 nM) reproducibly antagonized Shh, restoring 60% of lipid production relative to control cultures induced with insulin alone.

In the PTCH/P53 medulloblastoma mouse model of Hh pathway-driven tumors, PF-04449913 inhibited pathway activation (Gli1 expression) and produced rapid and complete tumor regression. Preclinical PK/PD modeling using this model suggests a target human dose of 15 mg/day is projected to yield at least 50% of tumor Gli1 mRNA inhibition from baseline levels and approximately 20% of skin Gli1 mRNA suppression. A 15 mg dose is projected to result in a C$_{min}$ of 62 ng/mL total (5.6 ng/mL free) and a C$_{ave}$ of 79 ng/mL total (7.2 ng/mL free).

PF-04449913 has been shown pre-clinically to have activity in imatinib resistant CML blast crisis disease. Patient derived CD34+ imatinib resistant blast crisis CML cells xenotransplanted into immunocompromised mice treated with PF-04449913 (100 mg/kg PO QD x 15 days) alone or in combination with dasatinib (50 mg/kg PO QD X 15 days) reduced
primary leukemic tumor burden. In addition, PF-04449913 treatment reduced leukemic tumor formation in secondary recipients, suggesting that PF-04449913 is able to inhibit the LSC population necessary for tumor propagation. Importantly, this was verified in CML T315I mutants, which have escaped TKI inhibition. Additional pre-clinical studies are underway to further characterize exposure levels of PF-04449913 required to both decrease leukemic tumor burden and affect pharmacodynamic biomarkers (PK/PD studies).

For more details on the pre-clinical data with PF-04449913, refer to the Investigator’s Brochure (IB).

1.2.7. PF-04449913 Preclinical Safety Data

PF-04449913 was well tolerated up to 50 and 5 mg/kg/day in rats and dogs, respectively, in oral toxicity studies up to 1-month in duration. In the 1-month rat toxicity study, the primary target organs included the kidney and bone (epiphyseal growth plate); the no observed adverse effect level (NOAEL) was 10 mg/kg/day (Day 29, male and female combined, free Cmax of 97 ng/mL and free Cave of 40 ng/mL). In the 1-month dog toxicity study, the primary target organ was the kidney; the NOAEL was 1 mg/kg/day (Day 29, free Cmax of 28 and 14 ng/mL and free Cave of 6 and 2.5 ng/mL, in males and females, respectively).

Kidney Effects: The kidney was identified as a target organ in both rat and dog toxicity studies.

In the rat 10-day study, kidney injury was dose-dependent. All animals in the 500 mg/kg/day group were euthanized by Day 9. Clinical signs preceding euthanasia included tremors, decreased activity, cold to the touch and fur staining. Body weight and food consumption were also decreased. The cause of morbidity was due to overt kidney injury. Microscopically, severe hyaline droplet deposition along with degeneration/necrosis, karyomegaly and vacuolation was observed in the kidneys of all animals given 500 mg/kg/day. Similar changes of lower severity were observed microscopically at 50 mg/kg/day.

In the 1-month rat toxicity study, the microscopic changes were similar to those reported in the 10-day rat study and were also dose dependent. Slight to minimal changes included cytomegaly/karyomegaly, tubular epithelial cells with syncytia within cortical regenerative tubules, degeneration/necrosis of tubular epithelium, and inflammatory infiltrates in all males and females given PF-0449913 at 50 mg/kg/day. Regeneration of tubule cells in the cortical region was moderate in 1/10 males and 8/10 females, with the remaining animals in the 50 mg/kg/day group exhibiting minimal to slight regenerative changes. These microscopic changes in the 50 mg/kg/day group correlated with significant increases in serum creatinine levels, a decrease in urinary pH and the presence of inflammatory cells and granular casts in the urine. These inflammatory changes may account for the minimal increase in fibrinogen in males given 50 mg/kg/day. At 10 mg/kg/day, minimal microscopic changes occurred in the absence of changes in clinical chemistry or urinalysis.
Evidence from both the rat and dog 1-month toxicity study suggested that the kidney changes are reversible. In the rat, the kidney changes did not completely reverse but were characterized as regenerative in nature. There was no evidence of necrosis/degeneration in any of the five males or females in the recovery group. In the dog, the two males exhibited complete recovery from the necrosis/degeneration while the effect was minimal in the two recovery females. The presence of regenerative tubules and inflammatory cells were considered a reparative response.

**Bone Effects:** Bone changes were limited to the 50 mg/kg/day group in the 1-month rat toxicity study. They occurred in all animals except for 1 female treated in that group. Changes in femur and sternum were characterized by slight to moderate epiphysis alterations and decreased medullary trabeculae. The epiphyseal chondrocytes were decreased in number and disorganized in appearance. These changes persisted throughout the 1-month recovery phase. The changes in the epiphyseal growth plate are consistent with inhibiting the Hh pathway in growing bone (Kimura et al, 2008) and chondrogenesis (Amando et al, 2008).

**Cardiovascular Effects:** To evaluate the potential effect on the cardiovascular system, PF-04449913 was evaluated for its effect on binding to the hERG (human ether-a-go-go gene) potassium channel stably expressed in human embryonic kidney (HEK-293) cells. The hERG IC50 for PF-04449913 was 3.1 μM, which is 163-fold above the projected free human efficacious (Cave) drug concentration of 19 nM, and 135-fold above the projected human free efficacious Cmax (23 nM). PF-04449913 produced dose related changes in electrocardiogram parameters in a single dose cardiovascular safety pharmacology study in dogs at 5 and 30 mg/kg. At 5 mg/kg, a small (5 msec) but statistically significant increase in QTc occurred 7 to 14 hour post-dose. At 5 mg/kg the peak free plasma concentration was 276 ng/mL, which is ≥49-fold above the projected free steady-state Cmax (8.6 ng/mL) at a human efficacious dose of 15 mg based on the PTCH/P53 mouse xenograft model. At 30 mg/kg, a statistically significant increase in heart rate (10 bpm) and statistically significant increases in QRS, QT and QTc intervals occurred during the 0.5 to 6 hour summary period (3, 12 and 18 msec, respectively) and the 7 to 14 hour summary period (2, 22 and 24 msec, respectively). Increases in QT and QTc intervals were still apparent during the 14 to 22 hour summary period. Of note, the statistically significant increases in heart rate at 30 mg/kg coincided with episodes of emesis, and therefore were most likely due to the emetic effect. The increased heart rate is consistent with the weak sodium channel inhibition observed in a functional patch clamp study. There were no statistical or remarkable changes in cardiovascular parameters in dogs treated with 1 mg/kg PF-04449913.

**Other Findings:**

- **Hematologic**

There were no histopathologic correlates suggestive of changes in normal bone marrow.
Lower red cell mass was observed at 50 mg/kg/day in the 1-month rat study (males) and increases in absolute reticulocyte counts (males and females) occurred on the last day of dosing. The increased reticulocyte count is consistent with regenerative response and was reversed at the end of recovery phase. Neutrophils and platelets were not decreased.

- **Gastrointestinal**

In a 7-day repeat dose toxicity study in dogs up to 100 mg/kg/day there were observations of emesis and liquid stool. In the 1-month toxicity study in dogs, vomiting and discolored/liquid feces was observed at 5mg/kg. At 30/15 mg/kg/day in dogs two high dose males had ulcerations and inflammation in the esophagus while one male had tongue and rectal ulcerations. These effects are believed to be secondary to vomiting, liquid stool and morbidity observed in the high dose group and was not believed to be a direct effect of PF-04449913.

- **Phototoxic**

PF-04449913 absorbs light with a peak absorbance observed at 204 and 280 nm. For the UVA-UVB/visible range important for phototoxic potential (290 nm–700 nm), PF-04449913 does absorb light at 290 nm and this is the tail of the large absorbance peak at 280 nm. The molar extinction coefficient for PF-04449913 at 290 nm is 9,622 L/mol/cm. Guidelines for the prevention of excessive sunlight exposure will be implemented in the study (Section 4.3.2).

**Impact of preclinical safety findings on patient management:**

Based on the pre-clinical safety studies, the kidney could be a target organ of toxicity in humans. However, given the ability to monitor for changes in kidney function, reversibility of the effects in both animal species tested along with safety margins greater than 5-fold, this suggests that this is a manageable risk for PF-04449913. Renal function and potentially related adverse events will be actively monitored in this study.

The pre-clinical data suggest there is a potential for PF-04449913 to induce QT prolongation in humans. The effect was small (5 msec) although statistically significant and occurred at ≥49 -fold above the projected free $C_{\text{max}}$ (8.6 ng/mL) at a projected human efficacious dose of 15 mg based on the PTCH/P53 mouse xenograft model. There was also a statistically significant increase in heart rate (10 bpm), however, this coincided with episodes of emesis, and therefore was most likely due to the emetic effect. ECGs and vital signs and potentially related adverse events will be monitored throughout the study (Section 7.1.2).

PF-04449913 has the potential to be phototoxic. Guidelines for the prevention of excessive sunlight exposure will be implemented in the study (Section 4.3.2).

Bone changes occurred only in the growth plate of the growing bone of the rat and did not occur in the closed plate of the dog, therefore these effects are not a risk for adult patients where the epiphyseal growth plate is also closed.
For more details on the preclinical and clinical safety of PF-04449913 refer to the IB.

1.2.8. Rationale for Selection of the Starting Dose

The starting dose for PF-04449913 in the first-in-patient (FIP) trial in cancer patients has been determined to be 5 mg daily, based on information derived from the 1-month repeat dose toxicology studies in rats and dogs (current PF-04449913 IB).

The doses tested in the 1-month toxicology study in the rat were 1, 10, and 50 mg/kg/day orally, and in the 1-month dog study were 1, 5, and 30/15 mg/kg/day orally.

