A Phase 2 Study of PF-04449913 for the Treatment of Acute Myeloid Leukemia Patients with High Risk of Post-Allogeneic Stem Cell Transplantation Relapse

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PARTICIPATING CENTER	**The Ohio State University**
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator _____ Date _____

Printed Name of Investigator _____

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY PERSONNEL

Sponsor:	University of Colorado Cancer Center 1665 Aurora Court Aurora, CO 80045
Study Locations:	University of Colorado Cancer Center, Aurora, CO The Ohio State University, Columbus, OH
Investigators:	Daniel A. Pollyea, MD, MS University of Colorado Cancer Center Mail Stop F754, Room 4328 1665 Aurora Court Aurora, CO 80045 Phone: 720-848-8084 Jonathan Gutman, MD University of Colorado Cancer Center 1665 Aurora Court Aurora, CO 80045 Phone: 720-848-0220 Sumithira Vasu, MBBS Ohio State University Division of Hematology B310 Starling Loving Hall 320 W 10th Avenue Phone: 614-293-8197 Fax: 614-293-7526 Email: sumithira.vasu@osumc.edu

Contents

1 PROTOCOL SYNOPSIS

PROTOCOL TITLE: A Phase 2 Study of PF-04449913 For the Treatment of Acute Myeloid Leukemia Patients with High Risk of Post-Allogeneic Stem Cell Transplantation Relapse

INDICATION: Post allogeneic stem cell transplantation for acute myeloid leukemia patients with high risk of relapse

STUDY PHASE: 2

BACKGROUND AND RATIONALE: Disease relapse is the most common cause of death after allogeneic stem cell transplantation for acute myeloid leukemia. Patients at high risk for relapse may benefit from a novel, biologically rational therapeutic intervention to prevent this outcome. PF-04449913 is a small molecule inhibitor of the hedgehog (Hh) pathway that inhibits the protein Smoothened (SMO). Aberrant Hh signaling may contribute to the survival and expansion of the leukemia stem cell, and inhibiting the Hh pathway can eliminate these cells. Therefore, targeting Hh may be a logical intervention in the post-transplantation setting for those with high risk of relapse. We propose a phase 2 study of PF-04449913 in patients with acute myeloid leukemia who have received an allogeneic stem cell transplantation and are at high risk of relapse.

STUDY OBJECTIVES:

Primary:

- Determine whether PF-04449913 can prevent relapse in high risk acute myeloid leukemia patients who receive an allogeneic stem cell transplantation

Secondary:

- Determine the toxicity profile of PF-04449913 in this population
- Determine the impact of this intervention on overall survival (OS)

STUDY DESIGN:

This is an open label, phase 2 study employing PF-04449913 in acute myeloid leukemia patients who received an allogeneic stem cell transplantation and are at high risk of relapse. Patients will receive consecutive 28-day cycles of PF-04449913 at 100 mg/day, beginning on post-transplantation day 28-50, after their routine post-transplant bone marrow biopsy. Treatment will continue for up to one year or until they experience toxicity or disease relapse. 50 patients will be required for a 90% power to detect a 20% difference in one-year relapse free survival.

STUDY ENDPOINTS

Primary:

- One year relapse-free survival

Secondary:

- Remission duration
- Incidence and severity of adverse events
- OS (one year)

STUDY DURATION: 5-7 years	**TOTAL SAMPLE SIZE:** 50

2 SCHEDULE OF STUDY ASSESSMENTS*

		PF-04449913	Hx/PE	Hematology	Chemistry	Screening Labs & Procedures	12-Lead EKG	MRD	BM Bx
Screening†			X	X	X	X	X		
Cycle 1	Days 1-28	X							
	Day 1		X¶	X¶	X¶		X		
	Day 15		X	X	X		X		
	Day 28‡		X	X	X				
Cycles 2 - 12	Days 1-28	X							
	Day 1‡		X	X	X		X†*		
Initiation of New Azole Antifungal Medication							X¶*		
Post-transplant day 80 +/- 10 days								X	X
Post-transplant day 175 +/- 15								X	X
Post-transplant day 365 +/- 30								X	X

DEFINITIONS:

Hx/PE: Complete or interim medical history, including ECOG performance status, adverse event monitoring and concomitant medications review; complete or focused physical examination. Drug compliance assessment will occur with each cycle's day 1, beginning with cycle 2.

Hematology: Complete blood count (includes hemoglobin, hematocrit, platelet count and total white blood cell count with differential)

Chemistry: Complete metabolic profile, including Na, K, calcium, CO2, BUN, creatinine, glucose, magnesium, phosphorous, protein, albumin, AST, ALT, alkaline phosphatase and total bilirubin

Screening labs & procedures: Prothrombin time (PT) and/or international normalized ration (INR), partial thromboplastin time (PTT); serum/urine pregnancy test for women of childbearing potential only must be performed within 72 hours of treatment initiation.

12-lead EKG: To be performed with QTc interval calculated by Fridericia's correction factor if indicated.

MRD: Minimal residual disease, as detected by multidimensional flow cytometry (see Section 5.12.5.6)

BM Bx: Unilateral core and aspirate samples, to be sent for morphological assessment, cytogenetics, flow cytometry and molecular testing

FOOTNOTES

*Variations of ±5 days of scheduled visits are permitted; unscheduled visits can occur at any time during the study. The date of the unscheduled visit and any data generated must be recorded on the appropriate case report form, and source documents for these visits must also be maintained.

†Includes review of exclusion/inclusion criteria and informed consent.

¶If screening and day 1 are ≤ 7 days apart, the Hx/PE, CMP and CBC performed at enrollment do not need to be repeated on day 1.

‡Day 28 visit and labs may be same as day 1 visit and labs of the subsequent cycle

***Perform 1-4 hours after first dose (at Cmax)

†* Perform 1-4 hours after first dose (at Cmax) for cycle 2, day 1 only; not necessary to routinely repeat on day 1 of each cycle unless clinically indicated

¶*Perform 2-5 days after initiation of new azole antifungal medication

3 INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is the only therapy with curative potential for high risk patients with acute myeloid leukemia (AML) [2,3] However, disease relapse remains the main cause of treatment failure and death after HSCT,[4] suggesting that even highly ablative therapies and the generation of immunological graft versus leukemia responses are very often unable to target the leukemia stem cell population and achieve the requisite cure. At relapse, salvage maneuvers such as secondary transplantations or donor lymphocyte infusions are highly toxic and seldom effective,[5-7] highlighting the need for tolerable therapies in this population.

Predicting imminent relapse in the post-transplant setting is becoming increasingly sophisticated. In post-transplant patients, flow-cytometry based minimal residual disease (MRD) detection for AML has been shown to be highly predictive of relapse and overall survival (OS).[8-10] Molecular analyses of leukemia fusion genes can also allow for disease monitoring in select patients,[11] and persistence of a cytogenetic abnormality at the time of transplantation is a poor predictor for relapse and OS after a myeloablative HSCT.[12]

Developing clinical trials for AML post-allogeneic HSCT patients with imminent or high-risk of relapse is an area of active interest that warrants further exploration using novel therapies.

3.1 Background and Rationale

The Hedgehog (Hh) signaling pathway regulates essential elements of embryonic development, homeostasis and tissue regeneration and development.[15] It is important in a broad range of cancers, including basal cell carcinoma, bladder, colorectal, lung, pancreas, prostate and stomach.[16] Hh signaling is activated by binding of one of three Hh ligands, Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), or Desert Hedgehog (Dhh) to their receptor, Patched (Ptch).[17] Binding of Hh ligand to Ptch alleviates repression of a second transmembrane protein, Smoothened (SMO), allowing SMO to transduce the signal to the cytoplasm resulting in activation of Gli family zinc finger transcription factors (Gli1, Gli2 and Gli3). Gli translocates into the nucleus and activates transcription of target genes, causing proliferation.

