A PHASE 1 DOSE ESCALATION STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVENOUS PF-06747143, ADMINISTERED AS SINGLE AGENT OR IN COMBINATION WITH STANDARD CHEMOTHERAPY IN ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA

Compound:	PF-06747143
Compound Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	125905
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Protocol Number:	B7861002
Phase:	1

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Document History

Document	Version Date	Summary of Changes and Rational
Original protocol	07 March 2016	Not applicable (N/A)
Amendment 1	14 June 2016	**Protocol Summary: Background; Protocol: Section 3.1. Study Overview; Section 4.1. Inclusion Criteria #1 across all populations** The date for the World Health Organization (WHO) classification was updated and the classification for inclusion was modified from Cheson 2003 to WHO 2008. Rationale: Typographical error and to align the diagnosis classification and management of acute myeloid leukemia (AML) throughout the protocol. **Protocol Summary: Study Objectives; Protocol: Section 2.1. Objectives – Part 1; Section 2.3. Objectives – Part 2; Section 3.1. Study Overview** The assessment of anti-leukemia activity was modified from Cheson 2003 to Dohner 2010. Rationale: To align the diagnosis classification and management of AML throughout the protocol. **Protocol Summary: Study Design, Part 2** Attributions to fit and unfit patient populations for Part 2 of the study will be based on consensus article by Ferrara, et. al. 2013. Rationale: Based on regulatory body feedback, the eligibility criteria were defined for Part 2 fit and unfit patient populations. **Protocol Summary: Part 2 Secondary Objectives and Endpoints; Protocol: Section 2.3. Objectives – Part 2; Section 2.4. Endpoints – Part 2** The objective and endpoint surrounding drug concentration data was modified.

Document	Version Date	Summary of Changes and Rational
		Rationale: Language modified to clarify that population PK evaluation will likely include PK data from both Part 1 and Part 2. **Protocol Summary Inclusion and Exclusion Criteria; Protocol: Section 3.1.2. Part 2; Section 4. PATIENT SELECTION** Part 1 and Part 2 Cohort 3: eligibility criteria for patients with refractory and/or relapsed AML were further defined. Part 2, Cohort 1 and Cohort 2 (fit and unfit), Ferrara 2013 was used to define the patient population for each cohort per regulatory body feedback. Exclusion criteria specific for the two patient populations was included as a separate set of criteria. Rationale: The eligibility criteria for the various parts of the study were broken out for clarity and consistency across the multiple patient populations based on regulatory body feedback. **Protocol Summary DLT Criteria; Protocol: Section 3.1.1.3. DLT Criteria** The language was modified so that all adverse events (AEs) meeting the definition of the criteria will be considered a DLT unless it can be clearly determined that the event is unrelated to PF-06747143. Rationale: in early human trials, the relationship of an AE to the drug is not fully known so all AEs should be considered relevant to determining dose limiting toxicities and reporting unless the event can clearly be determined to be unrelated to the drug. **Schedule of Activities (SOA) and Protocol: Section 7.2.** In addition to cardiac monitoring, patients in Part 2, Cohort 1 will be required to undergo pulmonary function tests.

Document	Version Date	Summary of Changes and Rational
		Rationale: standard requirements for treatment with daunorubicin. **Protocol: Section 3.1.1.4. MTD Definition** Maximum tolerated dose (MTD) determination in Part 2 was moved to create a new section (Section 3.1.2.2.3.). Rationale: protocol section consistency. **Protocol Section 5. STUDY TREATMENTS** Reference to the Dosage and Administration Instructions (DAI) was removed throughout the section. Rationale: Pfizer internal document. Sites are provided an Investigational Product manual with details of the internal DAI document. **Protocol: Section 5.8.4. Anti Diarrheal, Anti Emetic Therapy** Text was added that prophylaxis is not permitted in Part 1. Rationale: not permitted due to need to determine dose limiting toxicities in Part 1. In addition, typographical errors were corrected and editorial updates were made.
Amendment 2	06 March 2017	**PACL #2 – 27 February 2016:** **Protocol Summary: Study Design - Part 1, Inclusion Criteria (Part 1 and Part 2/Cohort 3) #3; Section 3.1.1.; Section 4.1, Inclusion Criteria (Part 1 and Part 2/Cohort 3) #3; Figure 1.** Removed 30% and 30-50% bone marrow blast criteria for 0.3 and 1.0 mg/kg dose levels. Rationale: Initial clinical data indicates total peripheral WBC count is a more relevant and practical safety measure (see addition of pre-dose total peripheral WBC assessment requirement).

Document	Version Date	Summary of Changes and Rational
		Protocol Summary: Inclusion Criteria (Part 1 and Part 2/cohort 3) #1; Section 4.1, Inclusion Criteria (Part 1 and Part 2/cohort 3) #1. Clarified statement regarding patient's lack of alternative therapeutic options. Revised relapsed/refractory criteria from two to one prior treatment regimens. Clarified prior lines of therapy to include standard of care and/or chemotherapy. Added Minimal Residual Disease (MRD) inclusion option for study participation. Removed age and cytogenetics profile distinctions. Rationale: Patients with relapsed/refractory disease in AML tend to have a poor outcome and shortened overall survival. There are very few effective therapeutic options available for patients with relapsed/refractory AML disease, and often, these patients are not eligible to receive re-induction chemotherapy with intensive regimen due to severe toxicities with high rate of treatment related morbidity and mortality. In addition, patients with MRD in AML have poor outcome and shortened overall survival, comparable to those patients with relapsed/refractory disease in AML.[26, 27,28,29] **Protocol Summary: Inclusion Criteria (Part 1 and Part 2/cohort 3) #1; Section 4.1, Inclusion Criteria (Part 1 and Part 2/cohort 3) #1.** Corrected AML blast diagnosis from "and" to "or" as per the referenced WHO guideline. Rational: Corrected statement as per referenced WHO guideline.

Document	Version Date	Summary of Changes and Rational
		Protocol Summary: Study Design - Part 1; SOA footnote "k", "l" and "r"; Table 1 and 2 footnote "e"; Section 3.1.1.; Section 5.4.1. Added requirement for pre-dose assessment of total peripheral WBC during Cycle 1. Rationale: Replaces bone marrow blast criteria as a more relevant and practical safety measure in response to PF-06747143 mediated WBC mobilization. **Protocol Summary: Study Design - Part 1, Inclusion Criteria (Part 1 and Part 2) #3 and #2; SOA footnote "w"; Section 3.1.1.; Section 4.1, Inclusion Criteria (Part 1 and Part 2) #3 and #2; Section 5.4.1; Section 5.8.1; Section 5.8.2.** Reiterated that hydroxyurea and/or leukapheresis can be used during Cycle 1 as needed to control total peripheral WBC counts. Revised statement regarding use of hydroxyurea and/or leukapheresis to treat hyperleukocytosis as clinically indicated. Rationale: The concomitant treatment options were originally allowed for in the protocol but sites were unaware of the treatment allowance. Hence, the option to use these treatments was added to additional sections to emphasize these options. The criteria for using such treatment options was also clarified based upon feedback from Investigators. **Protocol Summary: Statistical Method; Section 3.1.1., Figure 1; Section 3.1.1.2.; Section 9.2.1.; Section 9.3.** Revised minimum sample size of first two PF-06747143 dosing cohorts, 0.3 and 1.0 mg/kg/wk, from 4 to 2-4 patients.

Document	Version Date	Summary of Changes and Rational
		Rationale: Minimize exposure to potentially sub-therapeutic dose levels after safety assessment is performed. **Protocol Summary: Exclusion Criteria (Part 1 and Part 2/Cohort 3) #2; Section 4.2 Exclusion Criteria (Part 1 and Part 2/Cohort 3) #2.** Clarify and specify that systemic, but not topical, therapy for GVHD is exclusionary. Rationale: Unlike systemic therapy, topical immunosuppressive therapy is localized, and should not affect PF-06747143 mediated ADCC activity. CCI [redacted]

Document	Version Date	Summary of Changes and Rational
		Protocol Summary: Inclusion Criteria (Part 1 and Part 2) #4 and #2; Section 4.1, Inclusion Criteria (Part 1 and Part 2) #4 and #2. Removed 10,000/uL WBC statement. Rationale: 10,000/uL WBC did not serve as an inclusion criteria requirement, so this was removed to prevent misinterpretation. **SOA – Triplicate 12-Lead ECG and footnote j.** Added ECG time point to Day 1 of each Cycle after Cycle 2. Administrative changes. Rationale: Additional ECG data to be collected for First-in Human study of PF-06747143. **SOA footnote "k"; Table 1 and 2 footnote "e"; Section 7.1.3., Table 7.** CCI  **SOA footnote "k"; Section 7.1.3., Table 7 (Hematology).** Added percent blast cell assessment to the Hematology lab assessments. Rationale: Provides critical safety and disease burden data.

Document	Version Date	Summary of Changes and Rational
		Section 5.5.1.1. Revised initial sentence structure. Rationale: Clarified statement to avoid confusion. **Section 5.5.3.1: Body and Table 6.** Clarify that not all DLTs unless noted in Table 6 require dose modification**.** Correct Table 6 to include the DLT of hyperleukocytosis and corresponding dose modification recommendation. Rationale: Corrected Table 6 to include hematological DLTs. The dose modification text of Section 5.5.3.1. was inconsistent with the corresponding dose modification table (Table 6). Update made to body and table to correct inconsistency. **Section 7.6.** Clarified definition of disease progression according to original referenced guideline (Dohner et al.). Rationale: Minimize disease assessment heterogeneity. **All other changes are minor administrative in nature.**

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PROTOCOL SUMMARY

Background

The C-X-C chemokine receptor type 4 (CXCR4) (or CD184) is a G-protein coupled chemokine receptor, expressed on the cell surface, and has a 7-transmembrane structure. CXCR4 plays a role in the cross talking between cancer cells and their microenvironment by binding its ligand, chemokine ligand 12 (CXCL12), thereby activating the downstream signaling pathways leading to alteration of gene expression, actin polymerization, cell skeleton rearrangement, and cell migration and proliferation.

The tumor microenvironment consists of resident non-cancerous cells (stromal fibroblasts, endothelial cells, and immune cells), connective tissue and extracellular matrix, altogether supporting tumor structure, angiogenesis, and growth. CXCL12 is physiologically mainly expressed by mesenchymal stromal cells in various organs and tissues such as the liver, lungs, lymphatic tissues, and bone marrow. High levels of CXCL12 directly stimulate the proliferation and invasiveness of CXCR4-expressing cancer cells in an autocrine and paracrine manner. Nonclinical mouse models of non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and human multiple myeloma (MM) have shown that CXCR4-positive cancer cells can be recruited to CXCL12-rich mesenchymal stroma niches.

Since the CXCL12-CXCR4 interaction is considered crucial for attracting tumor cells to the bone marrow niche, CXCR4 inhibitors have been explored as treatment agents in the field of leukemia treatment. CXCR4 is overexpressed in 75% of cancers (hematological malignancies and solid tumors), and its expression correlates with poor prognosis in various cancers.

PF-06747143 is a humanized IgG1 monoclonal antibody (mAb) that is an antagonist of CXCR4. PF-06747143 has demonstrated robust anti-tumor activity in immune-compromised mice engrafted with human cells representing several human hematological malignancies including NHL, CLL, MM, and AML with a treatment regimen either as a single agent or in combination with standard of care agents. Based on the nonclinical studies conducted, the mechanisms of action of PF-06747143 include: 1) inhibition of CXCR4-CXCL12 signaling, thereby inducing cell mobilization from CXCL12-rich niches; 2) direct induction of caspase independent cell-death through an antibody (Ab) bivalency-dependent mechanism; and 3) induction of cell death through Fc-effector function (antibody-dependent cell-mediated cytotoxicity (ADCC)/complement dependent cytotoxicity [CDC]) inherent to the IgG1 backbone.

Given the extensive nonclinical anti-tumor activity of PF-06747143 demonstrated in a large number of animal models, this Phase 1 clinical trial of PF-06747143 will initially enroll patients with acute myeloid leukemia (AML).

The diagnosis of AML for the B7861002 study will be according to the World Health Organization (WHO) classification (2008). The study will be conducted in two parts, Part 1 single agent dose escalation and Part 2 PF-06747143 in combination with standard

chemotherapy with an option for single agent cohort expansion at the recommended phase 2 dose (RP2D). Assessment of anti-leukemia activity of PF-06747143 will be based on "Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet" [22].

Study Design

Part 1

This is a dose escalation, open-label, multi-center, single arm, non-randomized, multiple dose, safety, pharmacokinetic and pharmacodynamic study of single-agent PF-06747143 in sequential dose levels of adult patients with refractory and/or relapsed AML in order to establish the maximum tolerated dose (MTD), RP2D and/or maximally permitted dose (MPD).

Patients will receive PF-06747143 as a weekly infusion (QW) in 28 day cycles at escalating doses. The proposed dosing scheme includes 0.3, 1.0, 3.0, 10, 15, and 20 mg/kg. Patients enrolled in the first two dose levels (0.3 mg/kg and 1.0 mg/kg) will be required to stay in the clinic/hospital overnight (minimum of 24 hours) after receiving the first dose of PF-06747143 to monitor for the potential risk of hyperleukocytosis that might be caused by the inhibition of the CXCR4 pathway by PF-06747143. On an individual basis, patients may be monitored overnight for the additional doses in Cycle 1 at the treating physician's discretion.

In addition, the use of hydroxyurea and/or leukapheresis is permitted during Cycle 1 following first dose administration to control total peripheral white blood count (WBC) counts at the treating physician's discretion. However, hydroxyurea must be ceased 24 hours prior to the first dose of Cycle 1. Further, total peripheral WBC will be assessed by the investigator within 12 hours prior to study drug administration during Cycle 1. In the event a patient's total peripheral WBC count is ≥75,000/uL, the investigator shall consult with and obtain the sponsor's agreement to move forward with the study drug administration.

For the first three dose levels (ie, 0.3 mg/kg through 3.0 mg/kg), initiation of the first dose of PF-06747143 for each patient in the dose level must be at least 72 hours after the first dose of the previous patient. Patients enrolled in subsequent dose levels will be treated on an outpatient basis with no staggering of patients unless there are safety concerns based on findings at the lower doses.

Once MTD or MPD is identified, additional patients may be enrolled (to a minimum of 9) at that dose level to further investigate the anti-leukemia activity, safety, and pharmacokinetic (PK) profile of PF-06747143 prior to an expansion cohort with single agent PF-06747143 at the MTD/MPD/RP2D.

The total estimated number of patients to be enrolled for the Part 1 dose escalation study will be approximately 30-50 patients. Once the dose of 15 mg/kg in Part 1 is found safe and tolerable, the Part 2 combination cohorts will be initiated at 10 mg/kg while the Part 1 single agent dose escalation continues to 20 mg/kg for MPD or MTD assessment.

Planned Dose Levels for Part 1

Dose Level	PF-06747143 Dose (mg/kg) QW
1	0.3
2	1.0
3	3.0
4	10
5	15
6	20

Part 2

Part 2, dose expansion, is an open-label, multi-center, non-randomized study to assess the safety and tolerability and preliminary anti-leukemia activity of PF-06747143 in three cohorts (two combination cohorts and one potential cohort of single agent PF-06747143). The first cohort will be PF-06747143 in combination with standard dose of intensive chemotherapy (ie, cytarabine and daunorubicin; D/C 7+3) in fit, treatment naïve patients with AML (Cohort 1). The second will be PF-06747143 in combination with azacitidine or decitabine (based on drug availability and institutional guidance) in treatment naïve unfit patients with AML who are not candidates for or decline to receive intensive D/C 7+3 chemotherapy (Cohort 2). The third potential cohort is PF-06747143 as a single agent (Cohort 3) in patients with refractory and/or relapsed AML and will be opened if data from Part 1 warrants.

Expansion in combination cohorts 1 and 2 (identified as "E1" and "E2") will not be initiated until a safety lead-in (identified by an "S") group of approximately 3-6 patients is enrolled to ensure the combination treatment regimen is safe and tolerable in each patient population. The safety lead-in will use a standard 3+3 dose escalation method to evaluate safety profile (using the dose limiting toxicity (DLT) criteria described in Section 3.1.1.3) for duration of up to 2 cycles.

Attributions to fit or unfit will be based on "Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of Italian SIE, SIES and GITMO group on a new tool for therapy decision making" per Investigator judgment.[25]

Cohort 3 expansion (E3), at the MTD/RP2D, may be initiated in 15-30 refractory and/or relapsed AML patients. The initiation of this cohort will require that single agent PF-06747143 demonstrates encouraging clinical benefit (eg. significantly improved CR and response duration compared to historical data) in the dose escalation Part 1.