In the rat 1-month study, there were no deaths at any dose. The NOAEL was 10 mg/kg/day (free C_{ave} 40 ng/mL). The STD_{10} in rats was determined to be 50 mg/kg/day (free C_{ave} 307 ng/mL), with the primary target organs being the kidney and bone (epiphyseal growth plate). The kidney changes did not completely reverse but were characterized as regenerative in nature. There was no evidence of necrosis/degeneration in any of the five males or females in the recovery group. The changes in the femur and sternum bone persisted throughout the 1-month recovery phase in animals given 50 mg/kg/day of PF-04449913. In the 1-month dog study, the animals given 30 mg/kg/day were sacrificed moribund. Attempts were made to lower the dose to 15 mg/kg/day, but due to persistent adverse clinical signs and elevated BUN, creatinine and inorganic phosphorus, treatment was stopped and the remaining animals were put on recovery. The two males exhibited complete recovery from the renal necrosis/degeneration, while the effect was minimal in the two recovery females (ie, did not fully recover). The maximum tolerated dose (MTD) in the dog was 5 mg/kg/day (free C_{ave} 82/76 ng/mL [M/F]), and the NOAEL was 1 mg/kg/day (free C_{ave} 6/2.5 ng/mL [M/F]).

These data collectively indicate that the dog is the more sensitive species, based primarily on exposure and secondarily on reduced reversibility of the necrosis/degeneration of the kidneys.

According to DeGeorge et al (1998)\textsuperscript{39}, the currently accepted algorithm for calculating a starting dose in clinical trials for cytotoxic agents is to use one-tenth of the dose that causes severe toxicity (or death) in 10% of the rodents (STD\textsubscript{10}) on a mg/m\textsuperscript{2} basis, provided this starting dose does not cause serious, irreversible toxicity in a non-rodent species. If irreversible toxicities are produced at the proposed starting dose in non-rodents or if the non-rodent is known to be the more sensitive animal model, then the starting dose would generally be one-sixth of the highest dose tested in the non-rodent that does not cause severe, irreversible toxicity. The human equivalent starting dose was calculated to be ~55 mg based on the rat STD\textsubscript{10}, and ~6 mg based on the NOAEL of 1 mg/kg in the dog.

Because the dog was determined to be the more sensitive species, the starting dose of PF-04449913 (based on the dog NOAEL of 6 mg) will be rounded to 5 mg and used as the starting dose for the FIP study.
1.2.9. PF-04449913 Product Pharmacokinetics in Animals and Projection of Human Pharmacokinetics

In humans, PF-04449913 has been projected to have an oral bioavailability of 55%, a steady state volume of distribution of 2.7 L/kg, a systemic plasma clearance of 1.03 mL/min/kg, and an elimination half-life of 30 hours.

PF-04449913 exhibited high plasma protein binding with a fraction unbound of 0.091 in humans. All primary metabolites observed in-vitro and in-vivo appeared to be formed via oxidative metabolism, indicating that this is likely the major route of clearance of PF-04449913. CYP3A4 appeared to be the major enzyme mediating PF-04449913 metabolism (~99.8%). The contributions from the other ten P450s evaluated in the metabolism of PF-04449913 were negligible. In rats, 6.88% and 10.7% of the administered dose was eliminated unchanged from urine and bile, respectively.

In-vitro data indicates that PF-04449913 has minimal potential to inhibit all the major human CYP enzymes with IC_{50} values greater than 30 µM (11232 ng/mL) for CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. PF-04449913 does not inhibit the metabolic activity of CYP3A in a time dependent manner. PF-04449913 was evaluated in-vitro to determine if it is a substrate for human P-glycoprotein (P-gp) in monolayer Madine-Darby Canine Kidney cells transfected with human Multidrug Resistance gene. The resulting polarized efflux ratio was 14.9. In the presence of a combination of P-gp inhibitors, the efflux ratio reduced to unity. These data collectively suggest the involvement of P-gp in attenuating the absorptive transport of PF-04449913.

PF-04449913 exposure in rats and dogs, as defined by Cmax and AUC_{(0-24)}, increased with increasing dose over the dose ranges tested; however, there was a greater than dose proportional increase in exposure. In the 1-month rat and dog toxicity studies, a 5-fold increase in dose led to a 8- and 14-fold increase in exposure [AUC(0-24)], respectively.

For more details about the ADME of PF-04449913 refer to the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

1. To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of PF-04449913 when administered alone to adults with select advanced hematologic malignancies.
Secondary Objectives

1. To determine the safety and tolerability of PF-04449913 when administered alone to adults with select advanced hematologic malignancies.

2. To evaluate the pharmacodynamics of PF-04449913 alone in adults with select advanced hematologic malignancies.

3. To evaluate the pharmacokinetics of PF-04449913 alone in adults with select advanced hematologic malignancies including an evaluation of the effect of food.


5. To characterize the effects of PF-04449913 alone on QTc in adults with select advanced hematologic malignancies.

2.2. Endpoints

Primary Endpoint

1. First cycle dose limiting toxicities (DLTs) (Section 3.1.2).

Secondary Endpoints

1. Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

2. Pharmacodynamic biomarker modulation.

3. Pharmacokinetic parameters of PF-04449913.

4. Overall response (OR), time to progression (TTP), duration of response and progression-free survival (PFS) as defined by disease specific clinical practice guidelines (Appendix 4 through Appendix 8).

5. QTc interval.

3. STUDY DESIGN

This is an open-label, multi-center, Phase 1 study of PF-04449913 administered orally as single agent to adults with select advanced hematologic malignancies. Patients are eligible if they are refractory, resistant or intolerant to prior therapies. They may also be newly diagnosed and previously untreated (for all diseases with the exception of non-T315I CML and in compliance with national treatment guidelines for AML) but not eligible for standard treatment options, or for whom standard therapies are not anticipated to result in a durable response.
The study will assess PF-04449913 administered as single agent once daily in a continuous regimen to patients with select advanced hematologic malignancies. The later cohorts may be enriched for diseases which exhibit early signs of activity in the preceding dose escalation cohorts. A dose escalation design will be applied in 3-6 patient cohorts up to identification of the maximum tolerated dose (MTD) or attainment of the dosing cap. The starting dose will be 5 mg once daily. Dosing of PF-04449913 will be based on flat milligram increments without adjustment for body surface area. There will be a lead-in period on Day -6 for each dose escalation cohort in which the single-dose pharmacokinetics and pharmacodynamics of PF-04449913 will be characterized prior to initiation of continuous dosing in the first cycle of treatment. The lead-in period duration, PK time-points, doses and/or regimens used in subsequent cohorts may be modified based on the exposure (AUC) observed during the lead-in period (although the number of PK samples will not be increased).

Once the MTD is established or attainment of the dosing cap, the cohort will be expanded with at least 8 additional patients to further characterize safety and tolerability at the MTD/MAD or a lower dose that has already been tested, to conduct a pharmacokinetic food effect assessment (Section 3.1.3 and Section 5.2.4.2), and to collect blood and urine for metabolite profiling/urine PK.

Treatment with PF-04449913 may continue for up to 12-cycles or until disease progression, patient withdrawal or unacceptable toxicity occurs. Patients who complete 12-cycles of treatment will be considered to have completed the trial. Patients who are still on trial after 12-cycles and who continue to benefit from treatment may have the option to continue treatment upon agreement between the investigator and sponsor, and pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed at the same frequency listed in Table 1 (Schedule of Activities).

The RP2D will be determined after review and discussion of the study data by the sponsor and investigators. Consideration will be given to the PK profile, type and severity of drug related toxicity and clinical suitability for long-term administration.

Pre and post-PF-04449913 dose blood, bone marrow biopsies and normal skin may be obtained for biomarker assessments and evaluating potential genetic changes that could correlate to clinical outcome. These assessments will include pharmacodynamic analyses of Hedgehog target genes, proteins and other signaling pathways which may interact with the Hedgehog pathway.

3.1. Trial Design

The study will assess PF-04449913 as a single agent with escalating doses of PF-04449913 alone studied sequentially. Cycle 1 will be preceded by a single lead-in dose of PF-04449913 administered on Day -6. From Cycle 1/Day 1 onwards, PF-04449913 will be administered once daily, without interruption, in 28–day cycles. The starting dose of PF-04449913 will be 5 mg once daily (QD). Real time PK will be collected and evaluated for each dose level in the lead-in period, so that the doses and/or regimens used in subsequent cohorts, PK
time-points and lead-in period duration may be modified based on the PK and safety profile observed. If super-proportional PK is observed either following single dose administration or at steady-state, then the dose of PF-04449913 may be modified to account for the increase in exposure. If significantly less than dose proportional exposure is observed dose escalation may be stopped and one of the doses with the highest exposure may be selected as the RP2D. Additional subjects may be accrued at a lower dose level to define the MTD/RP2D.

Initially up to 3 patients will be treated at each dose level. Occasionally (due to logistical/clinical reasons) more than 3 but no more than 6 patients may be enrolled at each dose level. The DLT evaluation period is the first cycle of treatment, which is 28-days and starts from Cycle 1/Day 1 (DLT evaluation does not include the lead-in period). If a patient is not evaluable for MTD due to reasons other than treatment-related toxicities in Cycle 1, then an additional patient will be enrolled in the cohort (for example if a patient does not receive at least 80% of the planned dose of PF-04449913).

Dose escalation (opening of a new cohort of patients) will occur after the last patient in the previous cohort has completed Cycle 1.

- If none of the patients experiences a DLT by the end of Cycle 1, then dose escalation may proceed.
- If 1 of the patients experiences a DLT by the end of Cycle 1, then the cohort will be expanded to 6 patients. If none of these additional patients experiences a DLT, then dose escalation will continue. If ≥2 patients in the dose level experiences a DLT, no further escalation will occur; the MTD would have been exceeded and the previous lower dose level may be considered the MTD (Alternatively, if the Investigator(s) and Sponsor agree, the MTD may be set at a lower dose level).
- The MTD/MAD or a lower dose that has already been tested cohort will be expanded (with at least 8 additional patients) to better define the safety profile at that dose. In addition, this cohort will be used for a food effect evaluation (Section 3.1.3 and Section 5.2.4.2), assessment of renal clearance (CL_R) and metabolite profiling.

In order to identify the optimal MTD, one or more intermediate dose level(s) between the dose level that exceeds the MTD and the next lower dose level already tested, may also be investigated upon agreement between the sponsor and the investigators. If ≥2 patients in the intermediate dose level experiences a DLT, no further escalation will occur; the MTD would have been exceeded and the previous lower dose level may be considered the MTD.