Activation of the Hh pathway can occur by two mechanisms. First, mutations in Ptch or SMO genes result in constitutive activation of the pathway and upregulation of Gli. Mutations in Hh signaling members have been reported in basal cell carcinoma,

medulloblastoma, and rhabdomyosarcoma.[18,19] A direct link between mutation driven aberrant Hh signaling and human tumorgenesis is found in Gorlin Syndrome,[18] characterized by the development of multiple basal cell carcinomas, and are predisposed to medulloblastoma and rhabdomyosarcoma. These patients have a germline inactivating mutation in the repressor Ptch that results in constitutively active SMO and upregulation of Hh target genes. The link between mutations in Ptch and basal cell carcinoma was also reported in a majority of sporadic basal cell carcinoma tumors,[18,19] and a significant number of sporadic medulloblastomas can also be attributed to inactivating mutations in *Ptch*.[19] To test these findings, a genetically engineered mouse model of medulloblastoma was developed by genomic deletion of a Ptch allele;[20,21] the heterozygous Ptch deletion mutation, coupled with a deletion of p53, resulted in posterior fossa tumors with active Hh pathway signaling and upregulated expression of Gli target genes.[22]

The second method of Hh activation is through autocrine or paracrine mechanisms of ligand driven Hh pathway activation in adult tissues with a normally dormant Hh pathway. In some cancers Hh pathway members are expressed in the tumor cells and directly affect the growth of the tumor, resulting in an autocrine positive feedback loop. In other cases, Hh ligand produced by tumor cells may activate the pathway in adjacent stroma, leading to the release of growth factors that support tumor growth or angiogenesis as part of the tumor microenvironment.[23]

The Hh pathway is now recognized for its involvement in the maintenance, growth and drug resistance of hematological malignancies. Hh pathway signaling is preferentially activated in MDS-derived cells and $CD34^+$ AML blasts and cell lines, [24-26] including chemoresistant cell lines,[27] and patient derived AML samples express Gli-1 in proportion to the number of CD34+ blast cells (Jamieson et al, manuscript in preparation), suggesting aberrant Hh signaling may contribute to the survival and expansion of the leukemia stem cell. Hh signaling is also relevant in B-cell ALL[28] and potentially T-cell ALL,[29,30] and can be modulated by pathway inhibitors, which were also shown to limit the self-renewal of leukemia cells.[28] In addition, it was recently shown that inhibiting the Hh pathway can selectively eliminate leukemia stem cells (LSCs).[31] Therefore, 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, making this pathway an attractive target for residual, treatment resistant disease.

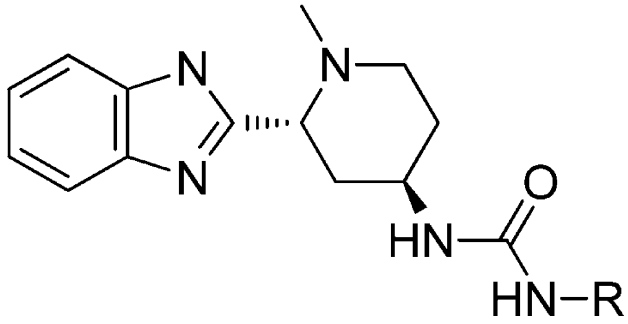
PF-04449913 (Pfizer) is a novel small molecule inhibitor of the Hh pathway that binds and inhibits SMO. This ultimately results in ubiquination of Gli1/2, leading to degradation and clearance of these transcription factors. Early phase clinical trials using this agent has shown it to be well tolerated and effective in patients with hematological malignancies.[32]

Hypothesis

PF-04449913 will be well-tolerated and effective therapy for acute myeloid leukemia patients who have received HSCT and have high risk of disease relapse. We aim to test this hypothesis with this phase 2 clinical study.

3.2 PF-04449913

Cyclopamine, isolated from the corn lily plant, interacts with and inhibits SMO.[33] PF-04449913 was synthesized to improve the hepatic clearance, decrease the lipophilicity and increase the solubility of cyclopamine. PF-04449913 is a potent and selective inhibitor of Hedgehog (Hh) signaling *in vitro* and has demonstrated significant antitumor efficacy *in vivo*.



Chemical Structure of PF-04449913

Molecular weight: 374.439 daltons

Chemical name: 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea dihydrochloride monohydrate

Molecular Formula: C21H26Cl2N6O2 (dihydrochloride monohydrate)

Physical description: White to pale-colored powder

Bioavailability: Oral

Pre-Clinical Data

Pharmacokinetics/Pharmacodynamics and Metabolism

Preclinical pharmacokinetic (PK) / pharmacodynamics (PD) modeling suggests a target human dose of 15 mg/day is projected to yield at least 50% of tumor Gli1 mRNA inhibition from baseline levels. A 15 mg dose is projected to result in a Cmin of 62 ng/mL total (5.6 ng/mL free) and a Cave of 79 ng/mL total (7.2 ng/mL free).

Absolute oral bioavailability of PF-04449913 following single dose oral administration was 33% in rats and 68% in dogs. Plasma protein binding of PF-04449913 in mouse, rat, dog, and human plasma ranged from 85% to 93%. A volume of distribution at steady state (Vss) of 4.78 and 4.21 L/kg was observed in rats and dogs, respectively.

PF-04449913 was evaluated in rat and dog repeat-dose toxicity studies up to 1 month in duration. PF-04449913 was well tolerated up to 50 mg/kg/day in the rat and 5 mg/kg/day in the dog. In both the rat and the dog, a greater than proportional increase in exposure occurred with increasing dose. In the rat study, the increase in mean AUC(0-24) values were approximately 175-fold and 232-fold greater than the dose (50-fold) range evaluated for Day 1 and Day 29, respectively. In the 1-month dog toxicity study, the mean AUC(0-24) values were approximately 165-fold (male) and 360-fold (female) greater than the dose (30-fold) range evaluated on Day 1.

In vitro metabolism of PF-04449913 was consistent across preclinical species and humans. All metabolites observed in human *in vitro* incubations were present in one or more of the evaluated preclinical species. PF-04449913 appeared to be metabolized to several oxidative metabolites. Preliminary assessment using individual recombinant P450 enzymes suggests that CYP3A4 plays a major role in mediating the metabolism of PF-04449913 *in vitro*.

PF-04449913 was evaluated *in vitro* in human liver microsomes for the potential to inhibit CYP enzymes. Preliminary results show that PF-04449913 does not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at concentrations up to 30 μM (11.2 □g/mL).

In cryopreserved human hepatocytes, PF-04449913 does not induce CYP1A2 or CYP3A4 mRNA levels and enzyme activities at unbound concentrations up to 100 □M (37.4 □g/mL). Considering the human pharmacokinetics observed to date, PF-04449913 is not expected to

reduce plasma concentrations of co-administered CYP1A2 or CYP3A4 substrates *in vivo*.

Toxicity

Deaths and/or moribund euthanasia occurred in the 7-day and 10-day rat, and 1-month dog studies at 250, 500 or 30/15 mg/kg/day, respectively. Cause of death/morbidity in both species was attributed to kidney toxicity. The target organ in the rat 1-month toxicity study included kidney (tubular degeneration/necrosis, cytomegaly, inflammation, regeneration) and bone (decreased/disorganized chondrocytes in epiphysis); the no observed adverse effect level (NOAEL) was 10 mg/kg/day (a 5× safety margin over the projected human Cave at steady state). The kidney changes showed some signs of reversibility but did not entirely reverse, while the bone changes persisted.