Objectives and Endpoints

Part 1: Single Agent PF-06747143 Dose Escalation	
Primary Objective	**Primary Endpoint**
To assess safety and tolerability at increasing dose levels of PF-06747143 in patients with refractory and/or relapsed AML for which no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).	Dose Limiting Toxicities (DLTs).
Secondary Objectives	**Secondary Endpoints**
To evaluate the overall safety profile;	• Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03), timing, seriousness, and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;
To characterize the single-dose and multiple-dose pharmacokinetics (PK) of PF-06747143 following IV administration;	PK parameters of PF-06747143: Single Dose (SD) - C_{max}, AUC_{last}, and if data permit, AUC_{inf}, V_d, CL, and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss}$ /AUC_{τ}), and if data permit, CL, V_{ss}, and $t_{1/2}$.
To evaluate the immunogenicity of PF-06747143 following repeated administration;	Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06747143.
To document any anti-leukemia activity.	Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria (Dohner, et. al 2010) including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).
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Part 2: PF-06747143: Single Agent and Combination Expansion Cohorts	
Primary Objective	**Primary Endpoint**
To evaluate safety and tolerability and preliminary anti-leukemia activity of PF-06747143 in combination with standard intensive chemotherapy (ie, cytarabine and daunorubicin; D/C 7+3) in patients with newly diagnosed fit treatment naïve AML patients (Cohort 1) or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients (Cohort 2) or PF-06747143 as a single agent in patients with refractory and/or relapsed AML ((Cohort 3) if data warrants).	• Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03), timing, seriousness, and relationship to study therapy; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing; • Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria (Dohner, et. al 2010) including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).
Secondary Objectives	**Secondary Endpoints**
To characterize the single and multiple dose PK of PF-06747143 in combination with standard intensive cytarabine and daunorubicin 7+3 therapy in newly diagnosed fit treatment naïve AML patients or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients;	PK parameters of PF-06747143: Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, V_d, CL, and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss}$ /AUC_t), and if data permit, CL, $V_{ss,}$ and $t_{1/2}$;
To collect PF-06747143 drug concentration data in patients from the dose expansion cohorts for evaluation of population PK.	Peak and trough PF-06747143 concentrations for selected doses;
To evaluate the immunogenicity of PF-06747143 following repeated administration.	Incidence of ADA and Nab against PF-06747143.
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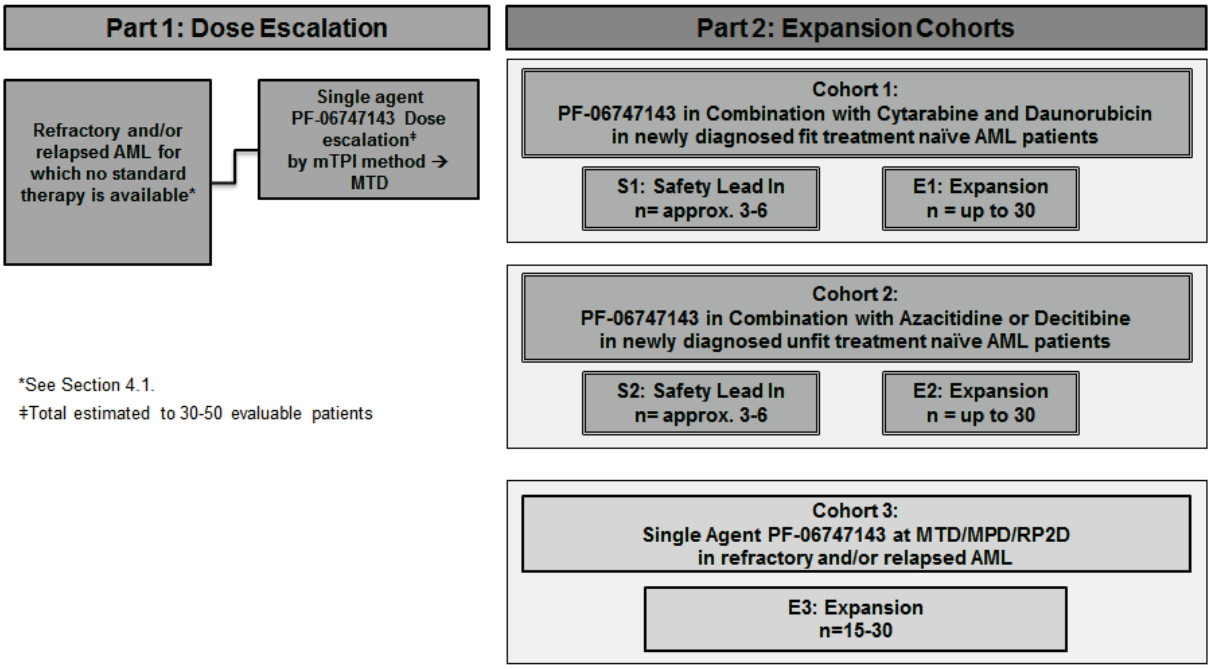
The overall study scheme is shown below:



Patient Selection

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

Inclusion (Part 1 and Part 2 Cohort 3)

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

1. Patients with AML (primary AML diagnosis is based upon the 2008 WHO classification with bone marrow (BM) or peripheral blood (PB) blast counts ≥20%[23]) refractory, relapsed and/or patients that are not candidates to receive standard of care and/or refusing the standard care of therapies:
    - Patient received prior chemotherapy and/or standard of care and have relapsed, refractory or Minimal Residual Disease (MRD).[26,27,28,29]
        - MRD is defined as patients showing residual blast 10-14 days post-induction chemotherapy.
2. Life expectancy at least 12 weeks.
3. Hydroxyurea is allowed prior to Day 1 but must be ceased 24 hours prior to first dose. Thereafter, hydroxyurea may be used during Cycle 1 as needed to control total peripheral WBC counts (see Section 5.8.1).
4. Age ≥18 years old.
5. Eastern Cooperative Oncology Group (ECOG) performance status: 0 to 2.
6. Patients must have been off previous anti-leukemia therapy for at least 2 weeks or 5 half-lives, whichever is shorter if the immediate prior regimen included only weekly chemotherapy; or 4 weeks from any therapy with therapeutic biologics and from any type of investigational therapy prior to the first dose of PF-06747143.
7. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for adverse events (AEs) not constituting a safety risk by investigator judgment.
8. At least 4 weeks since radiotherapy prior to the first dose of PF-06747143. Patients must have passed nadir WBC and platelet counts, have full recovery or stabilization of absolute neutrophil counts (ANC) and platelet counts, and ANC counts must have recovered from prior toxicity.

9. Adequate renal and hepatic function, including all of the following:

    - Creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;
    - Aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN);
    - Alanine aminotransferase (ALT) ≤3 x ULN;
    - Bilirubin ≤2.0 mg/dL (except patients with Gilbert's Syndrome who must have total bilirubin <3.0 mg/dL).

10. Negative serum/urine pregnancy test (for females of childbearing potential) at screening.

11. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.

12. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

14. Patients who are willing and able to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

Inclusion (Part 2 Cohort 1 and Cohort 2)

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

1. Newly diagnosed, previously untreated, de novo or secondary AML population (AML diagnosis is based on the 2008 WHO classification with BM or PB blast counts ≥20%[23]):

    - Cohort 1: Fit to receive intensive remission induction chemotherapy at the time of enrolment. Patients must have NONE of the following to be considered fit:
        - ECOG of 2 or 3;

- Serum creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;
- Severe cardiac disease (eg, left ventricular ejection fraction (LVEF) <45% by multigated acquisition scan (MUGA) or echocardiogram (ECHO) at screening.

- Cohort 2: Unfit to receive or not considered a candidate for intensive remission induction chemotherapy at the time of enrollment based on EITHER:
  - ≥75 years of age, OR
  - <75 years of age with at least 1 of following:
    - Poor performance status (ECOG) score of 2 or 3;
    - Clinically significant heart or lung comorbidities, as reflected by at least 1 of following:
      - LVEF ≤50%;
      - Diffusing capacity of the lungs for carbon monoxide (DLCO) ≤65% of expected;
      - Forced expiratory volume in 1 second (FEV_1) ≤65% of expected;
      - Chronic stable angina or congestive heart failure controlled with medication.
    - Liver transaminases >3 upper limit of normal (ULN);
    - Other contraindication(s) to anthracycline therapy (must be documented).
- Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy which must be documented and approved by the study medical monitor before randomization.

2. Hydroxyurea is allowed prior to Day 1 but must be ceased 24 hours prior to first dose. Thereafter, hydroxyurea may be used during Cycle 1 as needed to control total peripheral WBC counts (see Section 5.8.1).
3. Age ≥18 years old.
4. ECOG performance status: 0 to 3.

5. Adequate renal and hepatic function, including all of the following:

   - Creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;
   - AST ≤3 x ULN;
   - ALT ≤3 x ULN;
   - Bilirubin ≤2.0 mg/dL (except patients with Gilbert's Syndrome who must have total bilirubin <3.0 mg/dL).

6. Negative serum/urine pregnancy test (for females of childbearing potential) at screening.

7. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.

8. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

9. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

10. Patients who are willing and able to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

Exclusion Criteria (Part 1 and Part 2 Cohort 3)

Patients with any of the following characteristics/conditions will not be included in Part 1 and Part 2 Cohort 3 portions of the study:

1. Patients with acute promyelocytic leukemia (APL), AML with known central nervous system (CNS) involvement unless the patient has completed treatment for the CNS disease, has recovered from the acute effects of therapy prior to study entry, and is neurologically stable.

2. Chronic graft versus host disease (GVHD) requiring active systemic treatment, active GVHD with other than Grade 1 skin involvement, or GVHD requiring systemic immunosuppressive treatment. Patients with GVHD receiving systemic immunosuppressive treatment must be able to discontinue the therapy at least 2 weeks prior to the first dose of PF-06747143.

3. Patient is known to be refractory to platelet or packed red cell transfusions per institutional guidelines.

4. Patient is within 3 months post allogenic hematopoietic stem cell transplant or within 30 days post autologous stem cell transplant, and the patient has not recovered from transplant-associated toxicities prior to the first dose of PF-06747143.

5. Known active fungal, bacterial, and/or viral infection requiring systemic therapy within 3 days prior to the first dose of PF-06747143.

6. Prior treatment with a compound targeting CXCR4.

7. Liver cirrhosis Child B or C.

8. Active and clinically significant infection with hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

9. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of PF-06747143 and/or during study.

10. Major surgery within 4 weeks of first dose of PF-06747143.

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

12. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver, or recent (within the past year) or active suicidal ideation or behavior.

13. Uncontrolled neoplasia (other than AML).

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

15. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

16. Pregnant females; breastfeeding females; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 60 days after last dose of investigational product.

17. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, 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 New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or QTc Fridericia (QTcF) interval >470 msec at screening.

18. Known or suspected hypersensitivity to recombinant human proteins.

Exclusion Criteria (Part 2 Cohort 1 and Cohort 2)

Patients with any of the following characteristics/conditions will not be included in the Part 2 portions of the study:

1. Patients with acute promyelocytic leukemia (APL), AML with known central nervous system (CNS) involvement unless the patient has completed treatment for the CNS disease, has recovered from the acute effects of therapy prior to study entry, and is neurologically stable.

2. Patient is known to be refractory to platelet or packed red cell transfusions per institutional guidelines.

3. Known active fungal, bacterial, and/or viral infection requiring systemic therapy within 3 days prior to the first dose of PF-06747143.

4. Prior treatment with a compound targeting CXCR4.

5. Prior treatment with hypomethylating agents (eg, decitabine or azacitidine) or chemotherapy for antecedent myelodysplastic syndrome (MDS) (Cohort 2).

6. AML associated with favorable risk karyotypes including inv(16), t(8;21), t(16;16), or t(15;17) (Cohort 2).

7. Patients who are candidates for allogeneic stem cell transplant at the time of enrollment (Cohort 2).

8. Liver cirrhosis Child B or C.

9. Active and clinically significant infection with hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

10. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of PF-06747143 and/or during study.

11. Major surgery within 4 weeks of study entry.

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

13. Uncontrolled neoplasia (other than AML).

14. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver, or recent (within the past year) or active suicidal ideation or behavior.

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

16. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

17. Pregnant females; breastfeeding females; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 60 days after last dose of investigational product.

18. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, 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 New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or QTcF interval >470 msec at screening.

19. Known or suspected hypersensitivity to recombinant human proteins.

20. The presence of any one of the following hypersensitivities:

- Cohort 1: hypersensitivity to cytarabine (not including drug fever or exanthema) or daunorubicin;
- Cohort 2:
  - Hypersensitivity to decitabine or azacitidine;
  - Hypersensitivity to mannitol.

DLT Definition

A DLT will be classified according to NCI CTCAE version 4.03 and is defined as any of the following adverse events unless the event can clearly be determined to be unrelated to drug occurring in the first cycle of treatment (within 28 days of first dose or until patient receives a second cycle if there are treatment delays). Data from all cycles of treatment will be analyzed for safety, delayed toxicity, and cumulative toxicity. DLT is defined as:

- Hematologic:
  - Failure to achieve an ANC greater than 1,000/uL and/or a platelet count greater than 25,000/uL independent of platelet transfusion by day ≥42 after the start of therapy, with a hypocellular bone marrow (<10% marrow cellularity) and absence of persistent leukemia (ie, <5% marrow blasts) measured at the completion of Cycle 1 (approximately day 28-32);
    - If a subject with persisting cytopenias does not exhibit marrow hypoplasia on biopsy (or bone marrow aspirate) or demonstrates persisting leukemia, such subject will not be considered to have demonstrated a hematological toxicity and may continue to receive PF-06747143 at the scheduled time point for Cycle 2.
  - Hyperleukocytosis (WBC ≥100,000/uL) not managed by hydroxyurea and/or leukapheresis and/or resulting in an adverse event.

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.

- Non-hematologic:
  - Grade ≥3 toxicities, except for:
    - Grade ≥3 nausea or vomiting that resolves to Grade ≤1 within 72 hours with appropriate supportive therapy;
    - Grade ≥3 diarrhea that resolves to Grade ≤1 within 72 hours with appropriate supportive therapy;
    - Grade ≥3 fatigue, asthenia, or other constitutional symptom that resolves to Grade ≤1 within 7 days with appropriate supportive therapy;
    - Alopecia of any grade;
    - Grade ≥3 infection, fever (including febrile neutropenia), electrolyte abnormalities and ALT/AST elevation that returns to Grade ≤1 or baseline within 7 days;
  - Delay by more than 14 days to receive the next scheduled dose due to a persisting drug-related AE.

In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by the Investigators and sponsor. All DLTs need to represent a clinically significant shift from baseline.

Grade ≥3 cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs (as it is unlikely to be dose related), but may be a reason for study discontinuation, protocol amendment (eg, pre-infusion treatments, infusion duration) and should be reviewed with the sponsor.

In principle, a patient needs to be on study for at least 28 days to be evaluable for DLT observation, and may be replaced if they terminate study participation earlier than 28 days without experiencing a DLT.

Statistical Method

A modified toxicity probability interval method (mTPI) targeting a DLT rate of 25% with an equivalence interval (20%-30%) will be utilized in order to estimate MTD in dose escalation. For all dose levels, patients may be enrolled in cohorts of 2-4 (the target size of each cohort will be 3 patients). Intermediate dose levels to further evaluate the safety and/or PK may be evaluated following discussion between sponsor and Investigator.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to Section 7 of the protocol for detailed information on each assessment required for compliance with the protocol.

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

		Treatment Period (QW)													Off Treatment		
Time Points and Assessments	**Screen§**	**Cycle 1** (Day 1 to 28)					**Cycle 2** (Day 1 to 28)				**Cycle 3 and Subsequent Cycles‡**				**End of Treat.♦**	**28 Day F/U◊**	**60 Day F/U◊**
Visit Identifier	**Within 28 days**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**			
Informed Consent[a]	X																
Medical History[b]	X																
AML History (histology, cytogenetics, karyotype and mutation status)[c]	X																
Prior Medications	X																
Complete Physical Examination	X																
Baseline Signs and Symptoms	X[d]																
Registration	X[e]																
Abbreviated Physical Examination[f]		X		X	X	X	X	X	X	X	X				X	X	X
Height	X																
Weight	X	X[g]			X[g]		X[g]		X[g]		X[g]		X[g]		X		
Vital Signs[h] (BP/HR)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X					X				X				X	X	X
Triplicate 12-lead ECG[i]	X[j]	X[j]			X[j]		X[j]				X[j]				X[j]		
Hematology[k]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]		X[l]		X[l]				X	X	X
Coagulation[m]	X[l]	X[l]		X[l]	X[l]	X[l]	X[l]		X[l]		X[l]				X	X	
Chemistry[n]	X[l]	X[l]		X[l]	X[l]	X[l]	X[l]		X[l]		X[l]				X	X	
Urinalysis[o]	X[l]	X[l]			X[l]		X[l]		X[l]		X[l]				X	X	
Pregnancy test[p]	X	X					X				X				X	X	X
Contraception Check[q]	X																X
PF-06747143 Treatment[r]		X		X	X	X	X	X	X	X	X	X	X	X			
Overnight Stay (Part 1: 0.3 mg/kg and 1.0 mg/kg)[s]		X															
Cardiac Monitoring and Pulmonary Function Tests (Part 2, Cohort 1)[t]	X																

Time Points and Assessments	Screen§	Treatment Period (QW)													Off Treatment		
		Cycle 1 (Day 1 to 28)					Cycle 2 (Day 1 to 28)				Cycle 3 and Subsequent Cycles‡				End of Treat.♦	28 Day F/U◊	60 Day F/U◊
Visit Identifier	**Within 28 days**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**			
For Part 2, Cohort 1: Cytarabine and Daunorubicin	X	Cytarabine Days 1-7; Daunorubicin Days 1-3					Remission; Consolidation No remission; Per Investigator										
Part 2, Cohort 2: Azacitidine or Decitabine	X	Azacitidine Days 1-7 or Decitabine Days 1-5					Azacitidine Days 1-7 or Decitabine Days 1-5				Azacitidine Days 1-7 or Decitabine Days 1-5						
Disease Assessment[u]	X						X				X				X	X	
Adverse Event Monitoring[v]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant Medications[w]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Banked biospecimens (Prep D1) for biobanking[x]		X					X				X				X		
Banked biospecimen (Prep B1)[x]		X															

Notes to Table:

The requested assessments and procedures are to be performed unless otherwise specified.