If the mean free exposure (AUC_{0-24}) observed at a dose level (eg, 5 mg) using the lead in PK collected on Day -6 is lower than ~ 12 ng.hr/mL, which is 1/6th of the mean free AUC_{0-24} at the NOAEL (1mg/kg) observed in the one-month dog toxicity study, and that dose (eg, 5 mg) is safe and well tolerated then subsequent dose levels may be increased to account for the low exposure. Thereafter, dose escalation will occur in ≤100% increments (rounded to accommodate dosage strength availability) until either of the following occurs in Cycle 1: 1) toxicity of Grade 2 severity occurs in 2 or more patients within a dose level that is
considered possibly related to PF-04449913; or 2) one DLT occurs; or 3) the mean free 
AUC$_{0-24}$ exceeds 8.05 µg.hr/mL (50% of the mean free AUC$_{0-24}$ observed at 30 mg/kg in the 
one-month dog toxicity study). Escalation increments will then become ≤50% (rounded to 
accommodate dosage strength availability) following discussion between the sponsor and the 
investigators and a review of the safety, PK data and patient clinical assessment.

Dose escalation may be stopped if 1) MTD cannot be reached within a reasonable dose range 
(eg, up to 800 mg QD), or 2) significant modulation of PD biomarkers or clinical activity is 
observed, suggesting this dose level may be an optimal biological dose (OBD), or 
3) significantly less than a dose proportional increase in exposure is observed (non-linear or 
unfavorable PK).

3.1.1. Definition of MTD and RP2D

The MTD is the highest dose associated with the occurrence of DLTs in <33% of patients. 
Typically, the MTD is the dose level at which 0/6 or 1/6 patients experience a DLT before 
the end of the first cycle of treatment with the next higher dose having at least 2 of 3 or 
6 patients experiencing DLTs.

The RP2D will be determined at a dose below or equal to the MTD upon review of all study 
data by the sponsor and investigators.

3.1.2. DLT Criteria

A DLT will be classified according to CTCAE version 3.0 and is defined as any of the 
following adverse events occurring in the first cycle of treatment which are not clearly 
attributed to disease.

1. Grade ≥3 non-hematologic toxicity that has been maximally treated (eg,: nausea, 
vomiting, diarrhea);

   • In an asymptomatic patient, Grade 3 QTcF prolongation (QTcF >500 msec) will 
     first require repeat testing, re-evaluation by a qualified person, and correction of 
     reversible causes such as electrolyte abnormalities or hypoxia for confirmation. 
     If, after correction of any reversible causes, the Grade 3 QTcF prolongation 
     persists, then the event should be considered a DLT.

2. Prolonged myelosuppression that lasts longer than 42 days from the point of detection 
defined as ANC <500/Ul or platelet count <10,000/Ul, or Hgb<8g/dL in a normal 
bone marrow with <5% blasts and no evidence of disease or dysplasia;

3. Inability to deliver at least 80% of the planned PF-04449913 dose due to study 
drug-related non-hematologic and hematologic toxicities (except prolonged 
myelosuppression).
### 3.1.3. Food Effect Sub-Study

A food effect sub-study will be conducted at the MTD/MAD or a lower dose that has already been tested in which the effect of a high-fat, high-calorie breakfast on PF-04449913 pharmacokinetics will be studied. Once the MTD is identified or attainment of the dosing cap, a cohort will be expanded with additional patients to further characterize safety and tolerability at the chosen dose and to conduct the food effect sub-study. Of the additional patients, a total of 8 PK evaluable patients will be required for the food effect study (first 8 patients enrolled in the expansion cohort unless they have dietary or other restrictions). Each patient will serve as their own control in which PF-04449913 will be administered in the morning under either “fed” or “fasted” conditions on Day (-6) and Day 1 of Cycle 1. Pharmacokinetic sampling times are described in the Schedule of Activities (Table 1). The testing order for fed versus fasted conditions will be as follows: the first 4 patients to participate in this sub-study will be tested under fed followed by fasted conditions, the next 4 patients will be tested under fasted followed by fed conditions. Patients who have dietary or other restrictions, based on a physicians assessment and sponsor agreement, that preclude a 10-hour overnight fast (water permitted) or consumption of the high-fat, high-calorie meal (Section 5.2.4.2) will not be required to participate in this sub-study.

### 4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

#### 4.1. Inclusion Criteria

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

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

1. Patients with select advanced hematologic malignancies (Appendix 2 through Appendix 3 for definitions) who are refractory, resistant or intolerant to prior therapies. They may be newly diagnosed (patients with AML must be in compliance with national treatment guidelines, see below) and previously untreated (for all diseases with the exception of non-T315I CML (see below)), but not eligible for standard treatment options, or for whom standard therapies are not anticipated to result in a durable response. Eligible patients are limited to 1. Myelodysplastic Syndrome (any MDS International Prognostic Scoring System or IPSS score), 2. Myelofibrosis, 3. Chronic Myelomonocytic Leukemia (CMML), 4. CML T315I mutants (may be previously untreated), 5. non-T315I CML (any phase; must have received at least one prior treatment), 6. Acute Myeloid Leukemia (AML; not eligible to receive standard therapy based on national treatment guidelines [Morra et al, 2008; NCCN guidelines, AML 2010].)
2. Patients with CML:

   a. Must have a confirmed diagnosis as evidenced by the presence of the BCR-ABL translocation [(t9;22)] by fluorescence in situ hybridization (FISH), cytogenetics, or quantitative polymerase chain reaction (QPCR) for chronic myeloid leukemia in either chronic, accelerated or blast phase.

   b. Non-T315I CML must have received at least one prior therapy.

   c. May be resistant or intolerant as defined by:

      - In CML-CP, primary resistance is defined as failure to achieve a complete hematologic response (CHR) following 3 months on therapy; failure to achieve any cytogenetic response (CyR) following 6 months on therapy, failure to achieve a major cytogenetic response following 12 months on therapy, or failure to achieve a complete cytogenetic response following 18 months on therapy.

      - Secondary resistance is defined as a loss of CHR (defined by leukocytosis confirmed with at least one WBC>15K not felt to be due to a secondary cause); loss of a MCyR (defined by ≥30% increase in the number of metaphases); or disease progression to AP or BP. In CML-AP or CML-BC, resistance is defined as the failure to achieve a hematologic response, an increasing WBC, or an overt disease progression.

   d. Intolerance for all phases is defined as discontinuation of prior therapy due to adverse events at the lowest approved dose or if a patient can only tolerate prior therapy at less than the lowest approved dose.

      - In addition, for all phases (except patients with T315I mutations), patients are eligible in the case of unsatisfactory clinical response to the initial course of TKI, but who do not meet the definition for refractory, resistant or intolerant (eg, a CML CP patient who rapidly progresses on primary therapy, but does not meet the criteria for primary resistance because they have not been on TKI for 3 months; or patients with co-morbid diseases who cannot tolerate TKI therapy).

      - To be considered in chronic phase they must have all of the following criteria:

         - <15% blasts in peripheral blood and bone marrow;
         - <30% blasts and promyelocytes in peripheral blood or bone marrow;
         - <20% basophils in peripheral blood;
         - Platelets ≥100 x 10^9/L;
         - No EMD other than spleen or liver.
• To be considered in accelerated phase they must meet one or more of the following criteria:
  • ≥15% blasts in peripheral blood;
  • ≥30% blasts + promyelocytes in peripheral blood;
  • ≥20% basophils in peripheral blood;
  • Platelet count ≤100 x 10^9/L unrelated to therapy;
  • Clonal evolution.
• To be considered in blast phase they must have either:
  • ≥30% blasts in peripheral blood or bone marrow;
  • Extramedullary disease.

3. All anti-cancer treatments should be discontinued as follows:
  • Anagrelide should be discontinued 7 days prior to study entry.
  • Dasatinib should be discontinued from 1-day (24 hr) prior to study entry.
  • Nilotinib should be discontinued from 3-days (72 hr) prior to study entry.
  • Imatinib should be discontinued from 4-days (96 hr) prior to study entry.
  • Bosutinib should be discontinued from 4-days (96 hr) prior to the study entry.
  • All other anti-cancer treatments should be discontinued ≥2 weeks from study entry eg, chemotherapy (including intrathecal), radiotherapy, cytokines, investigational agents or hormones.

4. ≥18 years old;
5. ECOG performance status of 0 to 2;
6. Patients who have previously received an autologous stem cell transplant are allowed provided transplant was greater than 30-days prior to study entry and the patient has recovered from transplant-associated toxicities prior to study entry;
7. Patients with a history of allogeneic stem cell transplant are eligible for study participation provided transplant was greater than 60-days prior to study entry and the patient has recovered from transplant-associated toxicities prior to study entry;
8. Adequate organ function as defined by the following criteria:
   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) \( \leq 2.5 \times \text{upper limit of normal (ULN)} \), or AST and ALT \( \leq 5 \times \text{ULN} \) if liver function abnormalities are due to underlying malignancy;
   - Total serum bilirubin \( \leq 1.5 \times \text{ULN} \) (except patients with documented Gilbert’s syndrome);
   - Serum creatinine \( \leq 1.5 \times \text{ULN} \);
   - Creatinine clearance \( \geq 50 \text{ ml/min} \) as calculated per Institutional Guidelines;
   - Urinary protein <2+ by dipstick. If dipstick \( \geq 2+ \), then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g/24 hour.