The target organ in the 1-month toxicity study in the dog was limited to the kidney (tubular necrosis, granular/mineralized casts, dilated tubules); NOAEL was 1 mg/kg/day which is <1× the projected human Cave at steady state. Mild changes in the kidney were observed at 5 mg/kg/day which are 11× the projected human Cave at steady state. The kidney changes in the dog were completely reversed in males and partially reversed in females after a 6-week reversal period. In the acute central nervous system (CNS) and respiratory studies in the rat, no effects were observed at the high dose of 50 mg/kg (55× above the projected human efficacious Cmin at steady state). Increases in QT, QTc75 were noted after single doses of □5 mg/kg to dogs which is □49× above the projected human efficacious Cmax at steady state. PF-04449913 was negative in the definitive in vitro bacterial mutagenicity assay, human lymphocyte assay and the *in vivo* rat micronucleus. The molar extinction coefficient for PF-04449913 at 290 nm is 9622 L/mol/cm; therefore, PF-04449913 has the potential to be phototoxic.

To evaluate potential effects on the central nervous system, PF-04449913 was administered as a single dose to male rats, and motor activity, behavioral changes, coordination, sensory/motor reflex responses, and body temperature were evaluated. There were no effects in either the functional observational battery or locomotor activity assessment at doses up to 50 mg/kg. The maximum plasma concentration at 50 mg/kg free group mean Cmax of 617 ng/mL from the 1-month rat is 72-fold above the projected human free efficacious Cmax concentration of 8.6 ng/mL. To evaluate the potential effect on the cardiovascular system, PF-04449913 was evaluated for its effect on binding to the hERG potassium channel stably expressed in human embryonic kidney (HEK-293) cells

(PF4449913/ESD/1108/HERG). The hERG IC50 for PF-04449913 was 3.1 □M 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). To further investigate QT prolongation and any hemodynamic changes due to inhibition of several receptors outlined in the secondary pharmacodynamics section, PF-04449913 was administered by oral gavage to conscious telemeterized dogs at dose levels of 1, 5 and 30 mg/kg. At dose levels of 5 and 30 mg/kg, PF-04449913 produced a statistically significant and dose dependent increase in QT and QTc75 which was apparent up to at least 14 hours post-dosing. The maximum observed QTc75 prolongation was 6 and 24 msec at 5 and 30 mg/kg, respectively. Increases in heart rate (10 beats per minute) occurred in the 30 mg/kg treated dogs which were coincident with episodes of emesis and are most likely related to the latter effect. There was also a small increase (3 msec) in the QRS interval after the 30 mg/kg treatment and this was apparent up to 14 hours post-dosing. This latter effect is consistent with the weak sodium channel inhibition observed in a functional patch clamp study (see the secondary pharmacodynamics section). There were no statistical or remarkable changes in dogs treated with 1 mg/kg PF-04449913. At 5 mg/kg, the peak free plasma concentration in male and female dogs was 517 ng/mL and 420 ng/mL, respectively (from the 1-month dog). This represents a 49 to 60-fold margin above the projected free Cmax (8.6 ng/mL) at a human efficacious dose of 15 mg. PF-04449913 was administered as a single dose to male rats to assess potential effects on the respiratory system. PF-04449913 had no effect on respiratory rate, tidal volume or minute volume at doses up to 50 mg/kg. The maximum plasma concentration at 50 mg/kg (free mean Cmax of 617 ng/mL from the 1-month rat is 86-fold above the projected human (Cave) drug concentration of 7.2 ng/mL and 72-fold above the projected human free efficacious Cmax (8.6 ng/mL).

Clinical Data

See current PF-04449913 Investigator's Brochure – released by Pfizer (manufacturer).

Several clinical studies have been initiated to determine the safety, efficacy, pharmacodynamics and pharmacokinetics of PF-04449913 in patients with hematologic malignancies and advanced/metastatic solid tumors. Study B1371001 was a first-in-patient phase 1 trial with a 3+3 dose escalation design in patients with refractory, resistant or intolerant select hematologic malignancies. Patients received single

agent PF-04449913 orally once daily (QD) continuously in 28 day cycles. Eight dose levels were evaluated as of September 2011, ranging from 5 mg/d to 270 mg/d. Study B1371002 had a similar 3+3 dose escalation design in patients with select advanced/metastatic solid tumors. The starting dose of PF-04449913 in this study was 80 mg/d and additional dose levels of 160 mg/d and 320 mg/d have been completed to date. Protocol B1371003, a Phase 1b/2 study to evaluate the safety and efficacy of PF-04449913 in combination with various chemotherapy regimens in patients with AML and high-risk MDS, is ongoing.

Pharmacokinetics/Pharmacodynamics and Metabolism

Preliminary PK data indicate that PF-04449913 is rapidly absorbed following oral dosing with a median Tmax of ~1- 2 hr after single and multiple dose administration. Following attainment of Cmax, PF-04449913 plasma concentrations showed a bi-exponential decline and were eliminated relatively slowly with a mean terminal half-life (estimated from a single dose) ranging from 17.3 to 34.9 hours. Following repeated daily dosing, PF-04449913 steady state was achieved by Day 8 and showed a drug accumulation of ~ 1.5 fold, which is consistent with the estimated half-life. In general, low to moderate inter-individual variability were observed in Cmax and AUC values following single and multiple dose administration, though higher variability was observed at the 180 and 270 mg dose levels.

Hepatic metabolism is predicted to be the major clearance pathway for PF-04449913 in humans. In vitro metabolism of PF-04449913 was consistent across preclinical species and humans. PF-04449913 appeared to be metabolized to several oxidative metabolites. Preliminary assessment using individual recombinant P450 enzymes suggests that CYP3A4 plays a major role in mediating the metabolism of PF-04449913. All metabolites observed in human in vitro incubations were present in one or more of the evaluated preclinical species. In vitro, PF-04449913 did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at concentrations up to 30 µM. Based on in vitro and in vivo evaluations of PF-04449913, systemic plasma clearance, volume of distribution at steady state, elimination half-life and oral bioavailability in humans are projected to be 1.03 mL/min/kg, 2.7 L/kg, 30 hours and 55%, respectively.

Preliminary data indicates that renal excretion plays a minor role in PF-04449913 elimination, with 4% to 19% (n = 15) of the total

administered dose excreted unchanged in urine. The renal clearance ranged from 0.35 L/hr to 3.4 L/hr.

When 200 mg PF-04449913 was combined with ketoconazole, a strong inhibitor of CYP3A4, in healthy volunteers, there was evidence for a drug-drug interaction resulting in increased exposure (Cmax and AUC) of PF-04449913, potentially to the 400-600 mg range observed to result in grade 3 QTc prolongations in study B1371001.

Study B1371010, a healthy volunteer study investigating the effects of a high fat, high calorie meal on the PK of a single dose of PF-04449913, indicated that food resulted in a 12.7% decrease in AUC and a 34.1% decrease in Cmax for PF-04449913.

Toxicity

Preliminary results from a phase 1 study in patients with hematological malignancies revealed grade 3 toxicities of hemorrhagic gastritis, hypoxia and pleural effusions. All other adverse events (AEs) were less than grade 3, and included dysguesia (16%), alopecia (6%), arthralgia (6%), decreased appetite (6%), nausea (6%) and vomiting (6%).32 Roughly 50% of patients had at least a grade 1 AE. This study and others are ongoing.

Recommended Dose

Due to the potential interaction between azoles and PF-04449913, 100 mg of PF-04449913 has been selected as the recommended dose in the ongoing protocol B1371003.

4 STUDY OBJECTIVES

4.1 Primary Objective

- Determine whether PF-04449913 can prevent relapse in high risk acute myeloid leukemia patients who receive an allogeneic stem cell transplantation

4.2 Secondary Objectives

- Determine the toxicity profile of PF-04449913 in this population
- Determine the impact of this intervention on overall survival (OS)

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an open-label, phase 2 study of PF-04449913 administered to acute myeloid leukemia patients after allogeneic stem cell transplantation who have a high risk of disease relapse.