Tests and procedures should be done on schedule, but occasional changes by ±3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.

Sampling schedule for Pharmacokinetic, Immunogenicity and Biomarker sampling is contained in Table 1 and Table 2 below.

§ Screening assessments should be performed within 28 days prior to the first dose.
‡ To be done each cycle except where noted by footnote or other indication in protocol.
♦ End-of-Treatment (EOT) visit conducted at the visit that the patient is discontinued from the study medication.
◊ 28 and 60 days after last dose of PF-06747143.

a. **Informed Consent**: Must be obtained prior to any study-specific procedures and can be obtained >28 days prior to first dose of PF-06747143.
b. **Medical History**: Including history of prior treatments and any current medical treatments for any condition.

c. **AML History:** Collected for this study any time after informed consent. This should include details of primary AML diagnosis, biopsy information, and the patient's treatment history (systemic treatment, stem cell transplants, and radiotherapy). For screening, a fresh bone marrow aspirate sample and biopsy obtained within 14 days of screening is acceptable for patient eligibility and biomarker assessment.
d. **Baseline Signs & Symptoms**: patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Baseline Signs and Symptoms (BSS) Adverse Event (AE) case report form (CRF) page.
e. **Registration:** To occur within 5 days of first dose of PF-06747143.
f. **Abbreviated PE**: A symptom directed exam conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.
g. **Weight**: The patient's weight from Day 1 of each cycle should be used to calculate the amount of dose of PF-06747143 for all infusions. If a patient's weight fluctuates by more than 10% in either direction at the beginning of the next cycle, the dose should be recalculated for the infusions of that cycle (in cases where individual institution/pharmacy practices require more frequent weight measurements, weight can be obtained on each day of administration, and the dose can be adjusted for weight changes of ≤10%).
h. **Vitals**: Includes blood pressure and heart rate. Blood pressure should be taken after the patient has been seated quietly for at least 5 minutes.
i. **Triplicate ECG**: Three consecutive 12-lead ECGs will be performed approximately 2 minutes apart.
j. **Triplicate 12 lead ECGs** should be performed at:
    - Screening.
    - C1D1, C1D15 and Day 1 of each subsequent Cycle: pre-dose (collected within 6 hours prior to dosing) and post-dose (within 1 hour from the end of PF-06747143 infusion).
    - End-of-Treatment.
    - Additional ECGs may be performed as clinically indicated. When coinciding with blood sample draws for PK, ECG assessment should preferably be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.
k. **Hematology**: Hemoglobin (Hgb), platelets, total WBC, percent blast cell, absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils. For Cycle 1, CCI [redacted] noted in Table 1 and Table 2 will also function as the hematology safety assessment.
    - **NOTE:** During Cycle 1, the 0 hour (ie, "pre-dose") peripheral CBC lab must be assessed within 12 hours prior to study drug administration. If the patient's total peripheral WBC count is ≥75,000/uL, the Investigator shall consult with and obtain the sponsor's agreement to move forward with study drug administration.
l. Laboratory Assessments:
    - Screening labs to be performed within 7 days of randomization/registration.
    - Except for the 0 hour CBC, if screening labs are drawn within 7 days prior to C1D1 and are within 10% of eligibility criteria, labs do not need to be reviewed prior to Cycle 1 Day 1, but do need to be drawn prior to treatment. However, the 0 hour CBC lab must be drawn within 12 hours and reviewed prior to each PF-06747143 infusion during Cycle 1 including C1D1 (see Hematology footnote[k]).
    - For subsequent cycles, pre-dose laboratory assessments may also be drawn up to 72 hours in advance of scheduled dosing in order to obtain results prior to infusion (if necessary).
m. **Coagulation:** PTT and International Normalized Ratio (INR) or prothrombin time.
n. **Chemistry**: ALT, AST, alkaline phosphatase, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN or urea, creatinine, uric acid, glucose (non-fasting), albumin, phosphorus or phosphate.
o. **Urinalysis**: Protein and blood by dipstick.

p. **Pregnancy Test**: Patients of childbearing potential must have a negative blood or serum pregnancy test at screening and on C1D1 prior to dosing, on Day 1 of all subsequent doses, and at the End-of-Treatment and 60-Day F/U visit. Additional pregnancy tests may also be undertaken if requested by institutional review boards/institutional ethic committees (IRB/IECs) or if required by local regulations.

q. **Contraception Check**: The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and/or partner from the permitted list of contraception methods and will confirm the patient has been instructed in its consistent and correct use. Assessment should be performed within 7 days of C1D1 and at the 60 Day F/U visit. Refer to Section 4.3.1.

r. **Study Treatment**: PF-06747143 will be infused on Days 1, 8, 15 and 22 of each Cycle beginning in patients enrolled in dose level 1 (0.3 mg/kg). Please refer to the Investigational Product (IP) Manual for more information. **NOTE:** Prior to each PF-06747143 infusion during Cycle 1, the patient's total peripheral WBC must be assessed and if ≥ 75,000/uL, the Investigator shall consult with and obtain the sponsor's agreement to move forward with study drug administration (see footnote [k]).

s. **Overnight stay**: Patients enrolled in the first two dose levels (0.3 mg/kg and 1.0 mg/kg) will be required to stay in the clinic/hospital overnight (minimum of 24 hours) after receiving the first dose of PF-06747143 to monitor for the potential risk of hyperleukocytosis. On an individual basis, patients may be monitored overnight for the additional doses in Cycle 1 at the treating physician's discretion.

t. **Cardiac Monitoring and Pulmonary Function Testing**: Patients in Part 2, Cohort 1 will be required to have:
   - Cardiac Monitoring: Screening ECHO/MUGA scan to confirm eligibility. Additional scans will also be performed when the cumulative dose of daunorubicin reaches 400 mg/m^2, and every 2 cycles thereafter. Decreases in LVEF will be handled according to institutional guidelines.
   - Pulmonary Function Testing: Diffusing capacity of the lungs for carbon monoxide (DLCO) and forced expiratory volume ((FEV) measured during the first forced breath (FEV1)) will be performed to confirm eligibility. Additional assessments may be performed as clinically indicated.

u. **Disease Assessment:** Disease assessments will be made on the basis of Dohner et al. 2010 (see Section 7.6.). For screening, a fresh bone marrow aspirate sample and biopsy obtained within 14 days of screening is acceptable for patient eligibility and biomarker assessment. Peripheral CBC with WBC differential, percent blast cell and platelet count as well as bone marrow aspiration and biopsy to assess bone marrow cellularity and percent blasts, are to be conducted at completion of Cycle 1, approximately at Day 28, and prior to starting of every other new cycle of treatment (C3, C5, C7, etc.) until achievement of a complete response. Bone marrow aspirates and/or biopsies and peripheral CBC assessments may be obtained at other intervals, if clinically indicated. Responses should be confirmed with repeat blood counts and, as appropriate, bone marrow examinations and other tests. In patients who are discontinued from the study treatment for reasons other than disease progression, every attempt will be made to continue disease assessment until disease progression or another treatment is initiated.

v. **Adverse Event Monitoring**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Patients must be followed for AEs for 60 days after the last study treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anti-cancer therapy in the meantime. For serious adverse events (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. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

w. **Concomitant Medications:** all concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF. **NOTE:** Hydroxyurea and/or leukapheresis is permitted during Cycle 1 as needed to control total peripheral WBC counts (see Section 5.8.1), however must be ceased.

x. **Whole Blood (Prep D1) and Plasma (Prep B1) Biospecimens:** Unless prohibited by local regulations, or ethics committee decision these samples will be banked, in order to provide opportunities to evaluate molecular mechanisms of response and drug action that are manifest in the circulation of cancer patients. Whole blood (D1) samples are collected prior to the first dose, on Day 1 of each cycle from Cycles 1 through 6, and at End-of-Treatment. Plasma (Prep B1) biospecimens are collected predose on C1D1 only.

Abbreviations: AML = acute myeloid leukemia; BP = blood pressure; HR = heart rate; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; F/U = follow-up; C = Cycle; D = Day; PK = pharmacokinetics; → = ongoing/continuous event; PE = physical exam; ECHO = echocardiogram; MUGA = Multigated acquisition scan; AE = adverse event; SAE = serious adverse event.

Table 1. PF-06747143 Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule (Part 1 and Part 2: Cohorts S1, S2)

	Screen	Cycle 1													Cycle 2								Subsequent Cycles	EOT
Visit Day		1			2	3	5	8			15		22		1		2	3	5	8	15	22	1	
Hours Post-Dose*		0[a]	1	4	24	48	96	0[a]	1	4	0[a]	1	0[a]	1	0[a]	1	24	48	96	0[a]	0[a]	0[a]	0[a]	
Visit Window†				±0.5 hr	±8 hrs	±8 hrs	±24 hrs			±0.5 hr							±8 hrs	±8 hrs	±24 hrs					
PK blood sampling		X[b]	X		X	X	X	X			X[b]	X	X		X[b]	X	X	X	X	X	X	X	X[b]	X[b]
Blood sample for ADA/Nab[c]		X									X				X								X[d]	X[d]
CCI																								
CCI																								
																								X
																								X
																								X
CCI																								

Abbreviations: EOT = End-of-Treatment; hrs = hours; PK = pharmacokinetic; ADA = anti-PF-06747143 antibodies; CCI ; CCI ; Ribonucleic acid = RNA; ADCC = antibody-dependent cell-mediated cytotoxicity; CCI

***Collection Time**: Sampling times are related to the start of infusion.
†Sample collection windows: The 1 hr samples should be collected within 1 hr after the end of infusion. All other sampling should be within the protocol specified window in the table above.

a. 0 hour (ie, "pre-dose") timepoints must be collected within 6 hours prior to start of PF-06747143 infusion, unless otherwise noted.
b. A companion blood sample for the determination of PF-06747143 concentration will be collected in conjunction with the ADA sample collection to facilitate immunogenicity assessment.
c. Collection of serum to detect the presence of antibodies to PF-06747143 is to be obtained prior to the start of treatment and according to the schedule above. Patients having an unresolved AE that is possibly related to anti-PF-06747143 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at up to 3 month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.
d. After Cycle 2, ADA/Nab sample will be collected pre-dose on Day 1 of Cycles 3-6, and pre-dose on Day 1 every 3 cycles thereafter (eg, Cycles 9, 12, 15,

CCI

[redacted]

Table 2. PF-06747143 Pharmacokinetic, Immunogenicity and Biomarker Sampling Schedule (Part 2: Cohorts E1, E2 and E3)

	Screen	Cycle 1													Cycle 2				Subsequent Cycles	EOT
Visit Day		1			2	3	5	8			15		22		1				1	
Hours Post-Dose*		0[a]	1	4	24	48	96	0[a]	1	4	0[a]	1	0[a]	1	0[a]	1	24	0[a]	0[a]	
Visit Window†				±0.5 hr	±8 hrs	±8 hrs	±24 hrs			±0.5 hr							±8 hrs			
PK blood sampling		X[b]	X					X			X[b]		X		X[b]	X	X	X	X[b]	X[b]
Blood sample for ADA/Nab[c]		X									X				X				X[d]	X[d]
CCI																				
CCI																				

Abbreviations: EOT = End-of-Treatment; hrs = hours; PK = pharmacokinetic; ADA = anti-PF-06747143 antibodies; CCI ; CCI ; Ribonucleic acid = RNA; CCI

***Collection Time**: Sampling times are related to the start of infusion.
†**Sample collection windows**: The 1 hr samples should be collected within 1 hr after the end of infusion. All other sampling should be within the protocol specified window in the table above.

a. 0 hour (ie, "pre-dose") timepoints must be collected within 6 hours prior to start of PF-06747143 infusion, unless otherwise noted.
b. A companion blood sample for the determination of PF-06747143 concentration will be collected in conjunction with the ADA sample collection to facilitate immunogenicity assessment.
c. Collection of serum to detect the presence of antibodies to PF-06747143 is to be obtained prior to the start of treatment and according to the schedule above. Patients having an unresolved AE that is possibly related to anti-PF-06747143 antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at up to 3 month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.
d. After Cycle 2, ADA/Nab sample will be collected pre-dose on Day 1 of Cycles 3-6, and pre-dose on Day 1 every 3 cycles thereafter (eg, Cycles 9, 12, 15,

CCI

[redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06747143 is a humanized IgG1 monoclonal antibody (mAb) that is an antagonist for the chemokine CXCR4 and intended to be used for the treatment of adult patients with advanced hematological malignancies unresponsive to currently available therapies, and for which no standard therapy is available. This protocol is limited to patients with acute myeloid leukemia (AML) who have not obtained remission with induction therapy or who have relapsed after achieving remission.

1.2. Background and Rationale

The C-X-C chemokine receptor type 4 (CXCR4) (or CD184) is a G-protein coupled chemokine receptor, expressed on the cell surface, and has a 7-transmembrane structure.[1,2] CXCR4 plays a role in the cross talking between cancer cells and their microenvironment by binding its ligand, chemokine ligand 12 (CXCL12),[3,4] thereby activating the downstream signaling pathways leading to alteration of gene expression, actin polymerization, cell skeleton rearrangement, and cell migration and proliferation.[5]

The tumor microenvironment consists of resident non-cancerous cells (stromal fibroblasts, endothelial cells, and immune cells), connective tissue and extracellular matrix, altogether supporting tumor structure, angiogenesis, and growth.[6] CXCL12 is physiologically mainly expressed by mesenchymal stromal cells in various organs and tissues such as the liver, lungs, lymphatic tissues, and bone marrow.[7] High levels of CXCL12 directly stimulate the proliferation and invasiveness of CXCR4-expressing cancer cells in an autocrine and paracrine manner.[7] Nonclinical mouse models of non-Hodgkin's lymphoma (NHL), AML, chronic lymphocytic leukemia (CLL), and human multiple myeloma (MM) have shown that CXCR4-positive cancer cells can be recruited to CXCL12-rich mesenchymal stroma niches.

Since the CXCL12-CXCR4 interaction is considered crucial for attracting tumor cells to the bone marrow niche, CXCR4 inhibitors have been explored as treatment agents in the field of leukemia treatment.[8,9,10,11,12] CXCR4 is overexpressed in 75% of cancers (hematological malignancies and solid tumors), and its expression correlates with poor prognosis in various cancers.[8,9,10,11,12]

PF-06747143 is a humanized IgG1 monoclonal antibody (mAb) that is an antagonist of CXCR4. PF-06747143 has demonstrated robust anti-tumor activity in immune-compromised mice engrafted with human cells representing several human hematological malignancies including NHL, CLL, MM, and AML with a treatment regimen either as a single agent or in combination with standard of care agents. Based on the nonclinical studies conducted, the mechanisms of action of PF-06747143 include: 1) inhibition of CXCR4-CXCL12 signaling, thereby inducing cell mobilization from CXCL12-rich niches; 2) direct induction of caspase-independent cell-death through an antibody (Ab) bivalency-dependent mechanism; and 3) induction of cell death through Fc-effector function (antibody-dependent cell-mediated cytotoxicity (ADCC) /complement dependent cytotoxicity [CDC]) inherent to the IgG1 backbone.

Given the extensive nonclinical anti-tumor activity of PF-06747143 demonstrated in a large number of animal models, clinical trials of PF-06747143 alone or in combination with other agents are warranted.

1.3. PF-06747143

1.3.1. Nonclinical Efficacy

The in vitro characterization of PF-06747143 is summarized in Table 3 and described below. PF-06747143 is a potent and selective CXCR4 antagonist. PF-06747143 showed high affinity for the human CXCR4 receptor (K_D: 0.36 nM). The antibody showed similar half maximal effective concentration (EC_{50}) binding for native human and monkey CXCR4 (EC_{50}s: 0.27 nM and 0.16 nM, respectively). In vitro functional testing showed that the antibody is a potent antagonist of CXCR4, inhibiting ligand (CXCL12)-induced calcium flux with IC_{50} value of 1.75 nM and stimulating ligand-inhibited cellular cyclic adenosine monophosphate (cAMP) production with an EC_{50} of 9.45 nM.

The ability of the bivalent full-length PF-06747143 antibody, and its Fab (monovalent) and F(ab')2 (bivalent lacking Fc-portion) forms, to induce cell-death was evaluated in NHL Ramos cells. These studies demonstrated that PF-06747143 induces cell-death in a bivalency-dependent fashion. Moreover, the Fc portion of the antibody is not required for this activity, demonstrated by the fact that the (Fab')2 antibody form (bivalent but deprived of the Fc effector portion) is capable of inducing cell-death.

The effector function activity of PF-06747143 was evaluated on NHL Ramos cell line, in the presence of natural killer (NK) effector cell line (NK92 V158). The ADCC EC50 was 0.421 nM. PF-06747143 showed 20% specific lysis of NHL Daudi cells in the CDC assay conducted in the presence of 2.5% donor serum.

