A PHASE 1 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF PF-04449913 (GLASDEGIB), AN ORAL HEDGEHOG INHIBITOR, ADMINISTERED AS A SINGLE AGENT IN JAPANESE PATIENTS WITH SELECT HEMATOLOGIC MALIGNANCIES AND IN COMBINATION WITH INTENSIVE CHEMOTHERAPY, LOW-DOSE ARA-C, OR AZACITIDINE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA OR HIGH-RISK MYELODYSPLASTIC SYNDROME

Compound:	**PF-04449913**
Compound Name :	**Glasdegib**
US IND Number :	CCI
European Clinical Trial Database (EudraCT) Number:	**"Not Applicable"**
Protocol Number:	**B1371005**
Phase:	**Phase 1**

Document History

Document	Version Date	Summary of Changes
Protocol Amendment 8	25 March 2021	• Schedule of Activities Table 3: The tests and assessments in the Expansion Cohort of LDAC combination for efficacy (unfit patients) were simplified. • Section 1.2.8: Updated Summary of Safety, Efficacy and PK data • Section 7.1: Text was added to reflect the simplification of the safety assessment. • Section 9: Updated the final analysis. Following Table and Sections were update according to the Protocol Administrative Change Letter dated 02 June 2020 regarding COVID-19 related reasons. • Table 6 • Section 4.3 • Section 5.3.2 • Section 5.3.3 • Clarified throughout what is no longer required after Protocol Amendment 8 or will be conducted according to local clinical practice.
Protocol Amendment 7	21 January 2019	• The Expansion Cohort of LDAC combination for efficacy (unfit patients) was added and all protocol contents related to this Cohort were updated. • Minor administrative changes were made to correct typographical

Document	Version Date	Summary of Changes
		errors, emphasize subtle points, or improve internal consistency with the protocol.
Protocol Amendment 6	17 July 2018	• Survival follow-up was added in the Combination Cohort 1 (unfit patients). • Minor administrative changes were made to correct typographical errors, emphasize subtle points, or improve internal consistency with the protocol.
Protocol Amendment 5	8 November 2017	• The Continuation Cohort (Monotherapy Cohort) was added and all protocol contents related to Continuation Cohort were updated.
Protocol Amendment 4	4 July 2017	• The Combination Cohort 3 (Azacitidine Combination) was added and all protocol contents related to Combination Cohort 3 were updated. • Minor administrative changes were made to correct typographical errors, emphasize subtle points, or improve internal consistency with the protocol.
Protocol Amendment 3	2 March 2017	• Evaluation of PD data at the 25 mg QD dose was added. • Table 7: Sample collection timing was clarified. • Eligibility criteria corrected an inconsistency for Combination cohorts inclusion criteria #2 (Acute Promyelocytic Leukemia (APL) patients with t(15;17) are excluded). • Table 17: Recommended Dose Modifications for PF-04449913

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		related QTcF prolongation was added. • Table 18: Recommended Dose Modifications for PF-04449913 in case of drug class related AEs was added. • Sections 5.3.10 and 7.1.5: Revised dosing modification guidelines for treatment-related QTcF prolongation. • Minor administrative changes were made to correct typographical errors, emphasize subtle points, or improve internal consistency with the protocol. • Updated safety data throughout section 1. • Updated information in section 5.5. Concomitant Medications.
Protocol Amendment 2	11 August 2014	• Transplant exclusion criteria has been removed. • The schedule of events for biomarker sample collection has been modified. • The schedule of events added creatine kinase at select timepoints. • The bone marrow assessment schedule has clarified aspirate collection requirements, changed initial hematologic recovery bone marrow collection from 7 days to 14 days, and for Unfit patients changed the timepoints to Cycle 3/Day 1 and every third cycle to better align with standard of care and removed the treatment duration criteria.

Document	Version Date	Summary of Changes
		• For fit patients Maintenance Day 15 visit has been removed. • Continuous PF-04449913 dosing during induction and/or consolidation cycles > 28 days has been clarified. • Concomitant medication restrictions have been clarified. • Appendix 11 containing list of drugs with known risk of Torsade de Pointes has been added. • Appendix 12 containing list of strong and moderate CYP3A4/5 inhibitors has been added. • Appendix 13 containing list of strong and moderate CYP3A4/5 inducers has been added. • Updates to Adverse Event Reporting sections and Publication of Study Results section were added to align with revised protocol template. • Minor administrative changes were made to correct typographical errors, emphasize subtle points, or improve internal consistency with the protocol.
Protocol Amendment 1	12 December 2013	• An additional informed consent form will be obtained at the end of Cycle 1. • Removed previously untreated patients from the Inclusion Criteria for Monotherapy Cohort. • Administrative corrections and clarifications made throughout the protocol.