5.1.1 Dosing Schema

Enrolled patients will receive 100 mg PO daily of PF-04449913 continuously dosed for 28-day cycles. Patients will begin treatment no sooner than post-transplant day 28 and no later than post-transplant day 50, after their routine bone marrow biopsy is performed. Treatment cycles can continue for one year after initiation of study drug in the absence of the parameters listed in Section 5.10.1: Stopping Rules.

5.1.2 Continuation and Interruptions

Each treatment cycle will be initiated at the full 100 mg dose, provided patients have no evidence of disease relapse, excessive toxicity, or laboratory values outside of the following parameters:

- Either creatinine >1.5 x institutional upper limit of normal (ULN) or creatinine clearance <60 mL/min as calculated by institution's standard formula
- Total bilirubin > 2 x ULN (unless documented Gilbert's syndrome)
- AST and ALT > 5 x institutional ULN
- Absolute neutrophil count (ANC) < 1000/mm^3
- Platelet count <25,000/mm^3

Patients who experience toxicity may be eligible for dose de-escalation; please see Section 5.13.1 for Definition of Adverse Events and Section 5.10.2.2: Dose Delays and De-Escalation.

5.2 Study Endpoints

5.2.1 Primary Endpoint

- One year relapse-free survival

5.2.2 Secondary Endpoints

- Remission duration
- Incidence and severity of adverse events
- Overall survival (one year)

5.3 Selection of Study Population and Enrollment Procedures

All subjects will be screened for eligibility; see Section 2: Schedule of Study Assessments and Section 5.12: Study Activities and Assessments for screening details. All patients must meet the qualifications as outlined below.

5.3.1 Inclusion Criteria

To be eligible to participate in this study, a patient must meet the following criteria:

- WHO-confirmed AML
- Age ≥18 years
- Between days 28 and 50 post transplantation at the time of initiation of the study drug
- ECOG performance status ≤ 2 (See Appendix A: ECOG Performance Status Scale)
- Life expectancy > 2 months
- Recipient of a myeloablative or non-myeloablative allogeneic HSCT
    - Conditioning regimen to be prescribed at investigator's discretion, but will be prospectively defined as myeloablative or non-myeloablative
- Stable engraftment, as defined by absolute neutrophil count (ANC) ≥ 1000/mm^3 and platelets ≥ 25,000/mm^3
- In morphologic remission (< 5% marrow blasts) based on BM biopsy performed +/- 5 days of day 28 post-transplantation
- Without clinical signs of active central nervous system disease
- For non-myeloablative transplants, ≥50% CD3 donor chimerism at screening
- High risk of relapse after HSCT, defined as the presence of minimal residual disease as measured by flow cytometry in the absence of evidence of morphologic disease on a bone marrow biopsy prior to HSCT

- Adequate organ function as indicated by the following laboratory values:
    - Aspartate aminotransferase (AST), alanine aminotransferase, (ALT) ≤ 3.0 x institutional upper limit of normal (ULN)
    - Total bilirubin ≤ 2.0 x institutional ULN, unless documented Gilbert's syndrome
    - Either creatinine <1.5 x institutional upper limit of normal (ULN) or creatinine clearance >60 mL/min as calculated by institution's standard formula
- Serum/urine pregnancy test (for females of childbearing potential) that is negative within 72 hours prior to initiation of first dose of treatment (a patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active)
- Female patients of childbearing potential and sexually active males and female partners of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.
- Subject is able to comply with study procedures and follow-up examinations.

5.3.2 Exclusion Criteria

- Concomitant treatment with other anti-neoplastic agents, with the exception, when clinically indicated, of prophylaxis in the post-transplantation setting with intrathecal chemotherapy
- Use of any other experimental drug or therapy within 28 days of baseline
- Inability to swallow or absorb drug
- Active uncontrolled acute fungal, bacterial, or other infection that is unresponsive to therapy at time of study drug dosing
- Unstable angina pectoris
- New York Heart Association Class III or IV heart failure
- QTc interval (using Fridericia's correction formula, QTcF, if prolonged) >470 msec
- Active cardiac arrhythmias with rapid ventricular response (defined as heart rate greater than 100 beats/minute)
- Known HIV infection
- Grade III/IV acute GVHD

- Current use or anticipated need for food or drugs that are known moderate/strong CYP3A4 inducers (See Table 1 and section 5.9.2: Prohibited Concomitant Therapy), with the exception of azole antifungals, which are permitted.
- Any medical, psychiatric, addictive or other kind of disorder which compromises the ability of the subject to give written informed consent and/or to comply with procedures.
- Pregnant or lactating females

5.3.3 Lifestyle Guidelines

All male and female patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 90 days after the last dose of investigational product. The investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include:

1. Abstinence
2. Established use of oral, injected or implanted hormonal methods of contraception
3. Correctly placed intrauterine device or intrauterine system
4. Male condom or female condom used with a spermicide (i.e., foam, gel, film, cream, suppository)
5. Male sterilization with appropriately confirmed absence of sperm in the post- vasectomy ejaculate
6. Bilateral tubal ligation or bilateral salpingectomy

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, and will be advised to report any reaction to sun exposed skin.

5.4 Duration of Study

All patients will be followed for 30 days after the last study treatment, and with annual phone calls for five years. It is anticipated that the study will be completed within four to five years.

5.5 Drug Administration

5.5.1 Premedication

No premedication is required.

5.5.2 PF-04449913

PF-04449913 will be provided to research subjects for the duration of their participation in this trial by Pfizer at no charge to them or their insurance providers. PF-04449913 is formulated in tablets containing 10 mg, 25 mg and 100 mg of study medication. The tablets are packaged in high-density polyethylene bottles, with protection from moisture and should be handled with care. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers. PF-04449913 will be administered once daily and orally on a continuous basis for all patients. A cycle is defined as 28 days, regardless of missed doses or dose delays. PF-04449913 will be administered without adjustment for body size and irrespective of PO intake. Tablets must not be crushed or cut; they must be swallowed whole and not chewed. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next

day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-04449913. If a medication error is accompanied by an AE, such as an overdose (accidental or intentional), as determined by the investigator, the AE is captured on an AE CRF page (see Section 5.13.3: Procedures for Recording Adverse Events).

5.6 Assuring Patient Compliance

Patients will receive all dosages of PF-04449913 by self-administration in the outpatient setting, and will be instructed to continue if admitted to the hospital for reasons other than drug-related toxicity. Patients will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses. Patient compliance will be assessed on day 1 of cycles 2 and every cycle thereafter. Patients will be required to bring their diary and any remaining pills to clinic during this visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary. Any unused PF-04449913 will be returned in compliance with 21 CFR 312.59.

5.7 Laboratory Criteria for Initiation of Treatment Cycles

Before any treatment cycle after cycle 1 may be administered, blood samples collected within 72 hours of the first dose of each cycle must meet the following criteria:

- Either creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 60 mL/min as calculated by institution's standard formula
- Total bilirubin ≤ 2 x institutional ULN (unless documented Gilbert's syndrome)
- AST and ALT ≤ 5 x institutional ULN
- ANC > 1000/mm^3
- Platelets >25,000/m^3

5.8 Study Treatment Schedule

Patients will receive study treatment as detailed in Section 5.1: Overall Study Design, and assessments will be performed as outlined in Section 2: Schedule of Study Assessments. Routine

disease assessments, as dictated by usual standard of care, will occur; there are no study-specific disease assessments. Patients will be taken off of the study if they meet criteria listed in Section 5.10.1: Stopping Rules.

5.9 Concomitant Therapy

5.9.1 Permitted Concomitant Therapy

Transfusion of blood and blood products, antibiotics, antiemetics and other standard supportive care medications are permitted if necessary. Azole antifungals (fluconazole, voriconazole, posaconazole, itraconazole and ketoconazole) may be used.