Table 3. PF-06747143 in vitro Characterization Summary

Assay	Assay Conditions	Results
Binding Affinity to CXCR4 (Biacore)	Fab fragment of PF-06747143 binding kinetics measured by Biacore using human CXCR4-expressing lipoparticles	K_D: 0.36 nM Off-rate (kd): 2.9E-04 (1 /s)
Inhibition of Ligand-induced Intracellular Calcium Flux	Functional Potency by measuring Calcium flux in T-cell leukemia line (Jurkat) naturally expressing CXCR4, in presence of CXCL12 (ligand) at its EC80.	IC50: 1.75 nM
Stimulation of Ligand-Inhibited cAMP	Functional Potency by measuring cAMP accumulation in cell line CHO- K1 expressing CXCR4 (DiscoveRx), in presence of CXCL12 (ligand) at its IC80.	EC50: 9.45 nM
Cell-Death	Induced Cell-Death in NHL Ramos cell line, measured by Annexin V staining in flow cytometry.	32% Cell-Death at 100 nM of Ab
Fc-effector Function Mediated Cytotoxicity	ADCC assay: Ramos (NHL) tumor cells at 10:1 E:T ratio of NK-92(158V) effector cells to tumor cells. CDC assay: Daudi (NHL) tumor cells with 2.5% human single donor complement treated with 5 µg/mL (33 nM) of PF-06747143.	ADCC assay EC50: 0.421 nM CDC assay: 20% specific lysis compared to non-binding negative control hIgG1 Ab
Ab = Antibody; cAMP = Cyclic adenosine monophosphate; CDC = Complement-dependent cytotoxicity; CHO = Chinese hamster ovary; hIgG1 = Human immunoglobulin gamma 1; NHL = Non-Hodgkin's lymphoma.		

PF-06747143 has no cross-reactivity with the murine CXCR4, therefore efficacy and PK/PD studies were conducted in xenograft models in mice. Human tumor cell lines representing diverse hematological tumor types (NHL, AML, CLL and MM) were used to evaluate efficacy of PF-06747143 in various tumor models. A summary of PF-06747143 in vivo efficacy studies is shown in Table 4 and described below.

PF-06747143 efficacy was first examined in a human NHL xenograft subcut aneous mouse model (Ramos NHL cell line) at test doses of 0.1, 1.0, 10 and 30 mg/kg, every 7 days (q7d). At doses of 10 mg/kg and 30 mg/kg the antibody produced robust tumor regression that persisted for several weeks after dosing was suspended (Day 21). The non-clinical effective concentration (Ceff) resulting in tumor regression (25%) was determined to be 47.3 µg/mL in this study.

Treatment with PF-06747143 at 10 mg/kg subcutaneously q7d in a human AML disseminated xenograft mouse model, in which tumor cells are implanted intravenously and spontaneously migrated to bone marrow, produced significant bone marrow and peripheral blood tumor burden inhibition, with activity similar to daunorubicin, a component of standard of care for AML patients. The non-clinical Ceff resulting in less than 5% of blasts in the bone marrow at the end of the study was determined to be 63.5 µg/mL.

Moreover, in the AML MV4-11 model, a single dose of PF-06747143 at 0.3, 1.0, and 10 mg/kg induced rapid mobilization of tumor cells from bone marrow into peripheral blood (3-6 hrs post-dose), followed by a decrease in the number of mobilized cells back to baseline at 24 hrs post-dose. This confirmed the ability of PF-06747143 to block homing of malignant cells to bone marrow (PD marker) and to induce cell-death in vivo.

Efficacy of PF-06747143 was also evaluated in the CLL (JVM-13) model and in the MM (OPM-2) model at 10 mg/kg, q7d. Single agent treatment led to increased survival and decreased bone marrow tumor burden in both models, and it was more efficacious than components of standards of care bendamustine (used in CLL) and melphalan (used in MM), respectively.

PF-06747143 showed no anti-tumor effect in a CXCR4-negative TF-1 AML xenograft model, indicating that PF-06747143 in vivo efficacy is CXCR4-expression dependent.

Table 4. PF-06747143 in vivo Pharmacology Summary

Tumor Model	Indication	CXCR4 Expression	Study Name	Compound Tested and Dosage	Efficacy Observed
Ramos sc	NHL	Positive	CXCR4-032	PF-06747143 0.1, 1, 10, 30 mg/kg, sc q7d	PF-06747143 Tumor regression at 30 and 10 mg/kg. Dose response observed
MV4-11 Disseminated	AML	Positive	CXCR4-036	PF-06747143 0.1, 1, 10 mg/kg sc q7d Daunorubicin 2 mg/kg, Days 1,3 and 5	PF-06747143 dose-response. PF-06747143 10 mg/kg improved survival & reduced PB and BM tumor burden. Similar to daunorubicin
MV4-11 Disseminated	AML	Positive	CXCR4-043	PF-06747143 0.3, 1, 10 mg/kg iv, single dose	PF-06737143 induced malignant cell mobilization at all doses tested. Peak at 3-6 hrs -back to baseline at 24 hrs.
JVM-13 Disseminated	CLL	Positive	CXCR4-038	PF-06747143 10 mg/kg sc q7d Bendamustine 30mg/kg, ip, QDx2	PF-06747143 10 mg/kg reduced tumor burden and significantly improved survival. Superior to bendamustine.
OPM-2 Disseminated	MM	Positive	CXCR4-035	PF-06747143 10 mg/kg s.c q7d Melphalan 1 mg/kg, ip, 2x/week, for 3 weeks	PF-06747143 10 mg/kg reduced tumor burden and significantly improved survival. Superior to melphalan.
TF-1 Disseminated	AML	Negative	CXCR4-034	PF-06747143 10 mg/kg sc q7d	No activity.

AML = Acute myeloid leukemia; CLL = Chronic lymphocytic leukemia; iv = Intravenously; MM = Multiple myeloma; NHL = Non-Hodgkin's lymphoma; QDx2= two consecutive days on first week of treatment; q7d = Once every 7 days; sc=Subcutaneously.

In summary, the results from these studies demonstrated binding to the CXCR4 tumor antigen with high affinity and specificity. PF-06747143 treatment inhibited CXCL12-induced functional activity in calcium Flux and cAMP assays. PF-06747143 also induced bivalency-dependent cell-death and strong effector-function mediated ADCC and CDC. PF-06747143 demonstrated single agent anti-tumor activity against a broad spectrum of CXCR4 positive xenograft models including NHL, AML, CLL, and MM. PF-06747143 anti-tumor activity was superior to that of the standards of care components for the treatment of CLL and MM diseases. The in vivo activity of PF-06747143 is CXCR4-dependent, with no activity observed in a CXCR4-negative model.

1.3.2. Nonclinical Pharmacokinetics

PF-06747143 PK in cynomolgus monkeys has been characterized in 2 studies: Good Laboratory Practice (GLP) toxicology study where male and female cynomolgus monkeys received 10, 50, and 200 mg/kg PF-06747143 once weekly intravenous (IV) bolus for 5 doses, and low dose PK study where female cynomolgus monkeys received a single IV bolus does at 0.3 mg/kg. The PK exposure appeared to be linear at doses above 10 mg/kg, where a rapid elimination of PF-06747143 was observed at 0.3 mg/kg, suggesting target-mediated drug disposition (TMDD). TMDD model was implemented to fit the monkey PK data, and the derived PK parameters were scaled to human based on allometric scaling. PF-06747143 is likely to exhibit TMDD at low doses in patients with high CXCR4 expression. When drug concentration and dose above TMDD range, PF-06747143 is expected to have a clearance of 3.22 mg/kg/day and a volume of distribution (central compartment) of 38.3 mL/kg. At expected clinically relevant dose ranges (PF-06747143 ≥3 mg/kg), the apparent terminal elimination half-life is projected to range from 7-16 days.

1.3.3. Nonclinical Safety

The nonclinical safety profile of PF-06747143 was characterized in a series of nonclinical safety studies and included: A Tissue Cross-Reactivity in rat, cynomolgus monkey and human tissue panels; 2-week Exploratory Toxicity Study in Monkeys (0, 10, and 200 mg/kg/week by IV route); and a 1-Month GLP Toxicity Study in Monkeys (0, 10, 50 and 200 mg/kg by IV route). Additional studies included cytokine release assay and blood compatibility assay. Genotoxicity studies were not conducted with PF-06747143 in accordance with International Conference on Harmonisation (ICH) S6 (guidance for safety testing of biological products)[13] and ICH S9 (guidance for nonclinical evaluation of anticancer pharmaceuticals).[14] Carcinogenicity and Reproductive and Developmental Toxicity studies have not been conducted with PF-06747143 at this point.

PF-06747143 binding EC_{50}s on human and Cynomolgus monkey cells that endogenously express the receptor, is 3.02 and 2.59 nM, respectively, indicating similar binding kinetics. These results supported the use of Cynomolgus monkeys as a relevant species for toxicology studies with PF-06747143.

Cynomolgus monkeys were dosed with PF-06747143 once weekly by IV injection at 10 and 200 mg/kg/dose (2-week Exploratory Study) or at 10, 50 and 200 mg/kg/dose (1-month pivotal GLP Study) and findings were similar in both studies. In the exploratory study, all animals survived to scheduled necropsy and the main findings were leukocytosis, thrombocytopenia and decreased lymphoid cellularity of lymphoid organs.

In the pivotal 1-month monkey study, adverse thrombocytopenia (<50,000 μL/count) and nonadverse leukocytosis (2-5x) were observed at all doses. Thrombocytopenia and leukocytosis did not recover based on the 1-month recovery assessed only in the 200 mg/kg/week dose group. This is likely due to significant levels of serum PF-06747143 (>10x the C_{eff} for PF-06747143) in all animals throughout the recovery phase. Leukocytes and platelets have high expression of CXCR4 and these findings were expected and considered a consequence of the pharmacology of an anti-CXCR4 IgG1 mAb.

PF-06747143 at ≥50 mg/kg/week was associated with adverse oral lesions that were associated with skin lesions, microscopic observations of inflammation, gum necrosis and bone lysis coupled with clinical pathology findings of inflammation. Changes in the oral cavity contributing to poor clinical condition resulted in unscheduled euthanasia of 1/8 animals at 50 mg/kg/week and 2/12 animals at 200 mg/kg/week and were characterized by decreased body weight and food consumption, discoloration and/or hemorrhage of the gums and/or gingiva, hunched posture, decreased activity, dehydration, and/or decreased skin turgor and were likely related to a localized inflammatory response. The changes observed in the oral cavity and skin of animals going into recovery (200 mg/kg group only) fully recovered within the 1-month recovery period.

Other PF-06747143-related changes were considered nonadverse as they were not associated with any clinical signs, tissue damage, or alterations in clinical pathology parameters. These nonadverse changes consisted of decreased lymphoid cellularity in the spleen, thymus, gut associated lymphoid tissue (GALT) and lymph nodes and increased generalized cellularity of the liver, adrenal glands, alveolar septa in lungs, spleen, choroid plexus and bone marrow. Other nonadverse PF-06747143-related changes in hematology parameters included decreases in red cell mass (red blood cell [RBC], hemoglobin [HGB], and hematocrit [HCT]) along with increases in reticulocytes, indicating regeneration. Extramedullary hematopoiesis in the liver and spleen choroid plexus was also observed and correlated with changes in RBC mass. The nonadverse changes described showed partial to full recovery following the 1-month recovery period assessed in the 200 mg/kg group only.

There were no PF-06747143 related findings in electrocardiogram (heart rate or QTc), ocular exams, or cytokines released. The tissue cross reactivity characterization of PF-06747143 data generally shows similar tissue staining in the human and monkey samples. The highest non-severely toxic dose (HNSTD) was considered to be 10 mg/kg/dose in the pivotal monkey study. Systemic exposure of PF-06747143 at the HNSTD in the pivotal monkey study was maximum concentration (C_{max}) of 89.3 μg/mL and area under the curve to 168 hours (AUC_{168}) was 5520 μg*h/mL. The safety margin compared to the proposed clinical starting dose of 0.3 mg/kg is 14 based on C_{max} and 39 based on AUC. Overall, the

nonclinical profile of PF-06747143 has been adequately characterized and was consistent with ICH S6[13] and ICH S9 guidance[14] and supports its use in advanced cancer patients.

1.4. Starting Dose Rationale

The selection of the starting dose for the human Phase 1 trial was based on the preclinical safety study results following International Conference on Harmonisation (ICH) S9 Guidance entitled "Nonclinical Evaluation for Anticancer Pharmaceuticals".[14] The cynomolgus monkey was considered to be the most appropriate species for determining the proposed starting dose in patients. The HNSTD in cynomolgus monkey was determined to be 10 mg/kg administered once weekly. The proposed starting dose of 0.3 mg/kg given as an intravenous infusion once weekly (QW) represents approximately 1/10 of monkey HNSTD (based on human equivalent dose normalized to body surface area). In addition, given the projected human PK based on allometric scaling from cynomolgus monkey PK, the projected human AUC for PF-06747143 at the proposed starting dose of 0.3 mg/kg is expected to be approximately 1/39 of the observed monkey AUC at HNSTD (10 mg/kg).

Prediction of clinical efficacious dose was based on PK/PD modeling of tumor growth inhibition in the murine tumor models of Ramos NHL and the disseminated MV4-11 AML. Based on the observed biological responses in NHL and AML murine tumor models following administration of PF-06747143, the nonclinical Ceff range for PF-06747143 is 47.3-63.5 μg/mL. Given the predicted human PK based on allometric scaling from cynomolgus monkey PK, efficacious clinical doses of 5 mg/kg once every 2 weeks (Q2W) or 3 mg/kg QW were predicted.

Complete information for this compound may be found in the single reference study document (SRSD), which for this study is the investigator's brochure (IB).

1.5. Cytarabine, Daunorubicin, Decitabine and Azacitidine (Part 2 only)

1.5.1. Cytarabine

Cytarabine (Ara-C)[15] is an antimetabolite analogue of cytidine with a modified sugar moiety (arabinose instead of ribose). Cytarabine is converted to the triphosphate form within the cell and then competes with cytidine for incorporation into deoxyribonucleic acid (DNA). Because the arabinose sugar sterically hinders the rotation of the molecule within DNA, DNA replication ceases, specifically during the S phase of the cell cycle. This agent also inhibits DNA polymerase, resulting in a decrease in DNA replication and repair.

Standard induction regimens used for patients fit for intensive chemotherapy (usually <60 years) are based on cytarabine and daunorubicin and little has changed in the past 25 years.[16] A common therapy is "7+3" for first-line induction therapy, which involves 7 days of continuous infusion of cytarabine and 3 daily doses of daunorubicin.

The SRSD for Cytarabine is the local package insert.

1.5.2. Daunorubicin

Daunorubicin[17] is an anthracycline antineoplastic antibiotic with therapeutic effects similar to those of doxorubicin. Daunorubicin exhibits cytotoxic activity through topoisomerase-mediated interaction with DNA, thereby inhibiting DNA replication and repair and RNA and protein synthesis.

Standard induction regimens for patients <60 years are based on a backbone of cytarabine plus an anthracycline. Historically, daunorubicin has been the most commonly used anthracycline.[16]

The SRSD for Daunorubicin is the local package insert.

1.5.3. Decitabine

Decitabine[18] is a cytidine antimetabolite analogue with potential antineoplastic activity. Decitabine incorporates into DNA and inhibits DNA methyltransferase, resulting in hypomethylation of DNA and intra-S-phase arrest of DNA replication.

A Phase 3 trial randomly assigned 485 AML patients older than 65 years to receive decitabine (n=242) or their preferred choice (n=243) of either supportive care (n=28) or low-dose cytarabine (n=215). Although rates of CR + CRp (CR with incomplete platelet recovery) were more than double in the decitabine arm (17.8%) compared with the treatment-choice arm (7.8%) (P =0.001), median OS was not significantly improved for patients receiving decitabine (7.7 months) compared with the treatment of choice (5.0 months) (HR for death for decitabine, 0.85; 95% CI, .69-1.04; P = 0.11).[19] Decitabine is not approved for use in patients with AML, but is considered a standard of care in patients not fit to receive intensive therapy with cytarabine and daunorubicin.[16]

The SRSD for Decitabine is the local package insert.

1.5.4. Azacitidine

Azacitidine[20] is a pyrimidine nucleoside analogue of cytidine with antineoplastic activity. Azacitidine is incorporated into DNA, where it reversibly inhibits DNA methyltransferase, thereby blocking DNA methylation. Hypomethylation of DNA by azacitidine may activate tumor suppressor genes silenced by hypermethylation, resulting in an antitumor effect. This agent is also incorporated into RNA, thereby disrupting normal RNA function and impairing tRNA cytosine-5-methyltransferase activity.

Preliminary results from a Phase 3 trial randomly assigned AML patients older than 65 years to azacitidine compared with conventional care regimens of best supportive care, low-dose cytarabine, and 7+3 AML-type induction chemotherapy and similarly showed a nonsignificant difference in median OS for patients receiving azacitidine (10.4 months) versus conventional care (6.5 months) (HR for death for azacitidine, 0.84; 95% CI, 0.69-1.02; (P = 0.08).[21] Azacitidine is not approved for use in patients with AML, but is considered a standard of care in patients not fit to receive intensive therapy with cytarabine and daunorubicin.[16]

The SRSD for Azacitidine is the local package insert.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives – Part 1

Primary Objective

- To assess safety and tolerability at increasing dose levels of PF-06747143 in patients with refractory and/or relapsed AML for which no standard therapy is available in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile;
- To characterize the single-dose and multiple-dose pharmacokinetics (PK) of PF-06747143 following IV administration;
- To evaluate the immunogenicity of PF-06747143 following repeated administration;
- To document any anti-leukemia activity based on: Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet (Dohner et al. 2010).[22]

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2.2. Endpoints – Part 1

Primary Endpoint

- Dose Limiting Toxicities (DLTs).