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

10. Patients must give written informed consent.

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

4.2. Exclusion Criteria

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

1. Patient has undergone a donor lymphocyte infusion (DLI) in the prior 30-days;

2. Patient is known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines;

3. Patient with active malignancy with the exception of basal cell carcinoma, non-melanoma skin cancer, carcinoma-in-situ cervical or skin cancer. Other concurrent malignancies will be considered on a case-by case basis;

4. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsades de points, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/ peripheral artery bypass graft, symptomatic congestive heart failure (CHF NY Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism;

5. QTc interval >470 msec;

6. Bradycardia defined as HR <50 bpm;
7. Patient has an active, life threatening or clinically significant uncontrolled systemic infection;

8. Patients with active central nervous system (CNS) involvement by leukemia. Patients with prior history of CNS disease will qualify if active disease is ruled out by imaging studies or spinal tap;

9. Active graft versus host disease other than Grade 1 skin involvement;

10. Patients taking immunosuppressants for GVHD (including but not limited to: steroids, cyclosporine, tacrolimus, methotrexate or mycophenolate mofetil) from 14-days prior study entry;

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness or with active Hepatitis B or C infection;

12. Known malabsorption syndrome or other condition that may impair absorption of study medication (e.g., gastrectomy or lap band);

13. Prior or concurrent anti-cancer treatment with a Hedgehog inhibitor or concurrent treatment with other investigational or approved oncology agents

14. Concurrent administration of herbal preparations;

15. Current use or anticipated need for food or drugs that are known strong/moderate CYP3A4 inhibitors, including their administration within 7-days prior to study entry. Please refer to Section 5.5 for list of prohibited inhibitors;

16. Current use or anticipated need for drugs that are known strong CYP3A4 inducers, including their administration within 7-days prior to study entry. Please refer to Section 5.5 for list of prohibited inducers;

17. Current use or anticipated need of drugs that are P-gp inhibitors or P-gp inducers, including their administration within 7-days prior to study entry. Please refer to Section 5.5 for list of P-gp inhibitors/inducers;

18. Current use or anticipated need for drugs that are CYP3A4 substrates and have a narrow therapeutic index, including their administration within 7-days prior to study entry. Please refer to Section 5.5 for list of prohibited substrates;

19. Chronic systemic corticosteroid treatment, although topical applications, inhaled sprays, eye drops, local injections of corticosteroids and systemic steroids required for acute medical interventions are allowed;

20. Current non-prescription drug or alcohol dependence; Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to the use of effective contraception during the period of therapy. All female patients with
reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy;

21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.

4.3. Life Style Guidelines

4.3.1. Pregnancy and Contraception

Fertility, development and reproductive toxicity studies have not been conducted with PF-04449913 and the effects of the study medication on the fetus are unknown. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Female patients must be surgically sterile or be postmenopausal, or if of child-bearing potential must agree to use effective contraceptive during the period of the trial and for at least 90-days after completion of treatment. Women of childbearing potential must have a negative pregnancy test (serum or urine) prior to treatment with PF-04449913. Male patients must be surgically sterile or must agree to use adequate contraception during the period of therapy and for 90-days following the last dose. Accepted methods of contraception for females and males are listed below:

Accepted methods for females are:

- Abstinence.
- Or a combination of two of the following:
- Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing IUDs);
- Placement of a copper-containing intrauterine device (IUD);
- Condom with spermicidal foam/gel/film/cream/suppository;
- Male partner who has had a vasectomy for at least 4 months;
- Tubal ligation.

Acceptable contraceptive methods for males are:

- Abstinence;
• Use of condom for males with a vasectomy;

• Without a vasectomy, must use a condom and be instructed that their female partner should use another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or tubal ligation.

4.3.2. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients’ exposure to light including high intensity UVb sources such as tanning beds, tanning booths and sunlamps. Patients should be advised to apply sunscreen/sunblock daily.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Following full assessment and determination that the patient meets all eligibility criteria and has given informed consent for study participation, the investigator or designee will enroll the patient according to the procedures described in the study manual. The site staff will fax or e-mail a complete Registration Form to the designated Pfizer study team member. At the end of the enrollment process, a patient identification number will be assigned, which must be used in referencing the patient.

Dose level assignment will be operated centrally by the sponsor. The study site will receive confirmation of enrollment along with the next available date for dosing and the assigned dose level from the sponsor. Pfizer will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

No patient will receive study drug until the entire registration process has been completed.

5.2. Drug Supplies

Upon activation, study centers will receive a supply of PF-04449913 free of charge by Pfizer. Re-supplies of PF-04449913 will be made during the course of the study based on need.

The study monitor should be contacted for any issues related to drug supplies.

5.2.1. Formulation and Packaging

5.2.1.1. PF-04449913

PF-04449913 is formulated in tablets containing 5 mg, 10 mg, 25 mg and 100 mg of study medication. The tablets are packaged in High-density polyethylene (HDPE) bottles, with protection from moisture and should be handled with care. For storage conditions refer to the label.
5.2.2. Preparation and Dispensing

5.2.2.1. PF-04449913

PF-04449913 will be provided in HDPE bottles containing either 5 mg, 10 mg, 25 mg or 100 mg tablets with protection from moisture. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit.

PF-04449913 must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers.

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

5.2.3. Administration

It is mandatory for patients to record daily administration of each study drug in their patient diaries. If a patient misses a dose, they must be instructed not to “make it up” or double the next days dose. If a patient vomits anytime after taking a dose, they must be instructed not to “make it up”, but to resume subsequent doses the next day as prescribed.

With the exception of PK days (Schedule of Activities Table 1), the patients will be instructed to self-administer PF-04449913 in the morning at approximately the same time each day without treatment breaks until they experience unacceptable toxicity, disease progression or withdrawal from the study. On the PK days, the study drug(s) will be administered at the clinic. The actual dosing times should be captured in the Case Report Form (CRF).

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to ADVERSE EVENT REPORTING section for further details).

Patients will be instructed to swallow PF-04449913 tablets whole and not to chew them prior to swallowing. No tablet should be ingested if it is broken, cracked, or otherwise not intact. PF-04449913 should be taken with at least 8-oz (240 ml) of water once a day in the morning.
5.2.4. Food Requirements

5.2.4.1. Food Requirements (with the exception of the Food Effect Cohort)

PF-04449913 will be administered with at least 8-oz (240 mL) of water on an empty stomach, patients should refrain from food and beverages (except for water) for at least two hours before and two hours after dosing throughout the study. These fasting requirements may be removed if the data from the food effect study indicate that there is no effect of food on the bioavailability of PF-04449913.

5.2.4.2. Food Requirements in the Food Effect Cohort (Food Expansion Cohort)

For all patients participating in the food effect study, PF-04449913 will be administered following an overnight fast of at least 10 hours, regardless of if they are in the fed or fasted group. For those patients scheduled to receive the “fed” treatment, a high-fat, high-caloric breakfast will be provided and must be consumed over 30 minutes. PF-04449913 will be administered with approximately 8-oz (240 ml) of water 30 minutes after the start of the meal. No additional food will be allowed until at least 4 hours post-dose. For patients scheduled to receive the “fasted” treatment, PF-04449913 will be administered with 8-oz (240 mL) of water. No food will be allowed for an additional 4 hours post-dose. The testing order for fed versus fasted conditions will be as follows: the first 4 patients to participate in this sub-study will be tested under fed followed by fasted conditions, the next 4 patients will be tested under fasted followed by fed conditions. For either treatment day, water will be allowed ad libitum.

A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal is recommended as a test meal. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be two eggs fried in butter, two strips of bacon (may be replaced with ham and cheese of similar caloric content), two slices of toast with butter, four ounces (~113g) of hash brown potatoes and eight ounces (~227g) of whole-fat milk. Substitutions to this test meal can be made after discussion with the sponsor, as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity (if substituted the contents of the meal will be documented by a dietitian or designee to confirm it matches the FDA requirements for protein, carbohydrate and fat described above). However, it is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the standard breakfast that is consumed.

5.3. PF-04449913 Dose Modifications

Every effort should be made to administer PF-04449913 at the planned dose and schedule. In the event of significant toxicity dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, the dose modification should be based on the worst toxicity observed (according to the CTCAE v3). Any modifications to the PF-04449913 dose should be documented in the CRF.
Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in three ways:

- Within a cycle: Dose interruption until adequate recovery during a given treatment cycle;
- Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle;
- Dose reduction in the current cycle, or in the next cycle based on worst toxicity in the previous cycle.

5.3.1. Dose Interruptions/Delay/Reductions/Escalations

Dose reductions of PF-04449913 may be required based on the worst toxicity experienced. In the event of a study drug related toxicity in any cycle that meets criteria described in Section 3.1, administration of PF-04449913 should be held until the drug related toxicity has resolved to Grade ≤1 or baseline. Upon resolution of the toxicity, the patient should restart PF-04449913 at the same or next lower dose level after discussion with sponsor and depending on the severity and type of toxicity observed. Suggested dose reduction and interruption criteria are described in the following sections and are provided as guidance only. Depending on the type, severity and timing of the events, the investigator and sponsor together, will determine dose reductions and resumption of treatment (Table 2). Appropriate follow up assessments should be done until adequate recovery as assessed by the investigator. The following guidance should be used:

- After Cycle1/Day 1, a treatment delay or continuous interruption of more than 14 days (or greater than 42 days for prolonged myelosuppression) will result in discontinuation of the patient from the study unless the patient is receiving clinical benefit and after discussion between the sponsor and the investigator (Section 6.5).

- Doses of PF-04449913 are held or missed will not be made up (ie, cycles will not be prolonged beyond the 28th calendar day in order to make up any missed doses).

- If a treatment interruption continues beyond Day 28 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

Intra-patient dose escalations for PF-04449913 will not be allowed. For each study drug, no more than 2 dose reductions for PF-04449913 are allowed unless agreed by the sponsor.

Table 2 describes the recommended PF-04449913 dose modifications for Grade 3 or 4 non-hematologic toxicities not clearly attributed to disease.
Table 2. Recommended PF 04449913 Dose Modifications for the Management of Non-Hematologic Toxicities not Related to Disease\(^1,2\)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hematologic</td>
<td>Continue at the same dose level.</td>
<td>Continue at the same dose level.</td>
<td>Withhold dose until toxicity is Grade (\leq 1) or baseline, then resume treatment at the same dose level, or reduce the dose to next lower dose level tested at the discretion of the investigator in consultation with the sponsor.</td>
<td>Withhold dose until toxicity is Grade (\leq 1) or baseline, then reduce the dose to next lower dose level tested and resume treatment, or discontinue at the discretion of the investigator in consultation with the sponsor.</td>
</tr>
</tbody>
</table>

\(^1\) Assuming maximally treated (e.g., nausea, vomiting, diarrhea).

\(^2\) For recurrent and subjectively intolerable non-hematologic toxicities of any Grade (matching the DLT definition of being unable to receive 80% of the drug) that are not controlled by optimal supportive medication reduce the dose to the next lower dose level.

If a patient concurrently experiences both hematological and non-hematological toxicities, then dose modifications for PF-04449913 will be discussed with the investigator and sponsor.