5.9.2 Prohibited Concomitant Therapy

Chemotherapy, immunotherapy and radiotherapy are prohibited.

The following information is based on results from in vitro studies with PF-04449913 and a drug-drug interaction study with a strong CYP3A4/5 inhibitor in healthy subjects.

CYP3A4/5 Inhibitors: Because inhibition of CYP3A4/5 isoenzymes were expected to increase PF-04449913 exposure and the extent of this interaction in humans was unknown, the use of moderate/strong CYP3A4/5 inhibitors was previously prohibited. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of PF-04449913. Therefore a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and co-administration of PF-04449913 in combination with moderate/strong CYP3A4/5 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Moderate CYP3A4/5 inhibitors (Table 1) should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to PF-04449913, the guidance provided in Section 5.12.5.5 requiring additional EKG monitoring before, during and after starting the medication, electrolyte monitoring (including correction and re-checking values) and dose

modifications for QTcF prolongation per Section 5.10.2.2 must be followed. **Azole antifungals are permitted to be administrated concomitantly with PF-04449913.**

CYP3A4/5 Inducers: PF-04449913 metabolism may be induced when taking CYP3A4/5 inducers, resulting in reduced plasma concentrations. The impact of CYP3A4/5 inducers on PF-04449913 pharmacokinetics has not been studied in the clinic. Therefore co-administration of PF-04449913 in combination with any moderate/strong CYP3A4/5 inducers (representative medications in Table 1) is not permitted from study entry until study treatment discontinuation.

Drugs with known risk of Torsade de Pointes (TdP): PF-04449913 has been shown to have the potential to prolong the QTc interval in pre-clinical studies. In the first-in-patient study as single agent, Grade 3 QTcF prolongation was observed at the highest doses tested (400 mg and 600 mg). While the current clinical dose being evaluated in this study is 100 mg, the concomitant administration of PF-04449913 and drugs with known risk of torsade de pointes is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to PF-04449913 the guidance provided in Section 5.12.5.5 requiring additional EKG monitoring before, during and after starting the medication, electrolyte monitoring (including correction and re-checking values) and dose modifications for QTcF prolongation per Section 5.10.2.2 must be followed. QT prolonging medications should be avoided whenever possible.

Prior or concurrent treatment with a Hedgehog inhibitor or concurrent treatment with other investigational agents not specified in the protocol is not permitted.

Use of warfarin is strongly discouraged if alternate medication (erg, 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.

5.9.3 Table 1: Representative prohibited medications based on metabolic isoenzyme class.

Isoenzyme Class	Representative Drugs
Strong/moderate CYP3A4 inhibitors	aprepitant, clarithromycin, cimetadine, ciprofloxacin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, mibefradil, nefazodone, posaconazole, telithromycin, tofisopam, troleandomycin, verapamil and voriconazole **(NOTE: antifungal azoles are permitted concomitant therapies)**
Strong CYP3A4 inducers	carbmezapine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentin, St. John's Wort

However, because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as: http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information.

5.10 Safety Plan

Patient safety will be assessed by reviewing AEs during planned visits and physical and laboratory examinations from the time the patient receives the first dose of study drug until 30 days after the patient's last study treatment. See Section 2: Schedule of Study Assessments, and Section 5.13: Definitions and Reporting Procedures for Adverse Events.

5.10.1 Stopping Rules

5.10.1.1 Individual Patients' Stopping Rules

Patients may be terminated from the study for the following:

- Noncompliance with the study protocol
- Morphological disease relapse, defined as having a bone marrow biopsy with > 5% leukemic blasts on the aspirate differential, the presence of peripheral blood blasts or extramedullary disease
- Patient decides to withdraw from the study
- ≥ Grade 3 AE that is possibly related to the study drug and does not resolve or improve within 28 days (see Section 5.10.2.2)
- Serious AE (SAE) related or possibly related to the study drug; disabilities, hospitalizations, prolongation of

hospitalizations or required interventions that are related to the transplant are excepted
- Development of unrelated illness which compromises further participation in the study
- Investigator determines that continuation on study is no longer in the best interest of the patient or a change in the patient's condition renders them ineligible for further treatment
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.

5.10.1.2 Study Stopping Rules

- The study will be suspended pending further review if, at any time, there is sufficient evidence to suggest that the true probability of hematopoietic toxicity attributable to the drug exceeds 25% or the true probability of severe GVHD exceeds 25%. Sufficient evidence will be defined as an observed failure rate whose lower one-sided 80% confidence limit exceeds the thresholds listed above (25% for hematopoietic toxicity and GVHD). Operationally, the study will be suspended if any of the following proportions are observed (or exceeded): 3/3-5, 5/6-10, 7/11-15, 9/16-20, 10/21-25, 11/26-28. The probabilities of early termination based on this stopping rule for various rates of true toxicity are shown in the table below. The probabilities are based on a simulation with 1,000 replications.

	Probability of Early Stopping Due to Toxicity			
Number of Patients	**True Toxicity Rate**			
	15%	25%	35%	45%
28	0.0016	0.0693	0.375	0.787

- If any of the above stopping rules is met upon enrollment of the next patient, accrual will be held until it is determined that no stopping rules will be met with currently enrolled patients.

- The study will continue until the last patient is followed 30 days beyond receiving the last dose of study drug. Annual

phone calls will be made as appropriate for 5 years after discontinuation of the study.

5.10.2 Dosing Delays and Modifications

5.10.2.1 Missed Doses

Patients will be encouraged to stay on schedule even if a dose is missed. Dosing will be tracked in the patients' diaries. Lack of compliance with the study protocol may result in removal from the study. This will be decided on an individual basis by the investigators.

5.10.2.2 Dose Delays and De-escalation

Patients who experience a ≥ grade 3 related or possibly related non-hematological AE can have treatment interrupted for up to 28 days and restarted at the original dose or reduced by 50%, at the discretion of the investigator, if the abnormality returns to baseline or ≤ grade 1. An additional 50% dose reduction will be permitted for a second episode of a ≥ grade 3 related or possibly related non-hematological AE. No further dose reductions will be permitted. Dose re-escalation by 100% increments to full dose may be attempted if AEs remain resolved. For grade 4 related or possibly related hematological toxicities, the dose will be withheld for up to 28 days, when it returns to ≤ grade 3 it can be resumed at the original dose or reduced 50% at the discretion of the investigator. An additional 50% dose reduction will be permitted for a second episode of a grade 4 related or possibly related non-hematological AE. No further dose reductions will be permitted. Dose re-escalation by 100% increments to full dose may be attempted if AEs remain resolved. Cycles will not be prolonged beyond day 28 to make up for missed doses.

Treatment delays beyond 28 days will result in study discontinuation. The dose de-escalation table below is provided for guidance.

Myalgias and arthralgias are known to be associated with PF-04449913, and may be more significant in the post HSCT setting. For patients with ≥ grade 3 myalgias or arthralgias, dose interruption will occur until the symptoms resolve to ≤ grade 1. If this does not occur after an interruption of 28 days the patient will come off of the study. If it does occur within 28 days of interruption, resumption of PF-04449913 will occur at

the 100 mg dose, but after re-introduction the drug will be given for 21 days consecutively with 7 days off each cycle. If a subsequent ≥ grade 3 myalgia or arthralgia event occurs, dose interruption will occur until the symptoms resolve to ≤ grade 1. If this does not occur after an interruption of 28 days the patient will come off of the study. If it does occur within 28 days of interruption, resumption of PF-04449913 will occur at the 50 mg dose, again administered 21 days on and 7 days off. Another ≥ grade 3 myalgia or arthralgia event will result in the same interruption and resumption schedule as above, this time with a dose reduction to 25 mg, and an additional ≥ grade 3 myalgia or arthralgia event will result in termination of the study.