Secondary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03), timing, seriousness, and relationship to study therapy;

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;

- PK parameters of PF-06747143: Single Dose (SD) - C_{max}, AUC_{last}, and if data permit, AUC_{inf}, V_d, CL, and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss}$ /AUC_{τ}), and if data permit, CL, V_{ss}, and $t_{1/2}$;

- Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against PF-06747143;

- Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).[22]

CCI

[redacted]

2.3. Objectives – Part 2

Primary Objective

- To evaluate safety and tolerability and preliminary anti-leukemia activity (Dohner, et. al 2010)[22] of PF-06747143 in combination with standard intensive chemotherapy (ie, cytarabine and daunorubicin; D/C 7+3) in patients with newly diagnosed fit treatment naïve AML patients (Cohort 1) or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients (Cohort 2) or PF-06747143 as a single agent ((Cohort 3) if data warrants).

Secondary Objectives

- To characterize the single and multiple dose PK of PF-06747143 in combination with standard intensive cytarabine and daunorubicin 7+3 therapy in newly diagnosed fit treatment naïve AML patients or with standard dose of decitabine or azacitidine in newly diagnosed unfit treatment naïve AML patients;

- To collect PF-06747143 drug concentration data in patients from the dose expansion cohorts for evaluation of population PK;

- To evaluate the immunogenicity of PF-06747143 following repeated administration.

CCI

[redacted]

2.4. Endpoints – Part 2

Primary Endpoints

- Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03), timing, seriousness, and relationship to study therapy;

- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing;

- Preliminary evidence of anti-leukemia activity including objective disease response; as assessed using the standardized response criteria including objective response rate (ORR), duration of ORR, and relapse free survival (RFS).[22]

Secondary Endpoints

- PK parameters of PF-06747143: Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, V_d, CL, and $t_{1/2}$. Multiple Dose (MD) (assuming steady state is achieved) - $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, R_{ac} ($AUC_{\tau, ss}$ /AUC_{τ}), and if data permit, CL, V_{ss}, and $t_{1/2}$;

- Peak and trough PF-06747143 concentrations for selected doses;

- Incidence of ADA and Nab against PF-06747143.

CCI

[redacted]

3. STUDY DESIGN

3.1. Study Overview

PF-06747143 will initially be developed in patients with acute myeloid leukemia (AML). The diagnosis of AML will be according to the World Health Organization (WHO) classification (2008).[23] The study will be conducted in two parts, Part 1 single agent dose escalation and Part 2 PF-06747143 in combination with standard chemotherapy with an option for single agent cohort expansion at the RP2D.

Assessment of anti-leukemia activity of PF-06747143 will be based on Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. (Dohner et al, 2010).[22]

3.1.1. Part 1

Part 1, dose escalation, is an open-label, multi-center, single arm, nonrandomized, multiple dose, safety, pharmacokinetic and pharmacodynamic study of single-agent PF-06747143 in sequential dose levels of adult patients with refractory and/or relapsed AML in order to establish the MTD/RP2D and/or maximally permitted dose (MPD).

Patients will receive PF-06747143 as a weekly infusion (QW) in 28 day cycles at escalating doses. The proposed dosing scheme includes 0.3, 1.0, 3.0, 10, 15, and 20 mg/kg (Figure 1). Patients enrolled in the first two dose levels (0.3 mg/kg and 1.0 mg/kg) will be required to stay in the clinic/hospital overnight (minimum of 24 hours) after receiving the first dose of PF-06747143 to monitor for the potential risk of hyperleukocytosis that might be caused by the inhibition of CXCR4 pathway by PF-06747143. On an individual basis, patients may be monitored overnight for the additional doses in Cycle 1 at the treating physician's discretion.

In addition, the use of hydroxyurea and/or leukapheresis is permitted during Cycle 1 following first study dose administration to control total peripheral WBC counts at the treating physician's discretion. However, hydroxyurea must be ceased 24 hours prior to the first study dose of Cycle 1. Further, total peripheral WBC will be assessed by the Investigator within 12 hours prior to study drug administration during Cycle 1. In the event a patient's total peripheral WBC count is ≥75,000/uL, the Investigator shall consult with and obtain the sponsor's agreement to move forward with the study drug administration.

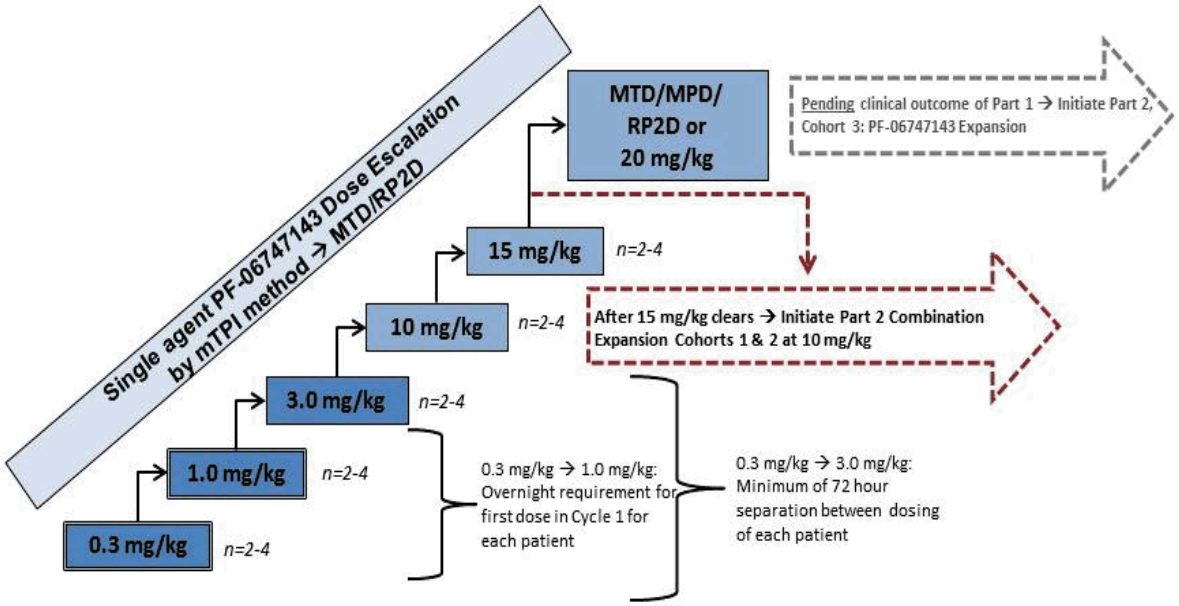
For the first three dose levels (ie, 0.3 mg/kg through 3.0 mg/kg), initiation of the first dose of PF-06747143 for each patient in the dose level must be at least 72 hours after the first dose of the previous patient. Patients enrolled in subsequent dose levels will be treated on an outpatient basis with no staggering of patients unless there are safety concerns based on findings at the lower doses.

Once MTD or MPD is identified, additional patients may be enrolled at that dose level (to a minimum of 9) to further investigate the anti-leukemia activity, safety, and PK profile of PF-06747143 prior to an expansion cohort with single agent PF-06747143 at the MTD/MPD/RP2D.

The total estimated number of patients to be enrolled for the Part 1 dose escalation study will be approximately 30-50 patients but it is pertinent to recognize that the exact sample size of the mTPI design in Part 1 cannot be pre specified in advance because it is a dynamic feature of the design.

Once the dose of 15 mg/kg in Part 1 is found safe and tolerable, the Part 2 combination cohorts will be initiated at 10 mg/kg while the Part 1 single agent dose escalation continues to 20 mg/kg for MPD or MTD assessment.

Figure 1. Part 1 Schema



3.1.1.1. Starting Dose

The starting dose will be 0.3 mg/kg, administered QW in 28 day cycles.

3.1.1.2. Criteria for Dose Escalation

A modified toxicity probability interval method (mTPI)[24] targeting a DLT rate of 25% with an equivalence interval (20%-30%) will be utilized in order to estimate MTD in dose escalation. For all dose levels, patients may be enrolled in cohorts of 2-4 (the target size of each cohort will be 3 patients). Intermediate dose levels to further evaluate the safety and/or PK may be evaluated following discussion between sponsor and Investigator.

The dose levels planned for Part 1 of the study are shown in Table 5. Additional dose levels may be explored, if appropriate based on emerging safety, PK or PD data.

Intra-patient dose escalation of PF-06747143 or the backbone chemotherapy (in Part 2 combination cohorts) will not be permitted.

Table 5. Possible Dose Levels

Dose Level	PF-06747143 Dose (mg/kg) (QW)
1	0.3
2	1.0
3	3.0
4	10
5	15
6	20

The mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine where future cohorts should be on dose escalation, no change in dose, or dose de-escalation. The algorithm will stop if any of the following criteria is met:

- the maximum sample size has been achieved (approximately 50 patients total);
- at least 9 patients have been accumulated on a dose that is predicted to be the MTD; or
- all doses explored appear to be overly toxic and the MTD cannot be determined.

Although dose levels are capped at 20 mg/kg, this mTPI will continue to operate subject to the constraints detailed above while allowing for doses higher than specified.

All clinically relevant adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the sponsor and Investigators after each dose level is complete to determine if the dose allocation schedule requires modification.

The modified toxicity probability interval (mTPI) design uses a Bayesian statistics framework and a beta/binomial hierarchical model to tailor dose-escalation and de-escalation decisions.[24] These rules are conceptually similar to those used by the 3+3 design and all the dose-escalation decisions for a given trial and can be pre-calculated under the mTPI design and presented in a two-way table (Appendix 4).

Patients will continue with study treatment until disease progression (refer to Section 7.6.) patient refusal or unacceptable toxicity occurs. Patients experiencing a DLT may be managed with dose modification (after dose interruption) or discontinuation. Subsequent dose levels may not be opened until all patients entered at the current dose level have been treated and observed for at least one complete cycle and the number of DLTs among those patients in their first cycle has been determined. Intra-patient dose escalation will not be permitted in this study.

3.1.1.3. DLT Definition

A DLT will be classified according to NCI CTCAE version 4.03 and is defined as any of the following adverse events unless the event can clearly be determined to be unrelated to drug occurring in the first cycle of treatment (within 28 days of first dose or until patient receives a second cycle if there are treatment delays). Data from all cycles of treatment will be analyzed for safety, delayed toxicity, and cumulative toxicity.

DLT is defined as:

- Hematologic:
  - Failure to achieve an ANC greater than 1,000/uL and/or a platelet count greater than 25,000/uL independent of platelet transfusion by day ≥42 after the start of therapy, with a hypocellular bone marrow (<10% marrow cellularity) and absence of persistent leukemia (ie, <5% marrow blasts) measured at the completion of Cycle 1 (approximately day 28-32);
    - If a subject with persisting cytopenias does not exhibit marrow hypoplasia on biopsy (or bone marrow aspirate) or demonstrates persisting leukemia, such subject will not be considered to have demonstrated a hematological toxicity and may continue to receive PF-06747143 at the scheduled time point for Cycle 2.
  - Hyperleukocytosis (WBC ≥100,000/uL) not managed by hydroxyurea or leukapheresis and/or resulting in an adverse event.
  - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding.
- Non-hematologic:
  - Grade 3 toxicities, except for:
    - Nausea or vomiting that resolves to Grade ≤1 within 72 hours with appropriate supportive therapy;
    - Diarrhea that resolves to Grade ≤1 within 72 hours with appropriate supportive therapy;
    - Fatigue, asthenia, or other constitutional symptom that resolves to Grade ≤1 within 7 days with appropriate supportive therapy;
    - Alopecia of any grade;
    - Infection, fever (including febrile neutropenia), electrolyte abnormalities and ALT/AST elevation that returns to Grade ≤1 or baseline within 7 days;

- Delay by more than 14 days to receive the next scheduled dose due to a persisting drug-related AE;

- All Grade 4 toxicities.

In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by the Investigators and sponsor. All DLTs need to represent a clinically significant shift from baseline.

Grade ≥3 cytokine release syndrome, infusion reaction, and allergic reaction will not be considered as DLTs (as it is unlikely to be dose related), but may be a reason for study discontinuation, protocol amendment (eg, pre-infusion treatments, infusion duration) and should be reviewed with the sponsor.

In principle, a patient needs to be on study for at least 28 days to be evaluable for DLT observation, and may be replaced if they terminate study participation earlier than 28 days without experiencing a DLT. Patients who are not able to receive at least 80% of the planned dose of the PF-06747143 and backbone chemotherapy (in Part 2 combination study) in the DLT assessment period are considered not evaluable for DLT and will be replaced. However, in some circumstances of a clear drug unrelated event (eg,, traffic accident, clear disease progression, or withdrawal of consent) that leads to study termination close to or before 28 days, the patient might be deemed evaluable if the Investigators and sponsor agree. In addition, patients not evaluable for assessment of DLT, as described in Section 9.1, may be replaced.

3.1.1.4. MTD Definition

The MTD would be any doses with true toxicity probabilities in the Equivalence Interval (EI) where the EI is defined as (20%-30%).

In practice, the MTD will be the highest dose associated with the occurrence of DLTs ≤33% (eg, 3/9 evaluable patients experience a DLT during the first treatment cycle).

3.1.1.5. Maximum Permitted Dose Definition

The Maximum Permitted Dose (MPD) is 20 mg/kg.

3.1.1.6. Recommended Phase 2 Dose (RP2D) Definition

The Recommended Phase 2 Dose (RP2D) is the dose chosen for further study based on Part 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. If the MPD is determined to be safe, then this becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

3.1.2. Part 2

Part 2 dose expansion, is an open-label, multi-center, non-randomized study to assess the safety and tolerability and preliminary anti-leukemia activity of PF-06747143 in three cohorts (two combination cohorts and one potential cohort of single agent PF-06747143). Figure 2.

Part 2 will assess the safety and tolerability and preliminary anti-leukemia activity of PF-06747143. In Part 2, PF-06747143 will be administered at 10 mg/kg QW (Section 3.1.2.1) on 28 day cycles in combination with chemotherapy in two separate cohorts each containing up to 30 patients with newly diagnosed AML, including Cohort 1 in fit treatment naïve AML patients, in which PF-06747143 will be combined with standard intensive 7+3 chemotherapy with cytarabine (100-200 mg/m^2 continuous infusion for 7 days) and daunorubicin (60-90 mg/m^2 daily for 3 days), and Cohort 2 in unfit treatment naïve AML patients who are considered to not tolerate or decline to receive standard intensive 7+3 treatment, in which case PF-06747143 will be combined with standard dose of azacitidine (75 mg/m^2 administered subcutaneously or intravenously daily for 7 days) or decitabine (20 mg/m^2 by continuous intravenous infusion over 1 hour daily for 5 days in a 4-week schedule) based on drug availability and institutional guidance.

Attributions to fit or unfit in Part 2 will be based on "Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of Italian SIE, SIES and GITMO group on a new tool for therapy decision making"[25] per Investigator judgment.

An additional single agent PF-06747143 expansion cohort, Cohort 3, at the MTD/RP2D may be initiated in Part 2 in 15-30 refractory and/or relapsed AML patients based on single agent PF-06747143 clinical benefit in Part 1.

3.1.2.1. Part 2 Combination Cohorts Starting Dose

After the DLT observation period in the first cycle of 15 mg/kg cohort is cleared, the dose of 10 mg/kg of PF-06747143 will be used to initiate the Part 2 combination studies, which may be escalated or de-escalated, depending on emerging data. Additionally, if an MTD in Part 1 is determined at or below the dose of 15 mg/kg, a lower dose than 10 mg/kg may be considered to move into Part 2 dose expansion combination studies.

3.1.2.2. Part 2/Cohort 1 and 2

In Part 2, Cohort 1 and 2 expansion cohorts (E1 and E2) will not be initiated until a safety lead-in (S) group of approximately 3-6 patients is enrolled to ensure the combination treatment regimen is safe and tolerable in each patient population (ie, fit and unfit AML). The safety lead-in will use the standard 3+3 dose escalation method to evaluate safety profile (using the DLT criteria described in Section 3.1.1.3) for duration of up to 2 cycles.

3.1.2.2.1. Part 2/Cohort 1 - PF-06747143 Combination in Fit Treatment Naïve AML Patients

Cohort 1 safety lead-in group (S1) will start with 10 mg/kg dose of PF-06747143 and may be escalated to up to 20 mg/kg (the MPD) or de-escalated to below 10 mg/kg based on the pre-defined DLT criteria (see Section 3.1.1.3) and emerging data. After completion of the S1 cohort, PF-06747143 will be administered in combination with intensive therapy (ie, 7+3 daunorubicin and cytarabine) as induction and continue during consolidation and in maintenance for up to a maximum of 6 months (6 cycles) starting from the completion of consolidation, until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first) in newly diagnosed treatment naïve fit AML patients. The expansion cohort (E1) will enroll up to 30 patients.