Document	Version Date	Summary of Changes
Original protocol	20 November 2013	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and Institutional Review Boards (IRBs)/Ethics Committees (ECs).

PROTOCOL SUMMARY

Indication:

Hematologic malignancies, including acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS).

Objectives:

The study incorporates six cohorts: 1) a monotherapy cohort in which PF-04449913 is administered as a single agent in up to 15 Japanese patients with select advanced hematologic malignancies, 2) two combination cohorts (combination cohorts 1 and 2) in which PF-04449913 is administered with different chemotherapy backbones in up to 12 Japanese patients (6 in each different combination cohort) with previously untreated AML or high-risk MDS, 3) expansion cohort of low-dose ara-c [LDAC] combination for efficacy in which PF-04449913 is administered with LDAC in 15 Japanese patients with previously untreated AML or high-risk MDS, 4) additional one combination cohort (combination cohort 3) in which PF-04449913 is administered with azacitidine in 6 Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy, and 5) a continuation cohort (monotherapy cohort) in which PF-04449913 is administered as a single agent in 1 Japanese myelofibrosis (MF) patient who has been treated in Study B1371013. Specific objectives and endpoints for each cohort are outlined below. A total of up to 49 patients will be treated across all six cohorts.

Monotherapy Cohort:

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered as monotherapy in Japanese patients with select advanced hematologic malignancies.

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of PF-04449913 as monotherapy in Japanese patients with select advanced hematologic malignancies;
- To evaluate the pharmacodynamics (PD) of PF-04449913 as monotherapy in Japanese patients with select advanced hematologic malignancies;
- To assess preliminary evidence of clinical efficacy of PF-04449913 administered as monotherapy in Japanese patients with select advanced hematologic malignancies.

Combination Cohorts 1 and 2 (Unfit and Fit Patients):

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered in combination with LDAC (Combination Cohort 1, unfit patients), or cytarabine/daunorubicin (7:3)

(Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML, or high-risk MDS.

Secondary Objectives

- To evaluate the PK of PF-04449913 and potential drug-drug interaction (DDI) between PF-04449913 and LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) administered to Japanese patients with previously untreated AML or high-risk MDS;

- To evaluate the PD of PF-04449913 administered in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS;

- To assess any preliminary evidence of clinical efficacy (including disease-specific measures) of PF-04449913 administered in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS.

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Primary Objective

- To evaluate the efficacy (Disease Modifying Response [DMR][a] rate) of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS.

Secondary Objectives

- To evaluate the safety of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS;

- To evaluate the efficacy (including overall survival [OS]) of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS;

- To evaluate the PK and PD of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS.

[a] Disease Modifying Response (DMR) rate includes Complete Remission (CR), CR with incomplete blood count recovery (CRi), Morphologic Leukemia-Free State (MLFS), marrow CR (mCR) and Partial Remission (PR) (Appendix 5 and Appendix 8).

Combination Cohort 3 (Azacitidine Combination):

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered in combination with azacitidine in Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy.

Secondary Objectives

- To evaluate the PK of PF-04449913 and azacitidine when administered to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;

- To evaluate the PD of PF-04449913 administered in combination with azacitidine to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;

- To assess any preliminary evidence of clinical efficacy including OS of PF-04449913 administered in combination with azacitidine to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy.

Continuation Cohort (Monotherapy Cohort):

- To assess the safety of PF-04449913 administered as monotherapy in the Japanese MF patient who has been treated with PF-04449913 in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013.

Endpoints:

Monotherapy Cohort:

Primary Endpoint

- First-cycle dose-limiting toxicities (DLTs); Type, incidence, severity [graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0], timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913;

- Potential biomarkers of target modulation, response or resistance to PF-04449913 in Japanese patients with advanced hematologic malignancies;

- Objective disease response as assessed using the response criteria for the hematologic disease under study.

Combination Cohorts 1 and 2 (Unfit and Fit Patients):

Primary Endpoint

- First-cycle DLTs; Type, incidence, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913 with: (i) LDAC, and (ii) cytarabine/daunorubicin (7:3) combinations;

- Potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with chemotherapy in Japanese patients with previously untreated AML or high-risk MDS;

- Objective disease response, as assessed using the appropriate response criteria for AML or MDS.