Other toxicities will be managed as follows:

Toxicity		
Grade 1 or 2	**Grade 3**	**Grade 4**
Continue at current dose	Withhold until toxicity returns to ≤ grade 1 for related or possibly related non hematologic toxicities then resume the same dose level or reduce by 50%, at the discretion of the investigator (nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy to require a dose reduction). One additional 50% dose reduction is permitted for a second episode. At the discretion of the investigator, dose re-escalation by 100% increments to full dose may be attempted if AEs remain resolved after dose reduction (s).	Withhold until toxicity returns to ≤ grade 1 for related or possibly related non hematologic toxicities and ≤ grade 3 for related or possibly related hematologic toxicities, then reduce by 50% or discontinue treatment, at the discretion of the investigator (nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy to require a dose reduction). One additional 50% dose reduction is permitted for a second episode. At the discretion of the investigator, dose re-escalation by 100% increments to full dose may be attempted if AEs remain resolved after dose reduction (s).

Recommended Dose Modifications for Treatment-Related QTcF Prolongation

QTcF Prolongation Grade			
1	2	3	4
• No change	• Withhold study treatment • Assess for and correct electrolyte abnormalities. • Withhold any concomitant medications that may cause QTcF prolongation. • Resume study treatment at prior dose if QTcF returns to ≤470 msec and to within 20 msec of baseline <7 days. β • Resume study treatment at one lower dose level if QTcF returns to ≤470 msec and to within 20 msec of baseline between 7-14 days, or if a prior dosing interruption for QTcF prolongation has occurred. β **Discontinue study treatment permanently if:** • The QTcF prolongation does not return to ≤470 ms within 14 days. • ≥ Grade 2 QTcF prolongation recurs after one dose reduction. • If anytime during the 14-day window, the patient has a confirmed mean QTcF interval >515 ms or becomes symptomatic.	• Withhold study treatment • Assess for and correct electrolyte abnormalities. • Withhold any concomitant medications that may cause QTcF prolongation. • Resume study treatment at prior dose if QTcF returns to ≤470 msec and to within 20 msec of baseline <7 days. β • Resume study treatment at one lower dose level if QTcF returns to ≤470 msec and to within 20 msec of baseline between 7-14 days, or if a prior dosing interruption for QTcF prolongation has occurred. β **Discontinue study treatment permanently if:** • The QTcF prolongation does not return to ≤470 ms within 14 days. • ≥ Grade 2 QTcF prolongation recurs after one dose reduction. • If anytime during the 14-day window, the patient has a confirmed mean QTcF interval >515 ms or becomes symptomatic.	• Discontinue study treatment permanently
QTcF = Fridericia's QT correction, ms = milliseconds β An ECG should be repeated approximately 7 days after study treatment resumption following dose interruption for QTcF prolongation.			

5.10.3 Data and Safety Monitoring

AEs and SAEs will be reviewed on an ongoing basis to identify safety concerns, and the investigators may discontinue the study if excessive toxicity is observed. In addition, the study will be monitored by the Cancer Center's data safety and monitoring committee (DSMC) at times designated by the committee.

Oversight and Monitoring

The Principal Investigator will be responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This will be accomplished under the oversight of the Data & Safety Monitoring Committee (DSMC) of the University of Colorado Cancer Center (UCCC). The DSMC is responsible for monitoring data quality and patient safety for all clinical studies at UCCC. A summary of the DSMC activities follows:

- Conduct of internal audits
- Ongoing review of all reportable adverse events and all serious/unanticipated adverse events
- Supervises internal DSM boards and/or performs as an internal DSMB
- Has the authority to close and/or suspend trials for safety or trial conduct issues and may submit recommendations for corrective actions to the Associate Directors Executive Committee
- Performs routine internal monitoring of both investigator-initiated and cooperative group clinical trials

Data regarding number of subjects, significant toxicities, dose modifications, and responses will be discussed at regularly scheduled disease-oriented working group meetings. The discussion will be documented in the minutes and summaries will be submitted to DSMC quarterly.

The Principal Investigator at the Coordinating Center is responsible for the overall conduct of the study at all of the participating institutions and for monitoring its progress. The University of Colorado Cancer Center is the Coordinating

Center for this study and this site will coordinate patient enrollment. There will be only one version of the protocol, and each participating institution will use that document. The protocol must not be rewritten or modified by anyone other than the Principal Investigator at the Coordinating Center. The Principal Investigator at the Coordinating Center is responsible for timely review of Adverse Events (AEs) to assure safety of the patients and for the review and timely submission of data for study analysis.

Each subject's treatment outcomes will be monitored at least monthly by a conference call with the investigators and CRAs from all participating institutions. Data regarding the number of patients, significant toxicities, dose modifications, and responses will be discussed and documented in meeting minutes.

The PI will provide a DSM report to the UCCC DSMC on a six month basis. DSM reports will contain data from all participating sites. The DSM report will include summaries of minutes taken at monthly meetings, the participants' demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues (including a summary of any protocol deviations), summary of AEs and SAEs, summary of dose modifications, and any actions or changes with respect to the protocol. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results from these reviews will be provided to all participating investigators to submit to their IRBs at the time of continuing review.

5.11 Study Completion and Termination

Study patients who have met any of the following endpoints will have completed the study:

- SAE related to the study drug
- Disease relapse
- Death

Study patients may be prematurely terminated from the study for the following reasons:

- Physician and/or patient decides to discontinue treatment for reasons other than an AE
- ≥ Grade 3 related or possibly related non-hematologic AE or grade 4 related or possibly related hematologic toxicity that does not resolve or improve within 28 days
- Noncompliance with the study protocol
- Development of unrelated illness which compromises further participation in the study
- The patient is lost to follow up (no further data collection or submission will be expected)
- The patient withdraws consent (no further data collection or submission will be expected)

At termination, both concomitant medications and ongoing AEs are to be recorded, including any new AEs reported at the end of the study. Any unresolved AE at discontinuation of the study treatment should be followed until they have resolved or stabilized. Patients may choose to stop study treatment for any reason without jeopardizing their relationship with healthcare providers.

5.12 Study Activities and Assessments

5.12.1 Schedule of Activities

The time each assessment is performed relative to dosing is shown in the Schedule of Study Assessments (Section 2).

5.12.2 Screening Period

Written consent must be obtained before performing any study-specific screening activities. The screening activities outlined in the Schedule of Study Assessments (Section 2) must be completed within 28 days of starting study treatment, unless otherwise specified.

The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for entry into the study. After the patient has signed and dated the informed consent form, all screening procedures have been completed and clinical eligibility has been confirmed, the patient can be officially enrolled in the study.

5.12.3 Treatment Schedule

Patients will receive study treatment as detailed in Section 5.1, and assessments will be performed as outlined in the

Schedule of Study Assessments (Section 2). Patients will continue treatment in the absence of toxicity or disease progression.

5.12.4 Follow Up

Patients will be followed for 30 days after their final drug administration for AEs and SAEs. Safety data beyond 30 days may be reported if deemed relevant by the investigator.

Annual phone calls to appropriate patients will be made and documented for five years after completion or discontinuation of the study.

Study can be terminated prior to the completion of five years, per Investigator discretion. Patients still in follow-up will be contacted by study team if study is terminated prematurely.

5.12.5 Study Assessments

5.12.5.1 Vital Signs and ECOG Performance Status

All vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) and ECOG performance status grade (See Appendix A) will be measured during screening and during study visits as specified in the Schedule of Study Assessments (See Section 2).

5.12.5.2 Physical Examination

A complete physical examination, including measurement of height during the first visit and weight at each visit, must be performed during screening (28 days before beginning study treatment) and during study visits as specified in the Schedule of Study Assessments (Section 2).