3.1.2.2.2. Part 2/Cohort 2 – PF-06747143 Combination in Unfit Treatment Naïve AML Patients

Cohort 2 safety lead-in group (S2) will start with 10 mg/kg dose of PF-06747143 and may be escalated to up to 20 mg/kg (the MPD) or de-escalated to below 10 mg/kg based on the pre-defined DLT criteria (see Section 3.1.1.3) and emerging data. After completion of the S2 cohort, PF-06747143 will be administered in combination with a hypomethylating drug (ie, either azacitidine or decitabine, based on institutional guidelines) and may continue for up to 1 year (~12 cycles) from start of therapy or until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first) in newly diagnosed treatment naïve unfit AML patients). The expansion cohort (E2) will enroll up to 30 patients.

3.1.2.2.3. MTD Definition

In Part 2, the MTD of the combinations of PF-06747143 and intensive daunorubicin/cytarabine or PF-06747143 and decitabine/azacitidine will be determined separately within each cohort.

3.1.2.3. Part 2/Cohort 3 – PF-06747143 Single Agent Expansion

An additional single agent PF-06747143 expansion cohort, Cohort 3 (E3), at the MTD/RP2D may be initiated in Part 2 in 15-30 refractory and/or relapsed AML patients. The initiation of this cohort will require that single agent PF-06747143 demonstrates encouraging clinical benefit (eg, significantly improved CR and response duration compared to historical data) in the dose escalation Part 1. Patients in this cohort will be treated until disease progression or relapse, patient refusal or unacceptable toxicity occurs (whichever comes first).

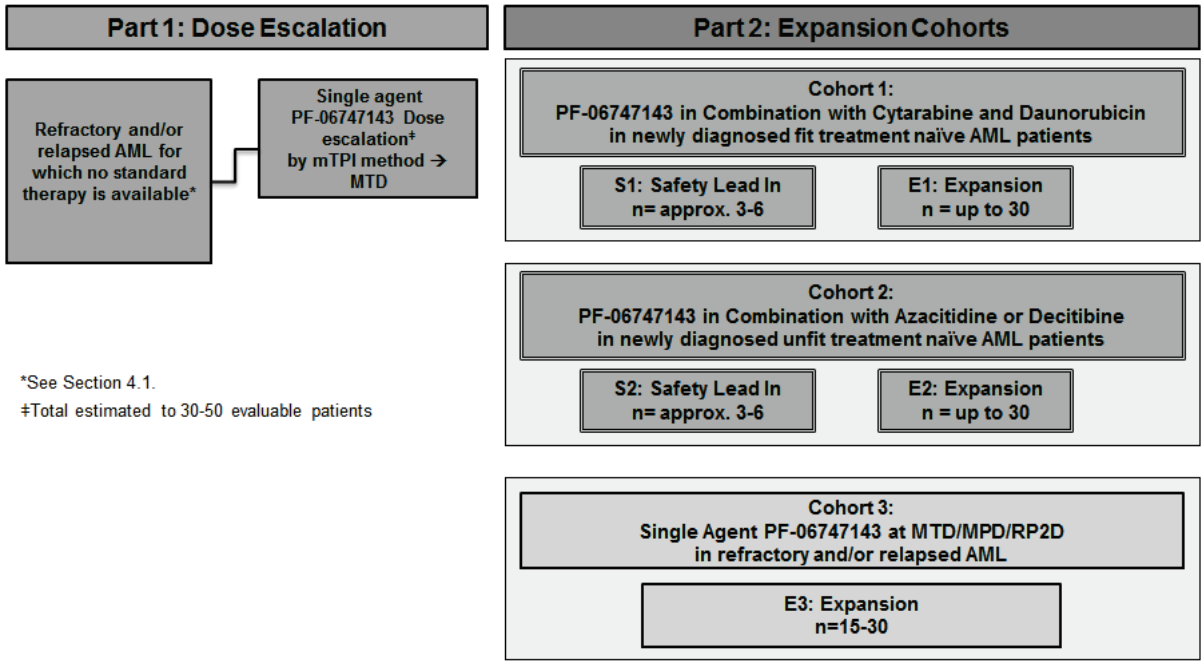
3.1.3. Summary

Approximately 125-140 patients are expected to be enrolled in this study (approximately 30-50 patients in Part 1 (actual number of patients enrolled for Part 1 will depend upon tolerability of PF-06747143 and the number of dose levels required to identify the MTD) and approximately 87-102 patients in Part 2). The study will be conducted in approximately 4 sites for Part 1 and approximately 12-15 sites for Part 2.

Patients who complete the maximum number of cycles/months on study treatment (Section 3.1.2.2.1 and Section 3.1.2.2.2), demonstrate clinical benefit with manageable safety profile and are willing to continue receiving the assigned treatment may be given the opportunity to do so upon agreement between Investigator and sponsor and pending investigational product availability.

All patients who completed treatment will have a 60-day post dose follow-up period.

Figure 2. Overall Study Schema



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 participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

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

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

Inclusion (Part 1 and Part 2 Cohort 3)

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

1. Patients with AML (primary AML diagnosis is based on the 2008 WHO classification with bone marrow (BM) or peripheral blood (PB) blast counts ≥20%[23]) refractory, relapsed and/or patients that are not candidates to receive standard of care and/or refusing the standard care of therapies:
    - Patient received prior chemotherapy and/or standard of care and have relapsed, refractory or Minimal Residual Disease (MRD).[26,27,28,29]
        - MRD is defined as patients showing residual blast 10-14 days post-induction chemotherapy.
2. Life expectancy at least 12 weeks.
3. Hydroxyurea is allowed prior to Day 1 but must be ceased 24 hours prior to first dose. Thereafter, hydroxyurea may be used during Cycle 1 as needed to control total peripheral WBC counts (see Section 5.8.1.).
4. Age ≥18 years old.
5. Eastern Cooperative Oncology Group (ECOG) performance status: 0 to 2.
6. Patients must have been off previous anti-leukemia therapy for at least 2 weeks or 5 half-lives, whichever is shorter if the immediate prior regimen included only weekly chemotherapy; or 4 weeks from any therapy with therapeutic biologics and from any type of investigational therapy prior to the first dose of PF-06747143.
7. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for adverse events (AEs) not constituting a safety risk by investigator judgment.
8. At least 4 weeks since radiotherapy prior to the first dose of PF-06747143. Patients must have passed nadir white blood cell (WBC) and platelet counts, have full recovery or stabilization of absolute neutrophil counts (ANC) and platelet counts, and ANC counts must have recovered from prior toxicity.

9. Adequate renal and hepatic function, including all of the following:

    - Creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;
    - Aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN);
    - Alanine aminotransferase (ALT) ≤3 x ULN;
    - Bilirubin ≤2.0 mg/dL (except patients with Gilbert's Syndrome who must have total bilirubin <3.0 mg/dL).

10. Negative serum/urine pregnancy test (for females of childbearing potential) at screening.

11. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.

12. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

14. Patients who are willing and able to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

Inclusion (Part 2 Cohort 1 and Cohort 2)

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

1. Newly diagnosed, previously untreated de novo or secondary AML population (AML diagnosis is based on the 2008 WHO classification with BM or PB blast counts ≥20%[23]):

    - Cohort 1: Fit to receive intensive remission induction chemotherapy at the time of enrolment. Patients must have NONE of the following criteria to be considered fit:

        - ECOG 2 or 3;

- Serum creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;
- Severe cardiac disease (eg, LVEF <45% by MUGA or ECHO at screening).

- Cohort 2: Unfit to receive or not considered a candidate for intensive remission induction chemotherapy at the time of enrollment based on EITHER:
  - ≥75 years of age, OR
  - <75 years of age with at least 1 of following:
    - Poor performance status (ECOG) score of 2 or 3;
    - Clinically significant heart or lung comorbidities, as reflected by at least 1 of following:
      - LVEF ≤50%;
      - DLCO ≤65% of expected;
      - FEV1 ≤65% of expected;
      - Chronic stable angina or congestive heart failure controlled with medication.
    - Liver transaminases >3 ULN;
    - Other contraindication(s) to anthracycline therapy (must be documented);
    - Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy which must be documented and approved by the study medical monitor before randomization.

2. Hydroxyurea is allowed prior to Day 1 but must be ceased 24 hours prior to first dose. Thereafter, hydroxyurea may be used during Cycle 1 as needed to control total peripheral WBC counts (see Section 5.8.1.).
3. Age ≥18 years old.
4. ECOG performance status: 0 to 3.
5. Adequate renal and hepatic function, including all of the following:
   - Creatinine clearance ≥45 mL/min as measured or as calculated using the method standard for the institution;

- AST ≤3 x ULN;
- ALT ≤3 x ULN;
- Bilirubin ≤2.0 mg/dL (except patients with Gilbert's Syndrome who must have total bilirubin <3.0 mg/dL).

6. Negative serum/urine pregnancy test (for females of childbearing potential) at screening.
7. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.
8. Female patients who are not of childbearing potential (ie, meet at least one of the following criteria):
   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved post-menopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.
9. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
10. Patients who are willing and able to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

Exclusion (Part 1 and Part 2 Cohort 3)

Patients with any of the following characteristics/conditions will not be included in Part 1 and Part 2 Cohort 3 portions of the study:

1. Patients with acute promyelocytic leukemia (APL), AML with known central nervous system (CNS) involvement unless the patient has completed treatment for the CNS disease, has recovered from the acute effects of therapy prior to study entry, and is neurologically stable.
2. Chronic graft versus host disease (GVHD) requiring active systemic treatment, active GVHD with other than Grade 1 skin involvement, or GVHD requiring systemic immunosuppressive treatment. Patients with GVHD receiving systemic immunosuppressive treatment must be able to discontinue the therapy at least 2 weeks prior to the first dose of PF-06747143.

3. Patient is known to be refractory to platelet or packed red cell transfusions per institutional guidelines.

4. Patient is within 3 months post allogenic hematopoietic stem cell transplant or within 30 days post autologous stem cell transplant, and the patient has not recovered from transplant-associated toxicities prior to the first dose of PF-06747143.

5. Known active fungal, bacterial, and/or viral infection requiring systemic therapy within 3 days prior to the first dose of PF-06747143.

6. Prior treatment with a compound targeting CXCR4.

7. Liver cirrhosis Child B or C.

8. Active and clinically significant infection with hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

9. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of PF-06747143 and/or during study.

10. Major surgery within 4 weeks of study entry.

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

12. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver, or recent (within the past year) or active suicidal ideation or behavior.

13. Uncontrolled neoplasia (other than AML).

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

15. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

16. Pregnant females; breastfeeding females; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 60 days after last dose of investigational product.

17. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, 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 New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or QTcF interval >470 msec at screening.

18. Known or suspected hypersensitivity to recombinant human proteins.

Exclusion Criteria (Part 2 Cohort 1 and Cohort 2)

Patients with any of the following characteristics/conditions will not be included in the Part 2 portions of the study:

1. Patients with acute promyelocytic leukemia (APL), AML with known central nervous system (CNS) involvement unless the patient has completed treatment for the CNS disease, has recovered from the acute effects of therapy prior to study entry, and is neurologically stable.

2. Patient is known to be refractory to platelet or packed red cell transfusions per institutional guidelines.

3. Known active fungal, bacterial, and/or viral infection requiring systemic therapy within 3 days prior to the first dose of PF-06747143.

4. Prior treatment with a compound targeting CXCR4.

5. Prior treatment with hypomethylating agents (eg, decitabine or azacitidine) or chemotherapy for antecedent myelodysplastic syndrome (MDS) (Cohort 2).

6. AML associated with favorable risk karyotypes including inv(16), t(8;21), t(16;16), or t(15;17) (Cohort 2).

7. Patients who are candidates for allogeneic stem cell transplant at the time of enrollment (Cohort 2).

8. Liver cirrhosis Child B or C.

9. Active and clinically significant infection with hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

10. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of PF-06747143 and/or during study.

11. Major surgery within 4 weeks of study entry.

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

13. Uncontrolled neoplasia (other than AML).

14. Current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver, or recent (within the past year) or active suicidal ideation or behavior.

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

16. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

17. Pregnant females; breastfeeding females; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 60 days after last dose of investigational product.

18. Any of the following in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, 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 New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or QTcF interval >470 msec at screening.

19. Known or suspected hypersensitivity to recombinant human proteins.

20. The presence of any one of the following hypersensitivities:

- Cohort 1:
  - Hypersensitivity to cytarabine (not including drug fever or exanthema); or
  - Daunorubicin;
- Cohort 2:
  - Hypersensitivity to decitabine or azacitidine;
  - Hypersensitivity to mannitol.

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive PF-06747143, a compound for which the teratogenic risk is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continued for 60 days after the last dose. The investigator or his or her designee, in consultation with the patient, will confirm the patient has selected two appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the patient or the patient's partner.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

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

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

6. Female partner who meets the criteria for non-childbearing potential, defined as:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; have a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for 60 days after the last dose.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study materials.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.[25]

5.1. Allocation to Treatment

Dose level allocation will be performed by the sponsor after patients have given their written informed consent and have completed the necessary screening assessments. The site staff will fax/e-mail a complete Registration Form to the designated sponsor study team member. The sponsor will assign a patient identification number, which will be used on all patient specific documentation at the clinical site.

No patient shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- confirmation of the patient's enrolment;
- specification of the dose level for that patient; and
- permission to proceed with dosing the patient.

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

For part 2 combination study, attribution to the fit or unfit category will be operated based on the patient's characteristics and eligibility by the Investigator and reviewed by sponsor.

5.2. Patient Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigational site.

The site will complete required dosage Preparation Record located in the study/pharmacy manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

5.3. Investigational Product Supplies

Upon activation, study centers will receive a supply of PF-06747143 free of charge by Pfizer. Re-supplies of PF-06747143 will be made during the course of the study based on need.

Cytarabine, daunorubicin, decitabine and azacitidine are commercially available. Locally obtained commercial supplies of these drugs will be used in accordance with local regulations and package insert.

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

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. PF-06747143

PF-06747143 is presented as a sterile solution for intravenous administration. Each vial contains 50 mg/ml in 4 ml (extractable) of aqueous buffered solution in a single use vial. The vial is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

5.3.1.2. Cytarabine, Daunorubicin, Decitabine and Azacitidine (Part 2 only)

Locally obtained commercial supplies of these drugs will be used in accordance with local regulations and package insert. Refer to the local package insert or Institutional Guidelines for detailed formulation, preparation and dispensing information.

5.3.2. Preparation and Dispensing

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

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.

5.3.2.1. PF-06747143

See the Investigational Product Manual (IP Manual) for instructions on how to prepare the investigational product for dispensing and administration.

5.3.2.2. Cytarabine, Daunorubicin, Decitabine and Azacitidine (Part 2 only)

Refer to the local package insert or Institutional Guidelines for detailed formulation, preparation and dispensing information.

5.4. Administration

Investigational product is administered in 28 day cycles, and bone marrow evaluations are performed at specified times to determine clinical response and duration of investigational product administration within the trial.

5.4.1. PF-06747143

PF-06747143 will be administered intravenously QW in 28 day cycles with adjustment for body weight at every cycle. Details for PF-06747143 infusion are provided in the current IP Manual.

All patients should be weighed prior to dosing for every cycle (or within 72 hours) to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of PF-06747143 required for dose preparation. Decision to recalculate

PF-06747143 dose based on the weight obtained at each cycle can be in accordance with institutional practice, however if the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the previous dose, the amount of PF-06747143 required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

Due to the inhibition of the CXCR4 pathway by PF-06747143, patients enrolled in the first two dose levels (0.3 mg/kg and 1.0 mg/kg) will be required to stay in the clinic/hospital overnight (minimum of 24 hours) after receiving the first dose of PF-06747143 to monitor for a potential risk of hyperleukocytosis. On an individual basis, patients may be monitored overnight for the additional doses in Cycle 1 at the treating physician's discretion.

In addition, the use of hydroxyurea and/or leukapheresis is permitted during Cycle 1 following first dose administration to control peripheral WBC counts at the treating Investigators discretion. However, hydroxyurea must be ceased 24 hours prior to the first dose of Cycle 1. Further, total peripheral WBC will be assessed by the Investigator within 12 hours prior to study drug administration during Cycle 1. In the event a patient's total peripheral WBC is ≥75,000/uL, the Investigator shall consult with and obtain the sponsor's agreement to move forward with the study drug administration.

For the first three dose levels (ie 0.3 mg/kg through 3.0 mg/kg), initiation of the first dose of PF-06747143 for each patient in the dose level must be at least 72 hours after the first dose of the previous patient. Patients enrolled in subsequent dose levels will be treated on an outpatient basis with no staggering of patients unless there are safety concerns based on findings at the lower doses.

5.4.2. Cytarabine, Daunorubicin, Decitabine and Azacitidine (Part 2 only)

Administration of commercially available drugs in Part 2 will follow Institutional Guidelines or the package insert.

5.5. Recommended Dose Modifications

Every effort should be made to administer investigational product on the planned dose and schedule.

In the event of significant toxicity dosing may be interrupted, delayed, and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

If a treatment interruption or delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

Refer to Section 5.5.3.1 for adverse events requiring dose reduction at the time of treatment resumption.

Dosing interruptions or delays for any reason of more than 14 days should be discussed with the sponsor before resumption of therapy.