- Survival status (only Combination Cohort 1)

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Primary Endpoint

- DMR rate

Secondary Endpoints

- Type, incidence, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities;

- OS;

- Objective disease response, as assessed using the appropriate response criteria for AML or MDS; complete remission (CR) rate; duration of response; time to response;

- PK and Potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with LDAC in Japanese patients with previously untreated AML or high-risk MDS.

Combination Cohort 3 (Azacitidine Combination):

Primary Endpoint

- First-cycle DLTs; Type, incidence, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913 and azacitidine;
- OS;
- Potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with azacitidine in Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;
- Objective disease response, as assessed using the appropriate response criteria for AML; duration of response; time to response.

Continuation Cohort (Monotherapy Cohort):

- Type, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; laboratory test abnormalities.

  Efficacy-related data will not be collected in this cohort.

Overall Study Design:

This is an open-label, multi-center, Phase 1 study of PF-04449913 in Japanese patients. PF-04449913 will be administered orally as a single agent in up to 15 patients with select advanced hematologic malignancies (Monotherapy Cohort), or in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine and daunorubicin (7:3) (Combination Cohort 2, fit patients) in up to a total of 12 (6 in Cohort 1 and 6 in Cohort 2) previously untreated patients with AML or high-risk MDS. PF-04449913 will be administered in combination with LDAC in a total of 15 patients with previously untreated AML or high-risk MDS (Expansion Cohort of LDAC combination for efficacy, unfit patients). PF-04449913 will also be administered in combination with azacitidine in a total of 6 patients with previously untreated AML who are eligible for non-intensive chemotherapy (Combination Cohort 3, Azacitidine Combination). PF-04449913 will be administered as a single agent in 1 Japanese MF patient who has been treated in Study B1371013 and on the study treatment at the time of the study discontinuation [Continuation Cohort (Monotherapy Cohort)].

Monotherapy Cohort:

The monotherapy cohort will evaluate the safety and tolerability of PF-04449913 administered as a single agent once daily continuously. Cycle 1 will be preceded by a single lead-in dose of PF-04449913 administered on Day -5 (lead-in period) in order to characterize the single-dose PK of PF-04449913 prior to initiation of continuous dosing in the first cycle of treatment. From Cycle 1/Day 1 onwards, PF-04449913 will be administered continuously once daily, in 28-day cycles.

A standard 3+3 dose escalation design will be used to evaluate the tolerability of PF-04449913 with 3-6 patients per dose level. Two dose levels of PF-04449913 (Dose Level 1: 50 mg once daily (QD) and Dose Level 2: 100 mg QD) will, in the first instance, be investigated in sequential cohorts of patients. Intermediate (such as 80 mg QD) or lower dose levels (such as 25 mg) may be explored at any time during the study if this is clinically and scientifically warranted. Study centers will receive a notification if additional dose levels are explored.

The DLT evaluation period includes the PK lead-in period, and the first cycle of treatment. Dose escalation to the 100 mg QD dose level will occur if <1/3 or <2/6 patients at the 50 mg QD dose level experience dose-limiting toxicities (DLT) during the first cycle of treatment. If ≤1 patient experiences a DLT event in the first 3 patients, an additional 3 patients will be enrolled to give a total of 6 patients in the 100 mg QD cohort. If ≤1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the 100 mg QD dose level in the monotherapy cohort will be deemed confirmed, and the study will proceed to the combination cohort. If 2 or more of the 6 patients treated at 100 mg QD in the monotherapy cohort experience a DLT by the end of Cycle 1, an intermediate dose level (80 mg QD) may be explored in the monotherapy cohort prior to proceeding with the combination cohort. If two or more of the 3 or 6 patients treated at 50 mg QD in the monotherapy cohort experiences a DLT by the end of Cycle 1, the dose escalation will be terminated, and a lower dose may be explored.

As of 7 August 2014, it was decided by the study team that a lower dose level (25 mg QD) will be explored in the study, since evaluation of PD data at the 25 mg QD dose is scientifically warranted. Up to 3 patients will be enrolled at the 25 mg dose level. DLT evaluation will be performed on this dose level, however, it will not be used for the dose escalation decision, or for the determination of whether or not to proceed with the combination cohort. The Sponsor will discuss with the Investigator to confirm that there is no safety issue for patients enrolled at this dose level.