5.12.5.3 Adverse Events

All AEs will be recorded from the first dose until 30 days after the last dose of study treatment. Patients who experience a non-serious AE considered to be possibly or definitely related to study treatment will be followed until all significant changes have stabilized or returned to baseline, the patient withdraws consent, or death. All SAEs will be followed as described, regardless of their relationship to study treatment. Safety data

beyond 30 days may be reported if it is deemed relevant by the investigators.

5.12.5.4 Laboratory Assessments

The following laboratory assessments will be performed at screening and at study visits throughout the course of the patient's participation in the trial. See the Schedule of Study Assessments (Section 2) for specific timing.

- Hematology: Hemoglobin, hematocrit, red blood cell count, total white blood cell count with differential, platelet count
- Chemistries: Albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein
- Coagulation: Prothrombin time, activated partial thromboplastin time
- Pregnancy test (if applicable, 72 hours prior to the first dose of PF-0444913)

5.12.5.5 EKGs and QTc Calculation

A 12-lead EKG will be performed during screening, 1-4 hours after the first dose of cycle 1, 1-4 hours after dosing on cycle 1, day 15, 1-4 hours after the first dose of cycle 2 and 2-5 days after the addition of any new azole antifungal medications. The QT interval will be calculated and corrected for heart rate (QTc) by Fridericia's formula if QTc is greater than 470 msec. (QTcF) is defined as: $QTc(F) = QT/(RR)^{0.33}$. The QTcF duration will be used to make all decisions based on QT criteria. If abnormal, triplicate EKGs should be performed and the average value used. Please refer to Section 5.10.2.2: Dose Delays and De-Escalation for guidance on dose adjustments required by prolonged QTcF intervals.

If a moderate/strong CYP3A4/5 inhibitor or TdP drug will be initiated in addition to PF-04449913 the following guidance must be followed:

- Prior to the start of a moderate/strong CYP3A4/5 inhibitor or TdP drug:
    - EKGs pre- PF-04449913 dose, 1 and 4 hours post- PF-04449913 dose

    - Follow dose modifications for QTcF prolongation (Section 5.10.2.2)
- After starting a moderate/strong CYP3A4/5 inhibitor or TdP drug:
    - EKGs on Day 2 or 3 and on Day 5, 6, or 7
    - EKGs pre- PF-04449913 dose, 1 and 4 hours post- PF-04449913 dose
    - Follow dose modifications for QTcF prolongation (Section 5.10.2.2).
- Perform additional EKG testing as appropriate.
- Perform routine electrolyte monitoring (Ca, K, Cl, Mg), implement timely electrolyte correction, followed by appropriate re-checking of values.
- When there is an urgent need to start a moderate/strong CYP3A4/5 inhibitor or TdP drug, administration of these medications should not be delayed; the Investigator should consider temporarily interrupting PF-04449913 dosing, and should implement these additional monitoring procedures as soon as it is reasonably possible.

5.12.5.6 Minimal Residual Disease (MRD)

MRD assessments using multiparameter flow cytometry will be performed on all bone marrow biopsy samples.

5.12.5.7 Disease Assessments and Response Criteria

Disease assessments will be performed on a routine basis according to standard of care practices. This involves blood tests, and when indicated, bone marrow biopsies.

Relapse definition will be based on the LeukemiaNet guidelines:[35] >5% blasts in the bone marrow, reappearance of blasts in the peripheral blood or development of extramedullary disease.

5.12.5.8 Correlative Assessments

Tissue will be banked for future testing and correlative studies. Each participating institution will employ their own IRB-approved tissue banking protocol for this purpose.

5.13 Definitions and Reporting Procedures for Adverse Events

Subjects will be evaluated for AEs at each visit with the NCI-CTCAE version 4.03 used as a guide for the grading of severity. All adverse clinical experiences, whether observed by the investigators or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study, and the patients' outcomes. The investigators will evaluate each AE for its severity and its relationship to the study. The investigators will appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigators will provide details about the action taken with respect to the study and the patients' outcomes.

5.13.1 Definitions of Adverse Events

5.13.1.1 Adverse Event

According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (Federal Register. 1997;62(90):25691-25709), Title 21 of the US Code of Federal Regulation (CFR) 312.32, and Investigational New Drug (IND) Safety Reports, an AE is defined as follows:

"Any untoward medical occurrence in a subject or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any untoward medical occurrence regardless of relationship to the medicinal (investigational) product."

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an AE unless an intervention is required (repeat testing to confirm the abnormality is not considered an intervention), the laboratory abnormality results in a SAE, or the AE results in study termination or interruption/discontinuation of study treatment. Medical conditions present at screening (i.e.: before the study treatment is administered) are not SAEs and will not be recorded on SAE pages of the case report forms. These medical conditions will be adequately documented in the patient chart. However, medical conditions present at baseline that worsen in intensity or frequency during the

treatment or post-treatment periods will be reported and recorded as AEs.

5.13.1.2 Serious Adverse Event (SAE)

An AE will be classified as an SAE if it meets one of the following criteria (Reporting see section 5.13.4 and Appendix B):

Fatal:	AE resulted in death.
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	AE that required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating:	AE resulted in substantial and permanent disruption of the patient's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

5.13.1.3 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on PF-04449913, or within 28 days of the subject's last dose of, are considered immediately reportable events. PF-04449913 is to be discontinued immediately, and the patient will discontinue the study.

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

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

- A male has been exposed (egg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, 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.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to PF-04449913 should also be reported.

5.13.2 Relationship of the Adverse Event to Treatment

The investigator will evaluate the relationship of each AE to study treatment using the following criteria:

Fatal:	AE resulted in death.
Unrelated:	Another cause of the AE is more plausible, a temporal sequence cannot be established with the onset of the AE and administration of the treatment, or a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of treatment, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when treatment is one of several biologically plausible AE causes.
Definitely Related:	The AE is clearly related to use of the treatment.

5.13.3 Procedures for Recording Adverse Events

5.13.3.1 Information to be Collected

Whether considered related or not, during the reporting period, all SAEs and non-serious AEs are to be recorded on an AE case report form (CRF). Patients who terminate the study early will be followed for 30 days after the last dose of study treatment for AEs and SAEs. Patients who experience a non-serious AE considered to be possibly or definitely related to study treatment will be followed until all significant changes have returned to baseline or stabilized, the patient dies, or the patient withdraws consent. All SAEs will be followed as described, regardless of their relationship to study treatment. During the reporting period, the following information should be collected:

- Description of the AE, including onset and resolution dates
- Relationship to treatment plan, treatment or other causality
- Action taken, including use of concomitant medications
- If the event is serious, note all criteria that apply

5.13.3.2 Recording Serious Adverse Events

- For SAEs, the primary event will be recorded on both an AE CRF and an SAE/Product Complaint Form; events occurring as a result of the SAE will be described on the SAE/Product Complaint Form in the narrative description of the case
- Death is an outcome of an event. The event that resulted in the death will be recorded and reported on both an SAE/Product Complaint Form and on an AE CRF.
- For hospitalizations or surgical or diagnostic procedures, the illness leading to the hospitalization or surgical or diagnostic procedure will be recorded as the SAE, not the procedure itself. The procedure will be captured in the narrative as part of the action taken in response to the illness.

5.13.4 Investigator Reporting Responsibilities

The conduct of the study will comply with all Food and Drug Administration (FDA) safety reporting requirements.

5.13.4.1 Investigational New Drug Annual Reports

If the FDA determines an IND is necessary, it is a requirement of 21 CFR 312.33 that an annual report be provided to the FDA within 60 days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report.