5.5.1. Dosing Interruptions

5.5.1.1. Part 1

Patients experiencing Grade 2 treatment-related toxicity(ies) that remain intolerable even with supportive care or Grade ≥ 3 treatment-related toxicityshould have their treatment interrupted or delayed. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 5.5.3.

If an adverse event requires 2 consecutive doses to be omitted, then treatment is considered interrupted. The doses omitted for toxicity are not replaced. The next scheduled dose will then be the nominal Cycle Day dose. If Day 8 and 15 doses are missed, the next dose will be Day 22. If the Day 15 and 22 doses are missed, the next dose will be Day 1 of the next cycle. If more than 2 doses are missed, dosing will resume as Day 1 of the next cycle. If more than 2 doses are missed, resumption of therapy should be discussed with the sponsor.

5.5.1.2. Part 2

Guidance related to how to manage dose interruption will be provided in a protocol amendment prior to the start of Cohort 1 and 2 in Part 2.

5.5.2. Dose Delays

5.5.2.1. Part 1

If only 1 dose is missed for any reason, the next dose should be given at the next scheduled dosing day. The dose will be considered delayed, and the Day of dosing considered the same as the missed dose. As an example, if the Day 8 dose is missed, the next dose should be given on Day 15, but the dose counted as Day 8.

Doses that are given within 3 days of the scheduled day are not considered missed or delayed. The next dose should be given at the next scheduled dosing Day. As an example, if a clinic appointment is rescheduled from Day 8 to Day 5 or Day 11 because of a clinic holiday, the next dose should be on the regularly scheduled Day 15.

Resumption of treatment following treatment delay for treatment-related toxicity may not occur until all drug-related toxicity has resolved to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the patient).

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 5.5.3, unless expressly agreed otherwise following discussion between the investigator and the sponsor.

5.5.2.2. Part 2

Guidance related to how to manage dose delays will be provided in a protocol amendment prior to the start of Cohort 1 and 2 in Part 2.

5.5.3. Dose Reductions

5.5.3.1. Part 1

Intra-patient dose escalation for PF-06747143 is not allowed.

Following dosing interruption or cycle delay due to toxicity, the PF-06747143 dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, Investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reduction of PF-06747143 by 1 and, if needed, 2 dose levels will be allowed depending on which dose level the patient was enrolled and the type and severity of toxicity encountered. Dose reduction below the starting dose of 0.3 mg/kg will not be permitted. Patients requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and Case Report Form (CRF).

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Patients experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved (see Table 6). Further, no dose reductions are planned for patients experiencing toxicities other than those listed in Table 6. However, patients experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

No dose reduction recommendation is provided for patients experiencing a DLT of prolonged myelosuppression as such patients will be withdrawn from study drug treatment even if adequate recovery is achieved. Patients whose hematologic indices improve prior to meeting the criteria for prolonged myelosuppression >42 days may resume dosing at the next lower dose level or permanently discontinue from treatment at the discretion of the Investigator.

Recommended dose reductions are described in Table 6.

Table 6. Dose Modifications for Investigational Product Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the Investigator.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the Investigator.
• *Grade 4 neutropenia lasting more than 5 days; Febrile neutropenia with any duration (ANC <1.0x 10^9/L and fever ≥38.5°C); • *Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion unexplained by underlying disease; • *Grade 4 anemia, unexplained by underlying disease; • *Treatment delay by more than 14 days due to a hematologic adverse event. • **Grade ≥ 3 Hyperleukocytosis (WBC ≥ 100,000/uL)	• *Hold PF-06747143 until recovery of ANC to ≥1,000/mm^3, platelets ≥50,000/mm^3 and Hgb ≥8.0 g/dL or until values/toxicities returns to pre-treatment levels. • Reduce PF-06747143 by 1 dose level. • If toxicity recurs despite dose reduction, study drug may either be held until recovery and continuation at same dose, or undergo further dose reduction by another dose level. • ** Hold PF-06747143 until total peripheral WBC ≤ 75,000/uL or returns to pre-treatment levels. Consult with sponsor prior to resuming PF-06747143. • Following recovery and consultation with the sponsor, PF-06747143 can be resumed either at the same dose level or reduced by 1 dose level. • If toxicity recurs, following resolution and sponsor consultation, PF-06747143 can be resumed after dose is reduced by 1 level or discontinued at the Investigator's discretion.			

5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the IP manual for storage conditions of the product once prepared.

Storage conditions stated in the SRSD (IB) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

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

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

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

All concomitant treatments must be approved by the sponsor at study entry.

5.8.1. Other Anti-leukemia/Anti-cancer or Experimental Drugs

For control of rapidly progressing leukemic disease, hydroxyurea is allowed prior to Day 1 of study treatment; however, hydroxyurea is to be ceased 24 hour prior to the first dose. However, the use of hydroxyurea and/or leukapheresis is permitted during Cycle 1 to control total peripheral WBC counts at the treating physician's discretion, but other anti-leukemic therapies will not be permitted.

No additional anti-cancer/anti-leukemia therapy will be permitted while patients are receiving PF-06747143. Additionally, the concurrent use of herbal supplements for anti-cancer/anti-leukemia treatment is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of PF-06747143 with radiotherapy, PF-06747143 treatment should be interrupted during palliative radiotherapy, stopping 1 week before and resuming treatment 1 day after.

5.8.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Allopurinol/rasburicase may be administered as needed for tumor lysis prophylaxis or treatment. As noted above, hydroxyurea and/or leukapheresis is also permitted during Cycle 1 to in response to elevated total peripheral WBC counts.

All transfusions provided to the patient during the study must be documented in the source documents and corresponding transfusion CRF page.

5.8.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[31]

Use of erythropoietic growth factors is allowed in Cycle 2 and beyond.

5.8.4. Anti-Diarrheal, Anti Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted in the first cycle for patients enrolled in Part 1. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval.

5.8.5. Anti-inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed.

5.8.6. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purposes is not permitted. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

5.8.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-06747143 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-06747143 is recommended at least 1 week prior to surgery. Postoperatively, the decision to reinitiate treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities.

6.2. Study Period

For treatment period procedures, see Schedule of Activities.

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits (patient withdraws consent for disclosure of future information or for further contact) no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (12-lead), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment-once at the start of screening and once at the baseline visit (predose on Cycle 1 Day 1), immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit (predose on Cycle 1 Day 1) before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the End-of-Treatment and Follow Up visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected.

In the case of a positive hCG test, the patient will be withdrawn from treatment and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

Laboratory assessments will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories.

Table 7. Laboratory Tests

Hematology*	Chemistry	Coagulation	Urinalysis	Pregnancy Test
Hemoglobin	ALT	PT or INR	Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine
Platelets	AST	PTT (or aPTT)		
WBC	Alk Phos			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
Percent Blast Cells	Total Bilirubin***			
	BUN or Urea			
	Creatinine			
	Uric Acid			
	Glucose (non-fasted)			
	Albumin			
	Phosphorous or Phosphate			

* For Cycle 1, the CBC with differential and blast cell assessment in perhipheral blood for pharmacodynamics biomarker labs will also function as the hematology lab safety assessment.
*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only.

7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram (ECG): Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (≥501 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.

If manual reading verifies a QTcF of ≥501 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. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 501 msec. If QTcF interval reverts to less than 501 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 501 msec the investigational product will be held until the QTcF interval decreases to ≤501 msec. Patients will then restart the investigational product at the

next lowest dose level. If the QTcF interval has still not decreased to the acceptable mean on treatment upper limit, ie, 501 msec (Fridericia) after 2-weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

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.

When matched with PK sampling, the ECG must be carried out 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).

7.2. Cardiac Monitoring and Pulmonary Function Tests (Part 2, Cohort 1)

Based on the requirements for treatment with daunorubicin, patients in Part 2, Cohort 1 will be required to have a screening ECHO/MUGA scan to confirm eligibility. Additional scans will also be performed when the cumulative dose of daunorubicin reaches 400 mg/m2, and every 2 cycles thereafter. Decreases in LVEF will be handled according to institutional guidelines.

In addition to cardiac monitoring, pulmonary function tests will also be required at screening. Diffusing capacity of the lungs for carbon monoxide (DLCO) and forced expiratory volume ((FEV) measured during the first forced breath (FEV1)) will be performed to confirm eligibility. Additional assessments may be performed as clinically indicated.

7.3. Pharmacokinetics Assessments

7.3.1. Blood for PK analysis of PF-06747143

Blood samples (3 mL whole blood) to provide serum for the analysis of PF-06747143 concentrations will be collected as outlined in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing and the exact time of the sample collection will always be noted on the CRF. However, samples obtained within the protocol-specified time window will be considered protocol compliant. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

PK samples will be assayed for PF-06747143 using a validated analytical method in compliance with Pfizer standard operating procedures. To increase the understanding of the PK of PF-06747143, samples may be used for the evaluation of the bioanalytical method as well as other internal exploratory purposes. These data will not be included in the clinical study report.

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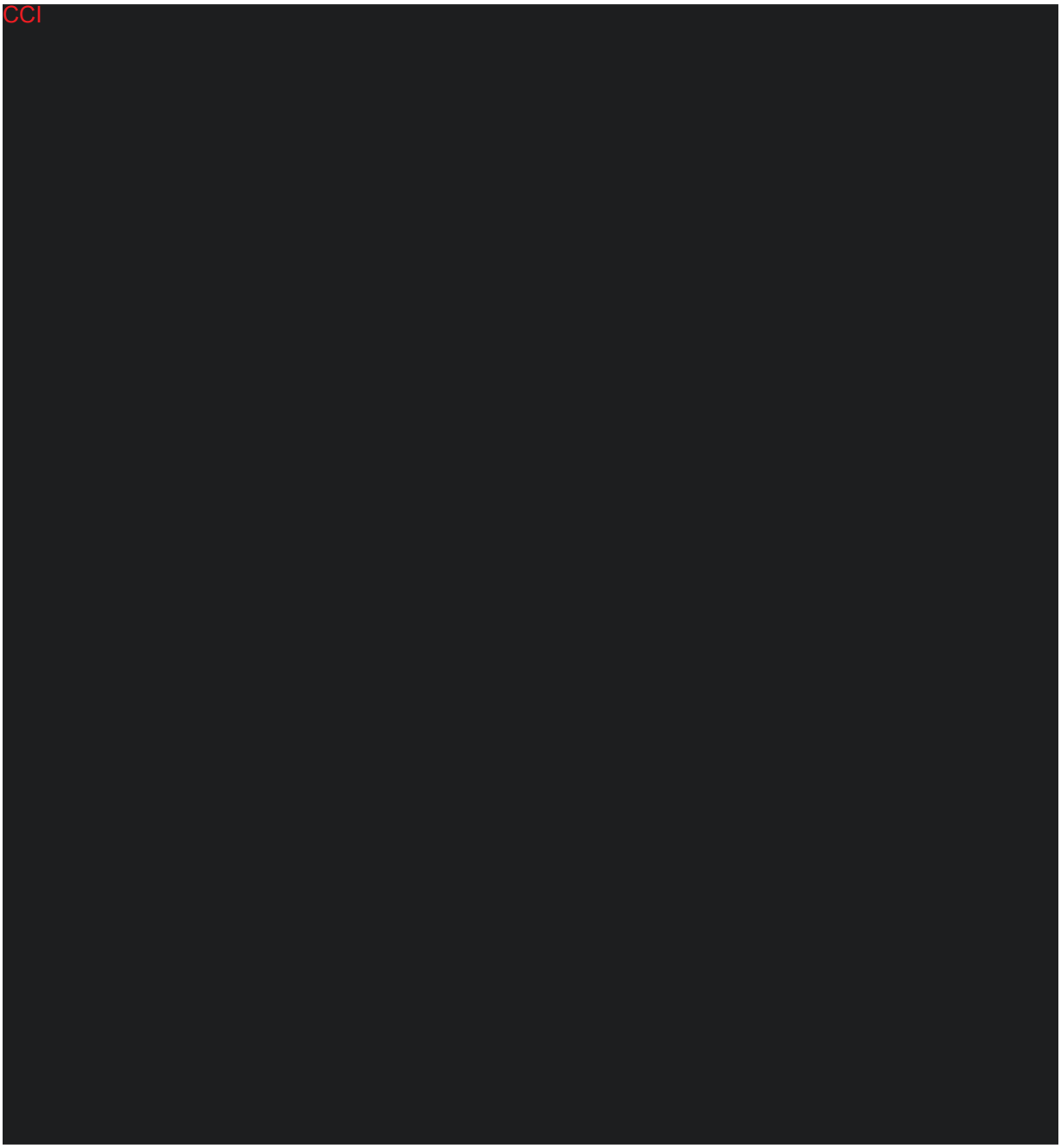

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7.5. Immunogenicity Evaluations

Blood samples (approximately 6 mL) to provide serum for detection of ADA and Nab against PF-06747143 will be collected into appropriately labeled tubes at times specified in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Laboratory Manual.

The ADA samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA will be further analyzed for Nab using a validated assay in compliance with Pfizer standard operating procedures.

For patients with an ongoing AE at the final study visit, ADA/NAb samples may be collected during follow-up at approximately 3 month intervals, if the unresolved AE is thought to be possibly related to ADA, until the AE or its sequelae resolve or stabilize to a level acceptable to the investigator and sponsor.

As part of understanding the immunogenicity of the study medication, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.6. Disease Response Assessment

Disease Response Assessments will be based on Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet.[22]

Note: Details of disease assessment for Part 2 will be provided prior to starting the combination cohorts.

For screening, a fresh bone marrow aspirate sample and biopsy obtained within 14 days of screening is acceptable for patient eligibility and biomarker assessment.

Complete blood counts with white blood cell differential, blast cell assessment and platelet count as well as bone marrow aspiration and biopsy, to assess bone marrow cellularity and percent blasts, are to be conducted at completion of Cycle 1, approximately at Day 28, and prior to starting of every other new cycle of treatment (C3, C5, C7, etc.) until achievement of a complete response. Bone marrow aspirates and/or biopsies and complete blood counts may be obtained at other intervals, if clinically indicated.

For Part 1 of the study and based upon the European LeukemiaNet guidelines[22], disease progression is defined as Relapse or Treatment Failure – Resistant Disease. In such cases, the Investigator should consult with the sponsor regarding PF-06747143 treatment discontinuation.

7.7. Banked Biospecimens

7.7.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA),

ribonucleic (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A 4-mL blood biospecimen **Prep D1 [K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis]** will be collected on Cycle 1 Day 1 and on Day 1 of every cycle through Cycle 6 (if patient remains on study) and at the End-of-Treatment visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

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The banked biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.7.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response Section will be used. Patients may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs 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 sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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 study.

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. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

- If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE 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 AEs 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;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- 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 AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength (a dose within 10% of the appropriate dose is not considered a medication error). Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an 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 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.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as 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 an SAE with CTCAE) grade 5 (see the section on Severity Assessment).

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller);

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute

hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute an hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg,, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg., for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive 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.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. 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 SAE 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 the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that 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 SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a 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 the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an 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 termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure 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, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported 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 infant death as related or possibly related to exposure to the investigational product.

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

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

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

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

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

8.13. Eliciting Adverse Event Information

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

8.14. 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.

8.14.1. 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 AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure 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 or her first awareness of the AE.

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

All 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 SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious 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 study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

Data analysis will be performed on the following analysis populations.

Safety analysis set

The safety analysis set includes all enrolled patients who receive at least one dose of study treatment.

Full analysis set

The full analysis set includes all enrolled patients.

Modified Intent to Treat (mITT) Population

The modified intent to treat (mITT) is the analysis population that will follow the ITT principle and include patients receiving at least 1 dose of study medication with baseline assessment and at least 1 post baseline assessment or disease progression or death before the first disease assessment. The mITT population may be used for conference presentations when the study is still ongoing.

Per protocol analysis set (evaluable for MTD)

The per protocol analysis set includes all enrolled patients who receive at least one dose of study treatment at the dose level of MTD and who do not have major treatment deviations during first cycle. Patients with major treatment deviations in Cycle 1 are not evaluable for the MTD assessment and may be replaced. Major deviations include failure to satisfy major entry criteria (eg, confirmation of the target disease population; signed informed consent), administration of less than 3 out of the 4 doses in Cycle 1 or 80% of the planned Cycle 1 dose (provided that the reduction is not due to toxicity attributable to PF-06747143) or use of other anti-cancer/anti-leukemia treatments during the active treatment and disease follow up phases other than as defined/allowed in this protocol.

PK analysis sets

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

The PK concentration population is defined as all patients who receive PF-06747143, have no major deviations affecting the PK assessment, and have at least one post-dose concentration measurement.

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9.2. Statistical Methods and Properties

9.2.1. Part 1

Part 1 of this study employs a mTPI design to estimate the MTD. The mTPI design employs a Bayesian statistics framework and a simple beta-binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT=0.25) with prior a conjugated prior beta (1,1). Decision rules are based on calculating the unit probability mass (UPM) of three intervals corresponding to underdosing, proper dosing, and overdosing in terms of dose limiting toxicity. A proper dosing interval is centered at the target toxicity rate(pT) of 25% with 5% uncertainty (0.20< pT <0.30). The underdosing interval is (0, 0.20), and the overdosing interval is (0.3, 1). The three dosing intervals are associated with three different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation, and proper-dosing corresponds to staying at the same current dose(S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, decision E, to escalate, will be executed, and the next cohort of patients will be treated at the next-higher dose level.[22]

Under the mTPI design, a trial is terminated when either the lowest dose is above the MTD or a prespecified maximum sample size 50 is reached. Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different trials with different toxicity parameters. More importantly, all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table. The decision rules to “dose escalate” E, “no change in dose” (S), “dose de-escalate” (D) or “dose de-escalate, unacceptable toxicity” (DU) are also described in Appendix 4.