Treatment with PF-04449913 may continue for up to 12 cycles or until disease progression or relapse, patient withdrawal, or unacceptable toxicity occurs (whichever is first). Patients who complete 12 cycles of treatment will be deemed to have completed the study. However, patients who complete 12 cycles of study treatment who demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving the study treatment, may be given the opportunity to do so following agreement between the Investigator and Sponsor, and

pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed as per Table 1 (See Schedule of Activities).

The study may at any time evaluate additional dose levels of single-agent PF-04449913 based upon the emerging data from the ongoing pre-clinical and clinical studies, following discussion between the Investigators and the Sponsor.

Combination Cohorts:

The combination cohorts will evaluate the safety and tolerability of PF-04449913 at the starting dose of 100 mg once daily continuously administered in combination with 3 different chemotherapy regimens.

Combination Cohort 1 (Unfit Patients):

In this cohort, patients who are "unfit for intensive chemotherapy" based on predefined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with LDAC over 28 day cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. The DLT evaluation period includes the first cycle of treatment. If ≤ 1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the combination will be deemed confirmed. If 2 or more of the 6 patients experience a DLT by the end of Cycle 1, additional lower dose levels may be tested, applying identical criteria to those outlined above with respect to DLT events.

Treatment with PF-04449913 in combination with LDAC may continue for up to 12 cycles or until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever is first). Unfit patients who complete 12 cycles of study treatment will be deemed to have completed the study. However, patients who complete the 12 cycles of study treatment and demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving the study treatment (monotherapy with PF-04449913 or combination therapy), may be given the opportunity to do so following agreement between the Investigator and Sponsor, and pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed as listed in Table 2 (Schedule of Activities). This cohort includes survival follow-up.

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

In this cohort, patients who are "unfit for intensive chemotherapy" based on predefined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with LDAC over 28-day cycles.

A total of 15 patients will be treated in this cohort and DMR rate will be evaluated. Treatment with PF-04449913 in combination with LDAC may continue until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever is first). All patients will be followed for survival every 8 weeks up to 2 years from the first dose of

the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy (follow-up on survival status will no longer be required after Protocol Amendment 8).

Combination Cohort 2 (Fit Patients):

In this cohort, patients defined as "fit for intensive chemotherapy" based on pre-defined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with daunorubicin and cytarabine during induction and consolidation. For the first induction cycle only, PF-04449913 will commence on Day -3 and will then be given once daily continuously for the duration of treatment. Following completion of induction and consolidation, single-agent PF-04449913 may be given to eligible patients as maintenance therapy for a maximum of 6 cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. If ≤1 of the 6 patients experiences a DLT event by the end of Induction Cycle 1, the tolerability of the combination will be confirmed. If 2 or more of the 6 patients experience a DLT by the end of Induction Cycle 1, additional lower dose levels may be tested using identical criteria to those outlined above with respect to DLT events.

Treatment will continue until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever is first). Fit patients who complete induction, consolidation and 6 cycles of maintenance with PF-04449913 will be deemed to have completed the study treatment. However, patients who complete the 6 cycles of maintenance and demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving single-agent PF-04449913, may be given the opportunity to do so following agreement between the Investigator and Sponsor, and pending study drug availability. If treatment continues beyond the 6 cycles of maintenance, study procedures should continue to be performed as listed in Table 3 (Schedule of Activities).

Combination Cohort 3 (Azacitidine Combination):

In this cohort, patients with previously untreated AML and eligible for non-intensive chemotherapy will receive PF-04449913 once daily continuously at the starting dose of 100 mg in combination with azacitidine over 28 day cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. The DLT evaluation period includes the first cycle of treatment. If ≤1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the combination will be deemed confirmed. If 2 or more of the 6 patients experience a DLT by the end of Cycle 1, the investigator and the sponsor will review all available safety data and discuss the next steps.

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until death, unacceptable toxicity, or patient refusal (whichever is first). If documentation of disease progression occurs within the first 6 cycles of study treatment, the patient **SHOULD NOT** be

withdrawn from study treatment following agreement between the Investigator and Sponsor if, in the Investigator's judgment, the patient is still likely to receive clinical benefit.