5.13.4.2 Format for Adverse Event Reporting

All AE reports will include the patient's number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to the study (fatal relationship, definitely related, possibly related, unrelated), date and time of administration of test medications and all concomitant medications, and subsequent medical treatment provided. An investigator-initiated research adverse event form will be utilized for reporting.

5.13.4.3 Reporting to the IRB

The Investigators will notify the IRB of an AE or SAE according to institutional policy.

The serious adverse event reports will be reviewed by PI. If the adverse event meets the coordinating center's criteria for reporting then an official signed report will be submitted to the coordinating center's IRB.

5.13.4.4 Reporting to Pfizer

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the PI will report to Pfizer any SAE that occurs within the SAE reporting period (see Section 5.13.4.6 and Appendix B).

5.13.4.5 Non-serious Adverse Event Reporting

All non-serious AEs that occur before study drug administration but after informed consent is obtained and are associated with protocol-specific procedures (eg: AEs associated with blood draws performed only for protocol purposes) will be reported according to local and coordinating center IRB guidlines.

Events that occur before informed consent is obtained should be documented as medical history. All non-serious AEs that occur between the first study treatment and the safety follow-up visit will be reported according to local and coordinating center IRB guidlines.

All non-serious AEs that occur subsequent to the safety follow-up visit and are considered to be pertinent in the opinion of the investigators may be reported according to local and coordinating center IRB guidlines.

5.13.4.6 SAE Reporting

SAEs will be reported within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening).

All sites will report SAEs directly to Pfizer Drug Safety and Surveillance. A copy of each SAE will also be sent to the University of Colorado (coordinating center) via email within 24 hours of the event.

The PI will then review and submit to the University of Colorado regulatory authorities and the FDA, if applicable, in accordance with 21 CFR 312.32.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Periods:

- All SAEs that occur after informed consent is obtained will be reported up to 30 days after administration of the last study treatment, regardless of relationship to study treatment.

- All SAEs that occur beyond 30 days after the administration of the last study treatment and are considered pertinent, in the opinion of the investigators, may be reported.

5.14 Statistical Methods and Sample Size Determination

The one-year probability of relapse-free survival for high-risk patients is roughly 30%.[12,36-38] Using this as a null hypothesis, and speculating that the use of PF-04449913 will increase the one-year probability of relapse-free survival to 50%, we will require 50 patients to allow for a 90% power to detect this 20% difference, with a significance level of 0.05.[39] We predict the need to screen roughly 60 patients to enroll 50 with high risk of relapse.

Kaplan-Meier estimates using SAS software will be utilized for statistical analysis.

5.15 Protocol Deviations

Data from patients who do not receive at least one full cycle of treatment due to early termination, death or non-compliance will be described. Protocol violations during treatment and follow-up will be listed. Additional analyses will include summaries of patient demographics, baseline characteristics, compliance and concurrent treatments. When an emergency occurs that requires a deviation from the protocol, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject for whom deviation from the protocol occurred is to continue on the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the investigators will notify the IRB, per IRB guidelines, in writing of such deviation from protocol. Non-emergency minor deviations from the protocol will be permitted with approval of the investigators.

6 ADMINISTRATIVE REQUIREMENTS

6.1 Data and Safety Monitoring Plan

Please refer to section 5.10.3: Data and Safety Monitoring.

6.2 Ethics

6.2.1 Institutional Review Board

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods

used for obtaining informed consent, are in accordance with principles enunciated in the Declaration, as well as ICH Guidelines, Title 21 of the CFR, Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards). The investigators will be responsible for preparing documents for submission to the IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number. Any amendments to the protocol after receipt of IRB approval must be submitted by the investigators to the IRB for approval. The investigators are also responsible for notifying the IRB of any serious deviations from the protocol, or anything else that may involve added risk to subjects. Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB prior to use. The IRB will be informed regarding the progress of the study and any changes made to the protocol, and will be updated at least once a year. For collaborating institutions, consents will be reviewed and approved by the local IRB.

6.2.2 Patient Information and Consent

The investigators must obtain informed consent of a subject or his/her designee prior to any study-related procedures as set forth in the CFR and ICH Guidelines for Good Clinical Practice. Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study must be maintained in the investigators' study files. No substantial deviations from the informed consent form will be made. The informed consent form will be submitted to and approved by the IRB prior to distribution to patients. Before initiating protocol-specific procedures that would not otherwise be done, written and signed informed consent must be obtained. This form must be signed and dated by the patient or by the patient's legally authorized representative if the patient is unable to sign. The case history for each patient will document that informed consent was obtained before the patient's participation. A copy of the informed consent must be provided to the patient or the patient's legally authorized representative, and if

applicable, it will be provided in a certified translation into a foreign language. Signed informed consents will remain in each patient's chart and will be available for verification at any time.

6.3 Record of Administration

Accurate records will be kept in the source documents of all drug administration, including prescribing and dosing. The investigators must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy (includes copies of CRF's and source documents such as: hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; SAE reports; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches, photographic negatives, microfilm, or magnetic media; x-rays; subject files; records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents) be retained for as long as needed to comply with national and international regulations. By signing the protocol, the investigators agree to adhere to the document/records retention procedures. CRFs for this study will be collected at standard intervals by the local PI or the study coordinator and transferred to the coordinating center. The local principal investigator will ensure that data collected for this study conform to all established guidelines for coding, collection, key entry and verification.

6.4 Confidentiality

The patient's medical information obtained in this study is confidential, and disclosure to third parties is prohibited, unless the patient allows information to be shared with his or her personal physician or other appropriate medical personnel responsible for his or her welfare. In compliance with United States federal regulations, data generated by this study will be available for inspection upon request by representatives of Pfizer, the FDA, national and local health authorities, and the IRB, who may review and/or copy relevant medical records in accordance with the law. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the investigators to obtain such permission in writing from the appropriate individual.

6.5 Study Auditing

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice and in the US CFR. Investigators must enter study data onto CRF's or another data collection system. The investigators will permit study-related audits by Pfizer or its representatives, IRB review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRF's, and to all other study documents. The investigators, or a designated member of the investigators' staff, must be available at some time during audits to review data, resolve any queries and to allow direct access to the subjects' records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. In addition, the Data Safety Monitoring Committee at the University of Colorado will audit the study according to institutional policy.

7 REFERENCES

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8

APPENDIX A - ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

9 APPENDIX B - Pfizer Safety Reporting Policy

Pfizer Serious Adverse Event Reporting Policy
For Investigator-Initiated Research Studies

Reporting of Serious Adverse Events. Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer by facsimile any Serious Adverse Event ("SAE," as defined below) that occurs during the SAE reporting period (as defined below) in a Study subject assigned to receive the Pfizer product that is the focus of the Study ("Pfizer Product"). Principal Investigator will report such SAEs using an FDA MEDWATCH form, CIOMS form, Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, or other Pfizer agreed upon form for SAE reporting. The *Reportable Event Fax Cover Sheet* provided by Pfizer should also be included. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

a. SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

b. Exposure During Pregnancy, Exposure During Lactation, and Lack Of Effect. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy and exposure to the Pfizer Product during lactation are reportable, and lack of effect of the Pfizer Product may also be reportable. This requirement is further explained in the training material provided by Pfizer (see Section f, below). In this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, and reportable instances of lack of effect.

c. SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through 28 calendar days after the last administration of the Pfizer Product or longer if so specified in the Protocol. In addition, investigators should submit SAEs to Pfizer any time after the administration of the last dose of the Pfizer Product, if the Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

d. Follow-Up Information. Institution will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

e. Regulatory Reporting. Reporting an SAE to Pfizer does not relieve Institution of responsibility for reporting it to FDA and/or other appropriate Regulatory Authorities, as required.

f. Pfizer-Provided Training. Pfizer will make available training material that provides information about the SAE reporting requirements for IIR studies. Principal Investigator will review this material and share it with any Study staff engaged in the reporting of SAEs."