For all dose levels, target size for each cohort will be n= 2 to 4 patients as described in mTPI design.[24] Intermediate dose levels to further evaluate the safety and/or PK may be evaluated following discussion between sponsor and Investigator.

The algorithm will stop if any of the following criteria is met:

- The maximum sample size has been achieved;
- MTD has been identified with sufficient accuracy: at least 9 patients have been accumulated on a dose that is currently estimated to be the MTDF; or
- All doses explored appear to be overly toxic and the MTD cannot be determined.

Due to binomial data variability in small samples, DLT may be observed in a first cohort(s) 0.3 mg/kg simply by chance even when the true P (DLT at 0.3 mg/kg) is fairly low. This could result in the estimated posterior DLT rate at 0.3 mg/kg (and all higher doses) to exceed the targeted 25% very early in the trial, triggering an early stop when very few patients (2-4) have been treated. The following table shows the probability of escalating to the next dose level for a range of underlying true DLT rates. For example, for a DLT that occurs in 10% of patients, there is a greater than 90% probability of escalating. Conversely, for a DLT that occurs with a rate of 70%, the probability of escalating is 3%. It is assumed that dose escalation occurs with either 0/3 or 1/6 patients with DLTs.

Table 9. Probability of Escalating Dose

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

9.2.2. Dose Expansion (Part 2)

Part 2 of this study is intended to confirm the safety and tolerability of the dose selected in Part 1 while assessing the anti-leukemia activity of PF-06747143 in combination with standard dose of intensive chemotherapy. The DLT rate and its 95% confidence interval at the selected dose may be estimated.

9.3. Sample Size Determination

Approximately 125-140 patients are expected to be enrolled in this study (approximately 30-50 patients in Part 1 and 87-102 patients in Part 2).

The exact sample size of the mTPI design in Part 1 cannot be pre specified in advance because it is a dynamic feature of the design. The maximum sample size after which the Part 1 will be stopped and MTD declared is 30-50 patients. Also, a minimum of 9 patients is required to establish the MTD. The actual sample size of Part 1 will depend on the underlying dose toxicity profile and variability in actual data realization.

As for the number of patients treated at each dose, it is expected that the typical number will be 2 to 4 patients for the doses actually studied. For the dose declared as MTD at the end of Part 1, this number will be at least 9 patients (to further investigate the anti-leukemia activity, safety, and PK profile of PF-06747143). However, since not every dose listed will be studied and variable cohort size is allowed, the actual number of patients treated at each dose will vary.

9.4. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the Safety Analysis Set.

AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

AEs, ECGs, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of patients. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical exam information collected during the course of the study will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic exams conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data collected at Screening will be included in the study database.

9.4.1. Analysis of Primary Endpoint

DLT is the primary endpoint of the dose escalation phase (Part 1) of the study. The occurrence of DLTs observed in the dosing cohorts is used to estimate the MTD as described in Section 3.1.1. AEs constituting DLTs will be listed per dose level. Because the intent is to find a desirable dose that meets the tolerability criteria based on DLT rate while demonstrating clinical activity based on response rate, descriptive statistics (n, frequency and percentage) will be reported. Corresponding listings of data will be generated.

9.4.2. Analysis of Secondary Safety Endpoints

9.4.2.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

9.4.2.2. Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

9.4.2.3. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on treatment ECG data. Baseline will be defined as the predose triplicate ECG on Cycle 1 Day 1.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's). Data will be summarized and listed for QT, HR, response rate (RR), PR, QRS, QTcF, and by study dose level in Part 1 and cohort in Part 2. Individual QT` (all evaluated corrections) intervals will be listed by study dose level in Part 1 and cohort in Part 2. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by time point and study dose level in Part 1 and cohort in Part 2. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time. QT intervals will be corrected for heart rate (QTc) using Fridericia's correction factors (QTcF).

The number (%) of patients with maximum post dose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

	Borderline (msec)	**Prolonged (msec)**
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of patients with corrected and uncorrected QT values ≥500 msec will be summarized.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction method will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline (pretreatment) vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.5. Efficacy Analysis

In this First In Patient study anti-leukemia activity is a secondary objective. Anti-leukemia activity will be presented in the form of patient data listings that include, but will not be limited to, AML type, starting dose, leukemia assessments, leukemia response at each visit, and best overall response. In addition, progression date, death date, date of first response and disease assessment date, and date of last assessment will also be listed.

Cohort 1 and 2:

Clinical assessment will be conducted while the study is ongoing and as these patients are receiving SOC, the enrollment can proceed until N=30 and depending on clinical observation of safety and activity, enrollment can stop prior to 30 patients. Posterior probabilities, calculated on a sample size of N=20-30, higher than 88% of an ORR ≥40% in the unfit combo group or a 60% of an ORR ≥70% in the fit cohort will be considered as sufficient evidence of activity for proceeding to Phase 2 in the respective indication (see table below).

True ORR	**Posterior Probability (x% that the true ORR ≥y%)**	**Posterior Probability (x% that the true ORR<y%)**
10/30=33%	40% (25%)	35% (54%)
15/30=50%	40% (88%)	35% (2.3%)
20/30=66%	70% (30%)	65% (47%)
25/30=83%	70% (93%)	65% (1.8%)

For example, a 50% true ORR (15 out of 30 patients) would predict a posterior probability equal to 88% that the true ORR is not inferior to 40% and a posterior probability equal to 2.3% that the true ORR is inferior to 35%. Posterior probabilities higher than 88% of an ORR ≥40% in the unfit combo group or a 60% of an ORR ≥70% in the fit cohort will be considered as sufficient evidence of activity for proceeding to Phase 2 in the respective indication.

Cohort 3:

Enrollment of patients in Cohort 3 (single agent PF-06747143) may be discontinued if minimal or no anti-tumor activity is observed in the first 15 evaluable patients for that cohort. Assuming a non-informative prior (ie, beta[1,1]) if ≤2 out of 15 patients have tumor response, this would predict a posterior probability (Beta-Binomial) equal to 0.90 and 0.65 that the true response is inferior to 30% and 20% respectively. On the other hand, if 10 out of 20 patients have tumor response, this would predict a posterior probability equal to 0.83 that the true response is not inferior to 40% and a posterior probability equal to 0.03 (3%) that the true response is inferior to 30%. Posterior probabilities may be calculated by using informative priors based on the antitumor activity that may be observed during Part 1 (eg, 3 out of 6 patients experience tumor response in the dose escalation phase). These

posterior probabilities will be assessed for Cohort 3 when at least the first 15 patient are enrolled. Posterior Probabilities >0.90 of an ORR<30% (eg, 0,1,2 out of 15) will provide evidence of no substantial anti-tumor activity for that indication. Posterior Probabilities >0.90 of an ORR<30% (eg, 0,1,2 out of 15) will provide evidence of no substantial anti-tumor activity for that indication.

9.5.1. Analysis of Overall Response

For patients to be considered evaluable for efficacy they must have received at least one dose of study medication and have a baseline disease assessment. The main goal of confirmation of objective response is to avoid an incorrect estimation of the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in leukemia measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

9.6. Analysis of Pharmacokinetics and Pharmacodynamics

9.6.1. PF-06747143 Pharmacokinetic Analysis

PF-06747143 concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose level (Part 1), cohort (Part 2: S1, S2), cycle, day and nominal time. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day (single dose and steady state) using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

Serum PF-06747143 concentrations from patients in Part 1 and Cohorts S1 and S2 in Part 2 will be analysed for PK parameters. Single dose PK parameters estimated will include the maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration versus time curve (AUC_{last}), and, if data permit, area under the concentration versus time curve to infinity (AUC_{inf}), apparent volume of distribution (V_d), terminal elimination half-life ($t_{1/2}$), clearance (CL), using non-compartmental analysis. Multiple dose PK parameters estimated will include $C_{max, ss}$, $C_{min, ss}$, $AUC_{\tau, ss}$, ($AUC_{\tau, ss}$ /AUC_{τ}), and if data permit, CL, $t_{1/2}$ V_{ss}, and accumulation ratio (R_{ac}) (assuming steady state is achieved). The PK parameters will be summarized descriptively by dose level (Part 1), cohort (Part 2: S1, S2), cycle, day and nominal time. For the concentration time data from the Cycle 1, Day 1 and Cycle 2, Day 1 dose, dose normalized AUC_{inf} (AUC_{τ} at steady state), and C_{max} will be plotted against dose (using a logarithmic scale) by dose level for Part 1 and by Cohorts S1 and S2 for Part 2. These plots will include individual patient values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

The observed accumulation 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 for each dose.

Trough concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady state.

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9.7. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, and analysis of biomarker endpoints. Data will also be displayed graphically, where appropriate. Additional details of the analyses are outlined in the SAP.

9.7.1. Immunogenicity

The development of anti PF-06747143 antibodies will be measured using validated assays. Listings and summary tabulations of number of patients and incidence of ADA at baseline (pretreatment) and post treatment will be generated.

Potential impact of immunogenicity on PK and clinical responses including PD markers, safety/tolerability and efficacy of PF-06747143 will be explored, if data is warranted.

9.8. Data Safety Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

Surveillance for serious adverse events (SAEs) according to regulatory guidelines;

Discussions between the Investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term 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 are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents 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 investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), 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.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board /Ethics Committee

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

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

12.2. Ethical Conduct of the 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 GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, 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 or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients’ personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study patient 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 before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that 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 (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial 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 Other Participating Countries

End of trial in all other participating countries is defined as last patient last visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06747143 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) prior to their next scheduled treatment day. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication 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, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicentre study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. 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, the 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 CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

Abbreviation	Term
Ab	Antibody
ACRIN	American College of Radiology Imaging Network
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
CCI [redacted]	
ANC	absolute neutrophil count
ANOVA	analysis of variance
APL	acute promyelocytic leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BM	bone marrow
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
C	Concentration
CCI [redacted]	
CDC	complement dependent cytotoxicity
CDS	core data sheet
Ceff	effective concentration
CHF	congestive heart failure
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
Cmax	maximum concentration
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response
CRF	case report form
CRM	Continuous Reassessment Method
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation

Abbreviation	Term
CCI [redacted]	
D	day
DLCO	diffusing capacity of the lungs for carbon monoxide
DLI	Donor Lymphocyte Infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	Duration of Response
EC	ethics committee
EC50	half maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
e.g.	for example
EFS	Event-Free Survival
etc	'and other things' or 'and so forth'
EudraCT	European Clinical Trials Database
FCGR3A	Fcgamma receptor
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GITMO	Italian Group for Bone Marrow Transplantation
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone agonist
GVHD	graft versus host disease
HAV	hepatitis A virus
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose)
HR	heart rate
IB	investigator's brochure

Abbreviation	Term
ICH	International Conference on Harmonisation
ID	identification
i.e.	that is
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDH	lactate dehydrogenase
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mITT	modified intent to treat
mTPI	modified toxicity probability interval
MD	multiple dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MM	multiple myeloma
CCI [redacted]	
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N/A	not applicable
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
CCI [redacted]	
OBD	optimal biological dose
OS	overall survival
pT	target probability
PB	peripheral blood
PCD	primary completion date
CCI [redacted]	
PD	progressive disease
PET	positron emission tomography
PFS	Progression-Free Survival
PFS	prefilled syringe
B- or T-PLL	prolymphocytic leukemia
PK	pharmacokinetics

Abbreviation	Term
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QW	every week
QD	every day
QT	time between the start of the Q wave and the end of the T wave
Q2W	every two weeks (every other week)
R	ratio
RBC	red blood cell
RD	Response/Remission Duration
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	single dose
SIB	suicidal ideation and behavior
SIE	Italian Society of Hematology
SIES	Italian Society of Experimental Hematology
SPEP	serum protein electrophoresis
SPC	Summary of Product Characteristics
SRSD	single reference safety document
T	Time
$T_{1/2}$	terminal elimination half-life
TBNK	T cell, B cell and natural killer cell
TBR	tumor background ratio
TMDD	target-mediated drug disposition
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
UVB	ultraviolet B light
V	volume of distribution
WBC	white blood cell count
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia

Appendix 2. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Criterion
0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90 - 100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example light housework or office work (Karnofsky 70 - 80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours (Karnofsky 50 - 60)
3	Capable of only limited self care, confined to bed or chair 50% or more of waking hours. (Karnofsky 30 - 40)
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair. (Karnofsky 10 - 20)
5	Death

Appendix 3. Management of Allergic Reactions/Cytokine Release Syndrome or Anaphylaxis

In the event of allergic/infusion reactions, Investigators should institute treatment measures according to best medical and nursing practice.

The following treatment guidelines should be employed:

If chills and fever occur, the infusion should be interrupted. Patients may be treated symptomatically and the infusion should be restarted at 50% of the original rate.

NCI-CTCAE Grade 1 allergic reaction or cytokine release syndrome

1. Decrease PF-06747143 infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion. Protocol treatment will be discontinued.

NCI-CTCAE Grade 2 allergic reaction or cytokine release syndrome

1. Stop PF-06747143 infusion.

2. Administer bronchodilators, oxygen, acetaminophen, etc. as medically indicated.

3. Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop infusion. Protocol treatment will be discontinued.

NCI-CTCAE Grade 3 or Grade 4 allergic reaction or cytokine release syndrome or anaphylaxis

1. A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.

2. A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 70% or less.

Treatment of Grade 3 or Grade 4 allergic reaction or cytokine release syndrome or anaphylaxis

1. Stop the PF-06747143 infusion immediately and disconnect infusion tubing from the patient.

2. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically indicated.

3. Telephone sponsor or designated representative to report an SAE and fax SAE worksheet.

For a NCI-CTCAE Grade 3 or 4 hypersensitivity reaction, protocol treatment will be discontinued.

Re-treatment following Grade 1 or Grade 2 allergic reactions or cytokine release syndrome

1. Once the PF-06747143 infusion rate has been decreased due to an allergic reaction or cytokine release syndrome, it will remain decreased for all subsequent infusions.

2. If the patient has a second reaction at the lower infusion rate, the infusion should be stopped and the patient should receive no further PF-06747143.

3. If the patient experiences a Grade 3 or 4 allergic reaction, cytokine release syndrome, or anaphylaxis at any time, the patient should receive no further PF-06747143.

4. If there are questions concerning whether an observed reaction is consistent with an allergic reaction, cytokine release syndrome, or anaphylaxis, the medical monitor should be contacted immediately to assist with grading the reaction.

PK, PD and ADA sampling should continue as long as the sampling does not interfere with the medical treatment of the patient.

Appendix 4. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design

Number of Patients

Number of Toxicities

	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	S	S	E	E	E	E	E	E
2		DU	D	D	S	S	S	S	S	S	S	S
3			DU	DU	DU	D	S	S	S	S	S	S
4				DU	DU	DU	DU	DU	D	S	S	S
5					DU	DU	DU	DU	DU	DU	D	S
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E=Escalate to the next higher dose

S=Stay at the current dose

D=De-escalate to the next lower dose

DU=The current dose is unacceptably toxic

Probability of target toxicity=0.25

Escalation/De-escalation algorithms for total number of patients treated at the current dose level (current and previous cohorts)

- With 2 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> de-escalate to the lower dose
  - 2 DLTs -> de-escalate and consider current dose as intolerable
- With 3 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> remain at the same dose
  - 2 DLTs -> de-escalate
  - 3 DLTs -> de-escalate and consider current dose as intolerable
- With 4 patients treated at current dose level
  - 0 DLT -> escalate
  - 1 DLT -> remain at the same dose
  - 2 DLTs -> de-escalate
  - 3-4 DLTs -> de-escalate and consider current dose as intolerable

- With 5 patients treated at current dose level
  - 0 DLT -> escalate
  - 1-2 DLTs -> remain at the same dose
  - ≥3 DLTs -> de-escalate and consider current dose as intolerable
- With 6 patients treated at current dose level
  - 0 DLT -> escalate
  - 1-2 DLTs -> remain at the same dose
  - 3 DLTs -> de-escalate
  - 4-6 DLTs -> de-escalate and consider current dose as intolerable
- With 7 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-3 DLTs -> remain at the same dose
  - >4 DLTs -> de-escalate and consider current dose as intolerable
- With 8 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-3 DLTs -> remain at the same dose
  - >4 DLTs -> de-escalate and consider currentdose as intolerable
- With 9 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-3 DLTs -> remain at the same dose
  - 4 DLTs -> de-escalate
  - 5-9 DLTs -> de-escalate and consider current dose as intolerable
- With 10 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-4 DLTs -> remain at the same dose
  - >5 DLTs -> de-escalate and consider current dose as intolerable
- With 11 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-4 DLTs -> remain at the same dose
  - 5 DLTs -> de-escalate
  - 6-11 DLTs -> de-escalate and consider current dose as intolerable
- With 12 patients treated at current dose level
  - 0-1 DLT -> escalate
  - 2-5 DLTs -> remain at the same dose
  - 6-12 DLTs -> de-escalate and consider current dose as intolerable