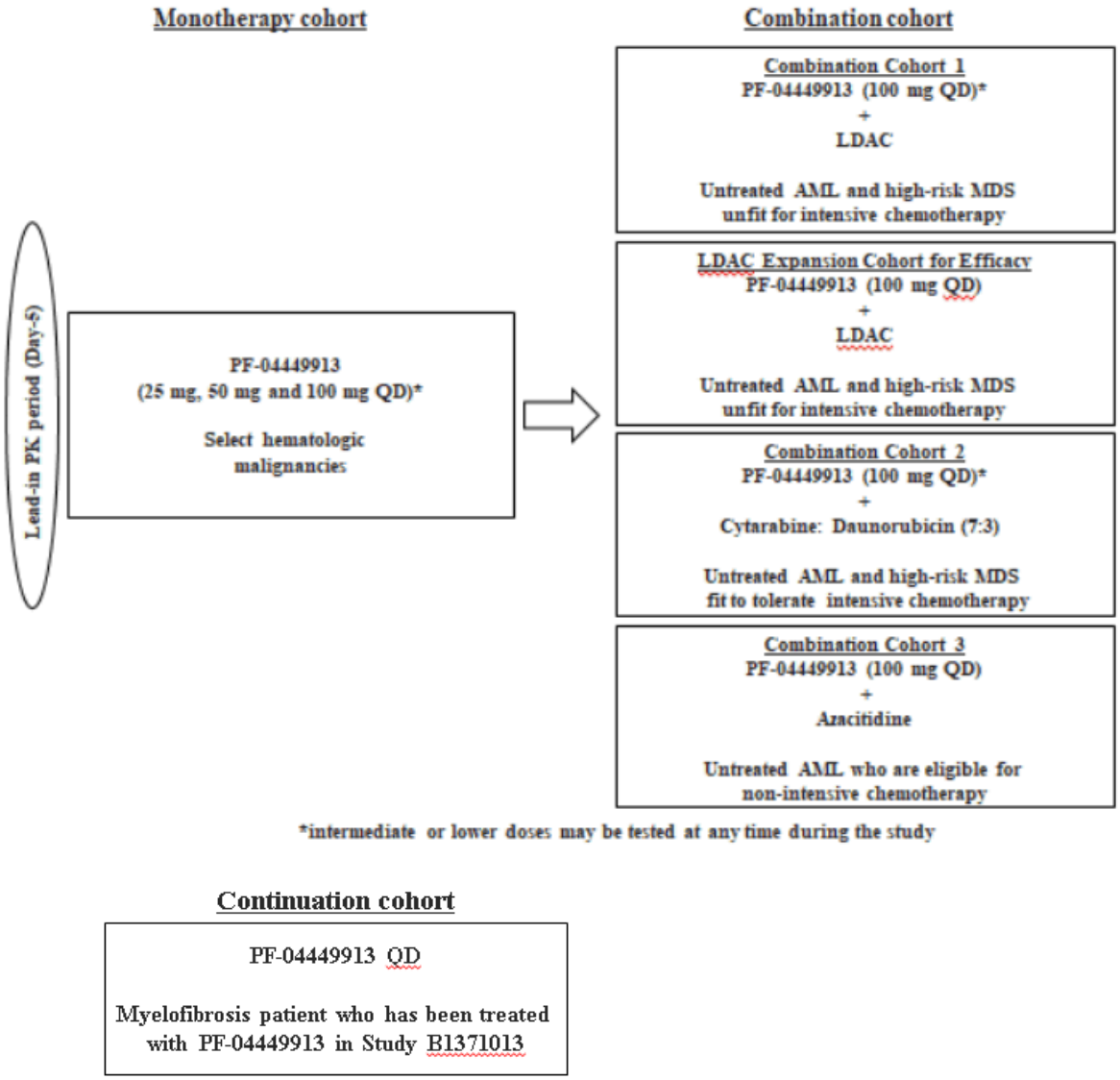
Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse (unless according to the Investigator there is reasonable evidence of clinical benefit, eg, HI [hematologic imiprovement], to justify continuation on treatment following agreement between the Investigator and Sponsor), death, unacceptable toxicity, or patient refusal (whichever is first). All patients will be followed for survival every 12 weeks up to 3 years from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy.

Continuation Cohort (Monotherapy Cohort):

PF-04449913 at the same dose as the patient was taking in Study B1371013 will be orally administered once daily continuously as a single agent over 28 day cycles in 1 Japanese MF patient who has been treated in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013.