5.3.2. Compliance

Patients will maintain dairies to include missed or changes doses, or significantly delayed doses. Patients will be required to return all bottles of PF-04449913 at the beginning of each cycle. The number of tablets remaining will be documented and recorded.

5.4. Drug Storage and Drug Accountability

PF-04449913 should be stored as described on the drug label with protection from moisture. Patients should be instructed to keep their medication in its original container. Returned medication should be stored separately from medication that needs to be dispensed.

The investigator, or an approved representative (e.g., pharmacist), will ensure that all trial drug is stored in a secured area, under recommended storage conditions provided in the Study Manual and in accordance with applicable regulatory requirements. Under no circumstances should the investigator or other site personnel supply trial drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Pfizer. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms (e.g., NCI form). In either case, the forms must identify the investigational product, including batch numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.
Adequate records documenting receipts, use, return, loss or other disposition of PF-04449913 tablets must be kept. PF-04449913 tablets must be used according to the protocol directions. The reason for missed dose should be entered on the CRF.

5.5. Concomitant Medication(s)

Drug interaction studies with PF-04449913 have not been conducted. The following information is based on results from in vitro studies with PF-04449913. All concomitant medications must be approved by the sponsor at study entry and up to the end of Cycle 1.

- Because inhibition of CYP3A4 isoenzymes may increase PF-04449913 exposure, leading to potential increases in toxicities, the use of known strong/moderate CYP3A4 inhibitors are not permitted from 7-days prior to study entry until study treatment discontinuation (eg, aprepitant, clarithromycin, cimetadine, ciprofloxacin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, mibefradil, nefazodone, posaconazole, telithromycin, tofisopam, troleandomycin, verapamil and voriconazole).

- PF-04449913 metabolism may be induced when taking strong CYP3A4 inducers, resulting in reduced plasma concentrations. Therefore co-administration of PF-04449913 in combination with any of the following and other strong CYP3A4 inducers is not permitted from 7-days prior to study entry until study treatment discontinuation (eg, carbamezepine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentin, St. John’s Wort).

- Concomitant use of PF-04449913 and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Therefore, co-administration of PF-04449913 with CYP3A4 substrates of a narrow therapeutic index is not permitted from 7-days prior to study entry until treatment discontinuation (eg, astemizole, cisapride, cyclosporine, ergot alkaloids (ergotamine, dihydroergotamine), pimozide, quinidine, sirolimus, terfenadine.)

- In vitro studies have indicated that PF-04449913 (Hiwase DK et.al, 2008) is a substrate for P-glycoprotein. Therefore, dosing of PF-04449913 in combination with P-gp inhibitors (cyclosporine, elacridar, erythromycin, itraconazole, ketoconazole, quinidine, tacrolimus, valspodar and verapamil) and P-gp inducers (rifampin and St. John’s Wort) is not permitted from 7-days prior to study entry until study treatment discontinuation.
The following concomitant medications are not permissible:

- Anagrelide should be discontinued 7 days prior to study entry. All other anti-cancer treatments should be discontinued ≥2 weeks from study entry eg, chemotherapy (including intrathecal), radiotherapy, cytokines, investigational agents or hormones;

- Immunosuppressants (including but not limited to chronic systemic steroids, cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) are not permitted from 14-days prior to study entry until treatment discontinuation;

- Chronic, systemic corticosteroid use is not permitted. However, topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed as well as short courses of systemic corticosteroids for acute medical interventions;

- Prior or concurrent anti-cancer treatment with a Hedgehog inhibitor or concurrent treatment with other investigational agents;

- Herbal medications;

- Use of warfarin is strongly discouraged if alternate medication (eg, low molecular weight heparin) can be substituted. Warfarin is a CYP3A4 substrate and drug interactions causing variability in INR are possible. Frequent monitoring of the INR is recommended in subjects taking warfarin. Dosage of warfarin should be adjusted as needed.

The following concomitant medications are permissible:

- Agents used for life-threatening medical problems may be given at the discretion of the investigator including blood transfusions.

- Medications intended solely for supportive care (ie, anti-emetics, analgesics [narcotics] and anti-inflammatories unless excluded by the sponsor due to the potential for a drug-drug interaction).

- Primary prophylactic use of granulocyte-colony stimulating factors is permitted during Cycle 2 and above and they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO, 2006) guidelines;

- Prophylactic use of erythropoietic growth factors in Cycle 2 and above.

Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF.
5.6. Concomitant Radiotherapy or Surgery

Although unlikely to be required, palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. PF-04449913 treatment should be interrupted during palliative radiotherapy, stopping 1 week before and resuming treatment 1 day after. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate CRF pages.

The effect of PF-0449913 on wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds. In the event surgery is necessary during study participation, PF-04449913 dosing should be stopped 1 week before surgery (based on a 30 hr human half-life for PF-04449913) and resumed no sooner than 1 day after surgery.

6. STUDY PROCEDURES

The term “Study entry” as used in this protocol is defined as the first day of lead-in treatment received.

6.1. Screening

For screening procedures see Table 1.

6.2. Study Period

For procedures during the study period see Table 1.

6.3. Follow-up Visit

For follow-up visit procedures see Table 1.

6.4. Post-Study Patient Interview

N/A

6.5. Patient Withdrawal

Patients may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, requests the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.
Patients will be withdrawn from treatment in the case of:

- Unequivocal disease progression;
- Unacceptable toxicity;
- Need for continuous treatment delay after Cycle 1/Day 1 >2 weeks due to ongoing toxicity (or greater than 42 days for prolonged myelosuppression) unless the patient is receiving clinical benefit and after discussion between investigator and sponsor has occurred;
- Need for anticancer therapy not specified in the protocol;
- Patient noncompliance;
- Patient lost to follow-up;
- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up).

Patients will be withdrawn from study in the case of:

- Withdrawal of consent;
- Patient lost to follow-up;
- Death.

Data to be collected for the end of study treatment/withdrawal are described in Table 1. Patients will be followed for at least 28 days after the last dose of study drug for adverse events.

7. ASSESSMENTS

Informed consent must be obtained prior to performing a study specific procedure on a patient and may occur prior to the 28-day screening period. All assessments are described in Table 1.

7.1. Safety Assessments

Safety assessments include collection of AEs, SAEs, triplicate 12-lead ECGs, vital sign measurements, physical examinations and safety laboratory tests. These will be performed periodically at baseline, during treatment and at End of Treatment (and/or at investigators’ discretion).
Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0), timing, seriousness, and relatedness.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

### 7.1.1. Laboratory Safety Assessments

Blood: Hematology, blood chemistry, and coagulation tests will be drawn at the time points described in Table 1. Investigators may order additional blood tests for planning treatment administration, dose modification, or further evaluation of adverse events.

Safety Laboratories should include:

- White blood cell count plus differential (including neutrophils, lymphocytes, eosinophils, basophils, monocytes), platelet count, hemoglobin, sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorus, magnesium, total protein, albumin, total bilirubin, direct and indirect bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, international normalized ratio, prothrombin time, and partial thromboplastin time.

- Microscopic urinalysis: pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite. If the urinary protein is $\geq 2^+$, then a 24-hour urine is required for quantitative measurements of protein, creatinine and glucose.

Pregnancy test: For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) to confirm the patient has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

### 7.1.2. Other Safety Assessments

The physical examination should include an examination of major body systems as well as measurement of spleen and liver size to assess EMD, ECOG performance status (Appendix 1), body weight, height (at Screening Visit only), and vital signs (oral temperature, blood pressure, pulse rate).
7.1.2.1. Electrocardiograms (ECG)

Triplicate 12-lead (with a 10-second rhythm strip) tracing in the supine position will be performed for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see Table 1), three consecutive ECGs will be performed approximately 2 minutes - but no longer than 5 minutes - apart, to determine the mean QTcF interval. If any patient has a mean pre-or post dose QTcF (Fridericia) value >480 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed.

The acceptable mean on treatment upper limit of QTc interval will be using the Fridericia correction method. The acceptable mean on treatment upper limit of QTcF interval is 500 msec. If the mean QTcF is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the site for confirmation, including verification that the machine reading is accurate. If manual reading verifies a mean QTcF at or above the acceptable upper limit, repeat ECGs should be performed hourly for at least 3 hours until the mean QTcF interval falls below the acceptable upper limit. If in that timeframe the mean QTcF intervals rise above the specific upper limit of acceptability the study drug(s) will be held until the mean QTc interval decreases to ≤500 msec. Patients will then re-start PF-04449913 at the next lowest dose level. If the mean QTc interval has still not decreased to the acceptable upper limit after 2-weeks, or if at any time a patient has a mean QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Throughout the study, additional ECGs and cardiac consultations will be obtained as clinically indicated.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) an ECG (triplicate) should be obtained at the time of the event.

Timing of ECGs may be modified based upon emerging PK data (as some ECGs are matched with the PK data).

When matched with PK sampling all efforts should be made to perform the ECG before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). A 15 min window for ECG collection is allowed around each nominal ECG time point except for the 24 hour ECG time point, where a 1 hour window is allowed.

7.2. Bone Marrow and Skin Samples

For AML and CML AP/BC patients, a bone marrow aspirate and/or biopsy will be collected at screening, on Day 1 of every even cycle, End of Treatment and at investigators discretion (±5 days of nominal time). For all other patients, the bone marrow aspirate and/or biopsy will be collected at screening, on Day 1 of Cycle 2, 6, 10 (and every subsequent 4-cycles) as well as at End of Treatment and at investigators discretion (± 5 days of nominal time).
If a bone marrow aspirate and/or biopsy has been collected within 28-days (excluding the screening sample) it need not be repeated. With sponsor approval, a bone marrow need not be performed based on the patient characteristics, or a bone marrow performed prior to screening may be used for study inclusion. The frequency of the bone marrow assessments for PD analysis may be reduced based on emerging data.

A normal skin sample will be collected (± 2-days) using a punch biopsy needle for PD analysis at screening and subsequently on Cycle 1/Day 21 (See Section 7.5).

7.3. Immunophenotyping, Cytogenetics and Mutation Analysis

For all patients, quantitative immunophenotyping and cytogenetics on blood and/or bone marrow must be collected at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy, at End of Treatment and at investigators discretion (timing discussed in Section 7.2). For all CML patients quantitative PCR for BCR-ABL will be conducted on blood and/or bone marrow at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy and at investigators discretion (Table 1), mutation analyses will be performed at screening only. If a bone marrow assessment is not performed a blood sample must be used for the clinical assessments (immunophenotyping, cytogenetics, mutation analyses).

7.4. Pharmacokinetic (PK) and Metabolite Profiling Assessments

7.4.1. Blood for PK Analysis

**PF-04449913 Single Agent**

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of PF-04449913 for all cohorts as outlined in the Schedule of Activities (Table 1): during the lead-in period on Day (-6), in Cycle 1 on Day 1, Day 5, Day 8, Day 15 and Day 21. For Cycles 2 and above a PK samples will also be collected on Day 1 as well as at End of Treatment. The PK assessments during Cycle 1 may be repeated if the PK sampling is missed for any reason or if the PK data collected are deemed inevaluable by the Sponsor.

Food Effect sub-study (Table 1): For patients participating in the food effect sub-study (first 8 patients), serial PK samples (2 mL of whole blood/sample to provide 1 mL of plasma) will be collected on Day -6 and Cycle 1/Day 1. On all other PK days, samples will be collected at the same time as the other cohorts.

Timing of sampling may be modified based upon emerging PK data, but number of samples will not increase.

Where noted in the schedule of activities, blood samples for PF-04449913 concentrations will be collected at approximately the same time as the pharmacodynamic samples and ECGs whenever possible (even accounting for scheduling changes).
Blood samples (except for the end of treatment sample) for PF-04449913 PK analysis will be collected only up to Cycle 15.

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

PK samples will be assayed for PF-04449913 using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Lab manual.

7.4.2. Blood for Metabolite Profiling of PF-04449913

Blood samples (to provide plasma) for metabolite profiling will be collected in:

- In the food effect expansion cohort only; first 8 patients, blood samples will be collected at screening and on Cycle 1/Day 21 (Table 1). One and one half (1.5) mL of blood will be collected at each time-point except at screening where the volume collected will be 2 mL.

The metabolite profiling assessments during Cycle 1 may be repeated if the sampling is missed for any reason or if the data collected are deemed not evaluable by the Sponsor.

Detailed collection procedures and shipping information will be provided in the Lab Manual. Timing of sampling may be modified based upon emerging PK data.

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

7.4.3. CSF for Analysis of PF-04449913

If a patient is required to undergo a lumbar puncture while on trial for disease related issues, if possible, an additional ~1mL sample of CSF should be collected for exploratory analysis of PF-04449913 concentrations. If this sample is collected, a plasma PK sample should also be collected at approximately the same time. Detailed collection procedures will be provided in the lab manual.

7.4.4. Urine for Analysis of PF-04449913 and Metabolite Profiling

Urine samples will be collected in:
In all cohorts, urine samples will be collected on Cycle 1/Day 21 over 0-24 hours post PF-04449913 dosing (Table 1). Patients will empty their bladder just prior to dosing on Cycle 1/Day 21. Urine will be collected in all cohorts for PK and metabolite ID, but the urine may only be analyzed for metabolite ID from the food effect expansion cohort; first 8 patients only.

At the end of the urine collection period, the total volume of urine will be measured and total volume recorded in the CRF. The urine will then be mixed thoroughly and a 20-mL aliquot will be withdrawn for PK analysis and a further 20-ml aliquot withdrawn for metabolite profiling (if there is insufficient urine collected, the urine volume apportioned for PK analysis will be prioritized as first). The samples will then be frozen at -20°C. Detailed collection procedures and shipping information will be provided in the Lab Manual. Timing of sampling may be modified based upon emerging PK data.

### 7.5. Pharmacodynamic Biomarker Assessments

Pharmacodynamic biomarker assessments will be performed in all patients enrolled in the study. These assessments will include evaluation of the effects of single agent PF-04449913 on Hh pathway related genes and proteins. Other biomarkers of PF-04449913 may also be measured. The number or frequency of all pharmacodynamic biomarker assessments may be modified based on emerging data.

**Blood samples:** Blood samples (~10 mL) will be collected for pharmacodynamic biomarker assessments of PF-04449913 as described in the Schedule of Activities (Table 1) during screening, the lead-in period on Day (-6) and Cycle 1/Day 21. If bone marrow biopsies are collected for clinical staging these may if feasible also be used for biomarker assessments. Samples will be collected in the appropriate tubes, processed, stored and shipped as described in the Lab Manual. The time of sampling may change, but the total number of samples will not increase. The PD assessments during Cycle 1 may be repeated if the PD sampling is missed for any reason or if the PD data collected are deemed not evaluable by the Sponsor. In addition, the frequency or need for the PD blood samples may be reduced based on emerging data.

**Normal skin biopsies:** Normal skin punch biopsies will be obtained from all patients at screening and Cycle 1/Day 21 (±1 day of nominal time on Day 21). Skin samples should be taken from the same approximate location. Skin samples will be analyzed for treatment-related changes in the RNA transcript levels of Hh pathway-regulated genes and potentially other signaling pathways. Samples will be processed and shipped as described in the Lab Manual. The time of sampling may change, but the total number of samples will not increase.
7.6. Efficacy Assessments

The study will enroll patients with select hematologic diagnoses, each having specific clinical response criteria (Appendix 4 through Appendix 8). The response criteria for CML are derived from Faderl et al (1999)\(^1\) and Cohen et al (2005).\(^2\) Response criteria for CMML/MDS, MF and AML are derived and defined by the disease specific International Working Groups and World Health Organizations (WHO) Guidelines.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient’s participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported.

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

If a patient begins a new anticancer therapy, the adverse event-reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.
8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error.

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

8.4. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms, and/or
• Test result requires additional diagnostic testing or medical/surgical intervention, and/or

• Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

• Test result is considered to be an AE by the investigator or sponsor.

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

8.5. Serious Adverse Events

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

• Results in death;

• Is life-threatening (immediate risk of death);

• Requires inpatient hospitalization or prolongation of existing hospitalization;

• Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

• Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with CTC Grade 5 (see Section on Severity Assessment).

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

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

The following expected, SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see 8.12.1 SAE Reporting Requirements) but will not be reported individually in an expedited manner because they are anticipated to occur in the study population:

- Neutropenic fevers or infections requiring hospitalization;
- Infections or complications from central lines;
- Central Nervous System involvement of disease.

8.5.2. Potential Cases of Drug-Induced Liver Injury

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

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

Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT $\geq$ 3 times the upper limit of normal concurrent with a total bilirubin $\geq$ 2 times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase $\leq$ 2 times the upper limit of normal or not available.

- For patients with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT $\geq$ 2 times the baseline values and $\geq$ 3 X ULN, or $\geq$ 8 X ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or $\geq$ 3 times the upper limit of normal (whichever is smaller).
The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT/INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy’s Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy’s Law cases should be reported as SAEs.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

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

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

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

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

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the following definitions of Severity in accordance with CTC Version 3.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Clinical Description of Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)</td>
</tr>
<tr>
<td>1</td>
<td>MILD Adverse Event</td>
</tr>
<tr>
<td>2</td>
<td>MODERATE Adverse Event</td>
</tr>
<tr>
<td>3</td>
<td>SEVERE Adverse Event</td>
</tr>
<tr>
<td>4</td>
<td>LIFE-THREATENING OR DISABLING Adverse Event</td>
</tr>
<tr>
<td>5</td>
<td>DEATH RELATED TO Adverse Event</td>
</tr>
</tbody>
</table>
Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

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

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

8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as in-utero [EIU] occurs if:

- A female becomes, or is found to be, pregnant either while receiving or being exposed to (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

- A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during his partner’s pregnancy.

If any study patient or study patient’s partner becomes or is found to be pregnant during the study patient’s treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).
Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.10. Withdrawal Due to Adverse Events

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

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

8.11. Eliciting Adverse Event Information

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

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

8.12.1. Serious Adverse Event Reporting Requirements

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

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

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

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

8.12.2. Non-Serious Adverse Event Reporting Requirements

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

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.
9. DATA ANALYSIS/STATISTICAL METHODS

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

As the primary purpose of this study is to define the MTD and RP2D, no confirmatory inferential analyses are planned. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, pharmacodynamic and pharmacokinetic parameters. Data will also be displayed graphically where appropriate.

9.1. Sample Size Determination

No formal sample size determinations were performed for the dose escalations. The sample sizes for assessing the food effect and pharmacodynamic biomarker analysis were chosen empirically.

The number of patients to be enrolled in the study will depend on the observed safety profile, and the number of dose escalations.

The expected number of patients is estimated to be 52.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

9.2.1.1. Primary Endpoint

Not applicable, as the primary endpoint is safety.

9.2.2. Analysis of Secondary Endpoints

All enrolled patients with adequate baseline assessment who receive C1D1 dose of PF-04449913 will be included in the efficacy analysis.

9.2.2.1. Secondary Endpoints

Response at each assessment, overall response, time to progression, progression-free survival, and duration of response based on the appropriate criteria will be listed by dose cohort and each hematologic malignancy (Appendix 4 through Appendix 8). If the numbers are adequate, overall response rate (ORR) will be calculated as the number of responders divided by the number of patients with each hematologic malignancy.
9.2.3. Patient Characteristics and Disposition

All enrolled patients who receive at least one dose of any study medication will be included in the listings and summaries of demographic characteristics, study drug administration, and disposition.

Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior therapy, prior medications, medical history, ECOG performance status and signs and symptoms will be tabulated.

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

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for deviations from planned therapy.

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary; patients who received concomitant medications will be listed.

9.2.4. Pharmacokinetic Analysis

9.2.4.1. Single- and Multiple-Dose PF-04449913 PK Analysis

The PK concentration population is defined as all enrolled patients treated who have at least 1 concentration. The PK parameter analysis population is defined as all enrolled patients treated who have at least 1 of the PK parameters of interest.

Standard plasma pharmacokinetic parameters including the maximum plasma concentration ($C_{\text{max}}$), time to maximum plasma concentration ($T_{\text{max}}$), and area under the plasma concentration versus time curve (AUC) for PF-04449913 will be estimated using non-compartmental analysis. If data permit or if considered appropriate, minimum plasma concentration ($C_{\text{min}}$), average plasma concentration ($C_{\text{ave}}$), area under the plasma concentration versus time curve to infinity ($AUC_{\text{inf}}$), terminal elimination half-life ($t_{1/2}$), oral plasma clearance ($\text{CL/F}$), apparent volume of distribution ($V_{d/F}$), accumulation ratio ($R_{\text{ac}}$) will be estimated. If data permit renal clearance ($\text{CL}_{\text{R}}$), cumulative amount recovered unchanged in the urine up to 24 hours post-dose ($AE_{24}$), and cumulative amount recovered unchanged in the urine up to 24 hours post-dose expressed as a fraction of administered dose ($AE_{24\%}$) will be also estimated. Descriptive statistics will be provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.
For PF-04449913 concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by dose, cycle, day of assessment, and nominal time in tabular form. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Dose normalized PF-0449913 AUC and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. The observed accumulation ratio for PF-04449913 and the linearity ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

The attainment of steady-state for PF-04449913 will be assessed by visual inspection of the pre-dose concentrations on Days 5, 8, 15 and 21 in Cycle 1.

9.2.4.2. Effect of Food on PF-04449913 PK

For the evaluation of the food effect, PF-04449913 plasma concentration-time data will be compared on Day (-6) to Cycle 1/Day 1. Natural log transformed AUC and C_{max} will be analyzed using a mixed effect model with sequence 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.

9.2.4.3. Population Pharmacokinetic Analysis or PK/PD Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using compartmental or mixed-effect modeling approaches and may also be pooled with other study results. PK/PD modeling may be attempted to investigate any causal relationship between PF-04449913 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.2.4.4. Metabolite Profiling

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

9.2.5. Pharmacodynamic Biomarker Analysis

Summaries of change from baseline to post-treatment in hedgehog signaling components will be provided, as appropriate.
9.3. Safety Analysis

Safety data, including adverse events and laboratory test results, will be summarized and listed for each dose cohort. All patients who receive at least one dose of any study medication will be included in these listings and summaries.

9.3.1. Analysis of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), with severity graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Frequencies of patients experiencing at least one AE will be displayed by body system class and preferred term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, the day of onset, the duration, the dose, whether the AE was serious, the nature of the event (single episode versus multiple episodes), the intensity, the relationship to study drug, any action taken, the clinical outcome, and whether the AE resulted in surgery or an alternate procedure. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Summary tables will be prepared to show the number of patients observed with AEs and corresponding percentages. The number and percentage of patients who experience AEs and laboratory abnormalities will be summarized counting worst toxicity grades observed. AE data will be presented across all cycles and for each cycle. The denominator for each cycle will be the number of patients available at the start of the cycle who received at least 1 dose of study drug for that cycle. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Individual patient listings will be prepared for all AE data. Listings of first cycle DLTs for each dose cohort within each Phase will be provided. Additional summaries of AEs and other safety data will be presented in tabular and/or graphical format and summarized descriptively, as appropriate.

9.3.2. Laboratory Tests

Listings and tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment. The tables will list the schedule, day and cycle of treatment, doses, and associated NCI CTCAE toxicity grade. Summary tables will be prepared to examine the distribution of these toxicities per cycle.

Graphic displays and shift tables may be provided to illustrate the results over time on study. Assessment of cumulative toxicities may be made.
9.3.3. ECG Analysis

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis. QT intervals will be corrected for heart rate (QTc). Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by drug, dose and by time point. For each patient and by treatment, the maximum increase from baseline as well as the maximum post-baseline value will be calculated across time points using the correction method that was deemed the most appropriate. Outlier analysis of the QTc (using the most appropriate correction method) data will be conducted and summarized as follows:

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

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

Study conclusions will be based on the most appropriate correction method for the analysis. The effect of PF-04449913 concentrations on QTc will be explored at multiple time points after PF-04449913 dosing and will be baseline corrected for each patient. Data may be pooled with other study results.

9.4. Interim Analysis

No interim analyses are planned.

9.5. Data Monitoring Committee

An independent third-party DMC will not be established for this study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team consisting of physicians, safety specialists, clinical pharmacologists and statisticians to review individual and summary data collected in the safety and clinical databases.

Procedures include:

- Surveillance for serious adverse events according to regulatory guidelines;
- Routine review of non-serious adverse events as they are recorded in the case report forms;
Periodic teleconferences with the principal investigators to share experiences and ensure communication.

Findings of the periodic safety reviews according to the Pfizer procedures will be documented in the project files and action taken as appropriate. Findings having immediate implication for the management of patients on study will be communicated to all principal investigators in the timeframe associated with unexpected and drug-related serious adverse events.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be patient to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

11.2. Record Retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

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

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

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

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

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

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

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

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

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

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

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Study Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as the date upon which enrollment is completed according to protocol planned sample size, and the last patient has completed the end of treatment visit (including all assessments and requirements as indicated by the protocol).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-04449913 at any time.

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

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

- The results are posted in a tabular format called Basic results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:
• For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

• For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval. or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

• For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

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

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

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

If the Study is part of a multi-centre study, investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, investigator is free to publish separately, subject to the other requirements of this Section.
For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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


## Appendix 1. ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
## Appendix 2. WHO Classification of Myelodysplastic Syndromes (MDS)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia</td>
<td>Erythroid dysplasia only</td>
</tr>
<tr>
<td></td>
<td>No blasts</td>
<td>≥ 15% ringed sideroblasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopeniæ (bic, pancytopenia)</td>
<td>Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts in marrow</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 x 10⁹L monocytes</td>
<td>&lt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)</td>
<td>Cytopeniæ (bic, pancytopenia)</td>
<td>Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>≥ 15% ringed sideroblasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 x 10⁹L monocytes</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopeniæ</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>&lt; 5% blasts</td>
<td>5% to 9% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 x 10⁹L monocytes</td>
<td></td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopeniæ</td>
<td>Unilineage or multilineage dysplasia</td>
</tr>
<tr>
<td></td>
<td>5% to 19% blasts</td>
<td>10% to 19% blasts</td>
</tr>
<tr>
<td></td>
<td>Auer rods =</td>
<td>Auer rods =</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 x 10⁹L monocytes</td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopeniæ</td>
<td>Unilineage dysplasia in granulocytes or megakaryocytes</td>
</tr>
<tr>
<td></td>
<td>No or rare blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td>No Auer rods</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anemia</td>
<td>Normal (no increased megakaryocytes with hypolobulated nuclei)</td>
</tr>
<tr>
<td></td>
<td>&lt; 5% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td>Platelets normal or increased</td>
<td>No Auer rods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>isolated del(5q)</td>
</tr>
</tbody>
</table>

Appendix 3. Diagnostic Criteria for Chronic Myelomonocytic Leukemia (CMML)*

- Persistent peripheral blood monocytosis greater than 1x10^9/L;
- No Philadelphia chromosome or BCR/ABL fusion gene;
- Fewer than 20% blasts* in the blood or bone marrow;
- Dysplasia in one or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are present and: an acquired, clonal cytogenetic abnormality is present in the marrow cells, or the monocytosis has been persistent for at least 3 months and all other causes of monocytosis have been excluded;
- Diagnose CMML-1 when blasts fewer than 5% in blood and fewer than 10% in bone marrow;
- Diagnose CMML-2 when blasts are 5% to 19% in blood, or 10% to 19% in marrow, or if Auer rods are present and blasts are fewer than 20% in blood or marrow;
- Diagnose CMML-1 or CMML-2 with eosinophilia when the criteria above are present and when the eosinophil count in the peripheral blood is greater than 1.5 x10^9/L.

*In this classification of CMML, blasts include myeloblasts, monoblasts, and promonocytes.

## Appendix 4. Response Criteria and Progression Definitions for Myelodysplasia and CMML

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Peripheral Blood</th>
<th>Bone Marrow Blasts (BMB) (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hgb (g/dL)</td>
<td>Neutrophils (L)</td>
<td>Platelets (L)</td>
</tr>
<tr>
<td><strong>Complete Remission</strong></td>
<td>≥11</td>
<td>≥1 x 10⁹</td>
<td>≥100 x 10⁹</td>
</tr>
<tr>
<td><strong>Partial Remission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marrow CR</strong></td>
<td>If hematologic improvement (HI) response, note in addition to Marrow CR</td>
<td></td>
<td>≤5% &amp; decreased by ≥50%</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse after CR or PR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Additional Response Criteria for Myelodysplasia and CMML

<table>
<thead>
<tr>
<th>Cytogenetic Response</th>
<th>Disappearance of chromosomal abnormality with no appearance of new ones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>≥50% reduction of chromosomal abnormality</td>
</tr>
<tr>
<td>Partial</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>For patients with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% increase to &gt;5% bone marrow blasts</td>
<td></td>
</tr>
<tr>
<td>≥50% increase to &gt;10% bone marrow blasts</td>
<td></td>
</tr>
<tr>
<td>≥50% increase to &gt;20% bone marrow blasts</td>
<td></td>
</tr>
<tr>
<td>≥50% increase to &gt;30% bone marrow blasts</td>
<td></td>
</tr>
</tbody>
</table>

At least 50% decrease from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥2 g/dL
Transfusion dependence

Proposed modified IWG Myelodysplasia and CMML Response Criteria for Hematologic Improvement (HI)

<table>
<thead>
<tr>
<th>Erythroid response (pre-treatment &lt;11 g/dl)*</th>
<th>Hb increase by ≥1.5 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks as compared to the pretreatment transfusion number in the previous 8 weeks (only RBC transfusions given for Hb≤9/dL pretreatment will count in the RBC transfusion evaluation).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet Response (pretreatment &lt;100 x10^9/L)*</th>
<th>Absolute increase of ≥30 x10^9/L if starting with &gt;20 x 10^9/L platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase from &lt;20 x 10^9/L to &gt;20 x10^9/L and by at least 100%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neutrophil Response (pretreatment &lt;1x10^7/L)*</th>
<th>At least a 100% increase and an absolute increase &gt;0.5 x10^7/L</th>
</tr>
</thead>
</table>

Progression or relapse after HI in the absence of another explanation
At least one of the following:
At least 50% decrease from maximum response levels in granulocytes or platelets;
Reduction in Hgb by ≥1.5 g/dL;
Transfusion dependence.

Hematologic responses (CR, PR and mCR) must last at least 4-weeks (stability of the improved counts is sufficient to define CR or PR without the need to repeat a second BM).*:
Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart.
## Appendix 5. 2008 WHO Diagnostic Criteria for Primary Myelofibrosis*

<table>
<thead>
<tr>
<th>Major Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Megakaryocyte proliferation and atypia† accompanied by either reticulin and/or collagen fibrosis, or</td>
</tr>
<tr>
<td>In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e., pre-fibrotic PMF).</td>
</tr>
<tr>
<td>2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm.</td>
</tr>
<tr>
<td>3. Demonstration of JAK2V617F or other clonal marker, or no evidence of reactive marrow fibrosis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Leukocytoclasticity</td>
</tr>
<tr>
<td>2. Increased serum LDH</td>
</tr>
<tr>
<td>3. Anemia</td>
</tr>
<tr>
<td>4. Palpable splenomegaly</td>
</tr>
</tbody>
</table>

**Abbreviations:** CML, chronic myeloid leukemia; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

*Diagnosis requires meeting all three major criteria and two minor criteria.

†Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

**Reference:** Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 2008; (22) 14.†
## Appendix 6. Response Criteria and Progression Definitions for Myelofibrosis

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Peripheral Blood</th>
<th>BM Blasts (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hgb (g/L)</td>
<td>Neutrophils (L)</td>
<td>Platelets (L)</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>≥110</td>
<td>≥1 x 10⁹</td>
<td>≥100 x 10⁹</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Cytogenetic Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Remission (PR)</td>
<td>≥110</td>
<td>≥1 x 10⁹</td>
<td>≥100 x 10⁹</td>
</tr>
<tr>
<td>Clinical Improvement (CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.

Appendix 7. Response Criteria and Progression Definitions for Acute Myeloid Leukemia

Hematologic Responses to Treatment

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Neutrophils (μL)</th>
<th>Platelets (μL)</th>
<th>Bone Marrow Blasts (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphologic Complete Response (CR)</td>
<td>&gt;1,000</td>
<td>≥100,000</td>
<td>&lt;5</td>
<td>Transfusion independent, no EMD</td>
</tr>
<tr>
<td>This is morphologic leukemia-free plus neutrophil &amp; platelet response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphologic CR with incomplete blood count recovery (CRI)</td>
<td>&lt;1,000</td>
<td>&lt;100,000</td>
<td>&lt;5</td>
<td>Either neutrophils or platelets not recovered, no EMD. Elderly AML (&gt;60 years) may be in a clinical CR with persistence of a cytopenia (usually neutropenia or thrombocytopenia)</td>
</tr>
<tr>
<td>Morphologic leukemia-free state</td>
<td>NA</td>
<td>NA</td>
<td>&lt;5 blasts in BM with spicules and no blasts with auer rods</td>
<td>Flow cytometry negative, No EMD</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>&gt;1,000</td>
<td>&gt;100,000</td>
<td>decrease to 5-25 &amp; ≥50% decrease from start</td>
<td>Blasts ≤5% if Auer rod positive</td>
</tr>
<tr>
<td>Partial remission with incomplete blood count recovery (PRI)</td>
<td>&lt;1,000</td>
<td>&lt;100,000</td>
<td>decrease to 5-25 &amp; ≥50% decrease from start</td>
<td></td>
</tr>
<tr>
<td>Minor Response</td>
<td>NA</td>
<td>NA</td>
<td>≥25% decrease from start</td>
<td></td>
</tr>
<tr>
<td>Stable Disease</td>
<td>NA</td>
<td>NA</td>
<td>Blasts stable ± 25%</td>
<td></td>
</tr>
</tbody>
</table>

Cytogenetic Responses to Treatment

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Neutrophils (μL)</th>
<th>Platelets (μL)</th>
<th>Bone Marrow Blasts (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic CR (CRc)</td>
<td>&gt;1,000</td>
<td>≥100,000</td>
<td>&lt;5</td>
<td>Cytogenetics – normal, no EMD</td>
</tr>
<tr>
<td>Molecular CR (CRm)</td>
<td>&gt;1,000</td>
<td>≥100,000</td>
<td>&lt;5</td>
<td>Molecular-negative, no EMD</td>
</tr>
</tbody>
</table>
Criteria for Treatment Failure

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF due to resistant disease</td>
<td>Pt survives ≥7 days post chemo; persistent AML in blood or BM</td>
</tr>
<tr>
<td>TF due to aplasia</td>
<td>Pt survives ≥7 days post chemo; death while cytopenic with aplastic bone marrow</td>
</tr>
<tr>
<td>TF indeterminate cause</td>
<td>Pt dies &lt;7 days post therapy; Pt dies &gt;7 days post therapy with no PB blasts, but no bone marrow exam; Pt does not complete 1st course of therapy</td>
</tr>
<tr>
<td>TF due to morphologic relapse</td>
<td>Reappearance of blasts post CR in PB or ≥5% blasts in bone marrow not attributed to another cause</td>
</tr>
<tr>
<td>TF due to molecular or cytogenic relapse</td>
<td>Reappearance of molecular or cytogenetic abnormality</td>
</tr>
</tbody>
</table>

### Appendix 8. Response Criteria and Progression Definitions for Chronic Myeloid Leukemia

**Hematologic Responses to Treatment; maintained for at least 4-weeks**

<table>
<thead>
<tr>
<th>Subjects with Accelerated or Blast Phase CML</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Responses</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Return to Chronic Phase</strong></td>
<td>Disappearance of features defining accelerated &amp; blast phases, but still in chronic phase (May have platelets (&lt;100 \times 10^9/L), if related to therapy) Persistence of clonal evolution, if present at the time of therapy, is acceptable for return to chronic phase</td>
</tr>
<tr>
<td><strong>Minor Response</strong></td>
<td>&lt;15% blasts in marrow and blood &lt; 30% blasts + promyelocytes in marrow and same in blood &lt; 20% basophils in peripheral blood No extramedullary disease other than spleen and liver</td>
</tr>
<tr>
<td><strong>No Evidence of Leukemia (NEL)</strong></td>
<td>Blast (\leq 5%) in bone marrow (0.5 \times 10^9 \leq ANC &lt; 1.0 \times 10^9/L) (20 \times 10^9 \leq \text{Platelets} &lt; 100 \times 10^9/L) No blood blasts or promyelocytes &lt;20% basophils in blood Myelocytes + metamyelocytes &lt;5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)</td>
</tr>
<tr>
<td><strong>Complete Hematologic Response</strong></td>
<td>Blast (\leq 5%) in bone marrow No peripheral blasts or promyelocytes Myelocytes + metamyelocytes &lt;5% in blood ANC (\geq 1.0 \times 10^9/L) WBC (\leq \text{institutional ULN}) Platelets (\geq 100) but (&lt;450 \times 10^9/L), unless related to therapy &lt;20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with Chronic Phase CML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Evidence of Leukemia (NEL)</strong></td>
</tr>
<tr>
<td>0.5 (\times 10^9 \leq ANC &lt; 1.0 \times 10^9/L) (20 \times 10^9 \leq \text{Platelets} &lt; 100 \times 10^9/L) No blood blasts or promyelocytes &lt;20% basophils in blood Myelocytes + metamyelocytes &lt;5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)</td>
</tr>
<tr>
<td><strong>Complete Hematologic Response</strong></td>
</tr>
<tr>
<td>No Peripheral blasts or promyelocytes Myelocytes + metamyelocytes &lt;5% in blood ANC (\geq 1.0 \times 10^9/L) WBC (\leq \text{institutional ULN}) Platelets (\geq 100) but (&lt;450 \times 10^9/L), unless related to therapy &lt;20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)</td>
</tr>
</tbody>
</table>
## Cytogenetic Responses to Treatment (Any Phase of CML)

<table>
<thead>
<tr>
<th>Cytogenetic Responses*</th>
<th>% Philadelphia chromosome positive cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Minimal</td>
<td>66-95%</td>
</tr>
<tr>
<td>Minor</td>
<td>36-65%</td>
</tr>
<tr>
<td>Partial</td>
<td>1-35%</td>
</tr>
<tr>
<td>Complete</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Based on analysis of 20 metaphases. Or For post-baseline disease assessments, FISH analysis may be used if the bone marrow sample is inadequate for cytogenetic analysis in order to confirm the presence of BCR-Abl fusion product and its percentage in marrow.

## Molecular Responses (MR) to Treatment (Any Phase of CML)

<table>
<thead>
<tr>
<th>Molecular Responses</th>
<th>PCR for BCR-Abl</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No Change</td>
</tr>
<tr>
<td>Partial</td>
<td>&lt; 3 log reduction from standardized baseline</td>
</tr>
<tr>
<td>Major</td>
<td>≥ 3 log reduction from standardized baseline</td>
</tr>
<tr>
<td>Complete</td>
<td>Undetectable BCR-Abl</td>
</tr>
</tbody>
</table>

## Definitions of Treatment Failure and Disease Progression

### Definitions of Treatment Failure
- Occurrence of at least one of the criteria for disease progression shown below
- Death (any cause)
- Withdrawal from treatment owing to an adverse event, subject refusal, or loss to follow-up

### Definitions of Progression

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Progressor from CP</td>
<td>For Chronic Phase: If subject enters study in chronic phase clearly progresses to advanced phase during the first 4 weeks of therapy (to be considered a progressor to accelerated phase, a subject must have an absolute increase of at least 10% in their count(s) qualifying the subject for accelerated phase).</td>
</tr>
<tr>
<td>Progressor to Accelerated Phase or Blast Crisis from Chronic Phase or Return to Chronic Phase</td>
<td>Subject evolving from chronic phase or return to chronic phase to accelerated phase or blast crisis (on two consecutive assessments at least a week apart).</td>
</tr>
<tr>
<td>Progressor to Accelerated Phase to Blast Crisis</td>
<td>A subject evolving from accelerated phase to blast crisis (on two consecutive assessments at least a week apart).</td>
</tr>
<tr>
<td>Loss of Confirmed CHR</td>
<td>Loss of confirmed CHR that is confirmed by a subsequent hematologic assessment ≥ at least 2 weeks after the initial finding of loss</td>
</tr>
<tr>
<td>Loss of MCyR</td>
<td>Loss of MCyR- Ph+ rate increased by 30%</td>
</tr>
</tbody>
</table>