In this cohort, the patient receiving PF-04449913 will continue to receive study treatment until the time of disease progression, unacceptable toxicity, death, withdrawal of consent or termination of the study by Sponsor, whichever comes first. The patient may continue PF-04449913 treatment after objective progression of disease has been determined if the patient continues to experience clinical benefit, in the opinion of the investigator, and following discussion with the Sponsor.

Figure 1. Schematic of Study Design



SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. The Assessments section of the protocol contains detailed information relating to each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table as necessary, in order to conduct evaluations or assessments required to ensure patient well-being and safety.

Table 1. Monotherapy Cohort: Single-Agent PF-04449913 in Select Hematologic Malignancies

	Screening	Lead-in PK Period[14]	Cycle 1 (28-day Cycle)					Even-Numbered Cycles*		Odd-Numbered Cycles*			
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day -5****	**Day 1**	**Day 5 (±1 day)**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 21 (±1 day)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[18]**
Baseline documentation													
Informed Consent[1]	X												
Medical/Oncologic History[2]	X												
ECOG Performance Status[3]	X		X					X		X		X	
Safety Labs/Measurements													
Vital Signs (BP and pulse) ***	X		X		X	X	X	X	X	X	X	X	
Physical Examination[4]***	X	X	X			X		X		X		X	
CBC (Complete Blood Count) with differential[5]***	X	X	X		X	X	X	X	X	X	X	X	
Blood Chemistry[6]***	X	X	X		X	X	X	X	X	X	X	X	
Urinalysis with micro[7]***	X		X		X	X		X	X	X	X	X	
PT/PTT (or aPTT)/INR***	X		X			X		X	X	X	X	X	
Pregnancy Test[8]	X	X						X		X		X	
Triplicate 12-lead ECG[9]	X	X	X		X	X	X	X		X		X	
Other Clinical Assessments													
Adverse Event (AE)[10]		X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications and Treatments[11]	X	X	←X→					←X→		←X→		X	X
Drug Compliance[12]		←X→										X	
Study Treatments													
PF-04449913 Dosing[13]		X	←X→					←X→		←X→			
Special Laboratory Studies													
Blood samples for PF-04449913 PK[14]		X	X		X	X	X	X		X			
Bone marrow aspirate and/or biopsy for clinical staging and pharmacodynamic (PD) biomarker analysis [15] (±5 days)	X							X				X	

	Screening	Lead-in PK Period[14]	Cycle 1 (28-day Cycle)					Even-Numbered Cycles*		Odd-Numbered Cycles*			
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day -5****	**Day 1**	**Day 5 (±1 day)**	**Day 8 (±1 day)**	**Day 15 (±1 day)**	**Day 21 (±1 day)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[18]**
Immunophenotyping and Cytogenetics[16]	X							X				X	
For CML Patients: mutation status and PCR for BCR-ABL[20]	X							X				X	
For Non-CML patients: mutation status[21]	X												
Blood samples for PD biomarkers[17]			X				X					X	
Normal Skin Punch Biopsy[19] (±7day)	X						X						
CCI [redacted]	[redacted]												

* For Cycles ≥7, only a Day 1 assessment is required.
** Days -5 should be considered Baseline for all assessments (except when the assessments are required only at screening). There is no Day 0 in the study.
*** If assessment obtained within 48 hours of scheduled time points, it need not be repeated.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Must be obtained additional Informed consent form for confirmation of patient's willingness to continue participation in the study at the end of Cycle 1.
2. Medical History: To be collected within 28 days prior to first dose of PF-04449913. Includes oncology history, history of other diseases (active or resolved), and concomitant illnesses. During study treatment, any new or worsened conditions since baseline should be reported on the Adverse Event CRF. Include information on prior regimens, dosing, and duration of administration as well as a description of the best response observed and treatment failure based on appropriate Disease Specific Guidelines.
3. ECOG performance scale is provided in Appendix 1.
4. Physical Examination includes major body systems as well as measurement of spleen and liver size to assess extramedullary disease (EMD). Weight must be recorded at Screening and on Day 1 of each cycle. Height need not be recorded following the first measurement.
5. CBC (Complete Blood Count): WBC (White Blood Cell) with differential, hemoglobin, and platelet count. Additional hematology tests may be performed as clinically indicated.
6. Blood Chemistry: Total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, magnesium, chloride, calcium, phosphorus, BUN or Urea, creatinine, uric acid, glucose, creatine kinase. These tests may be repeated as clinically indicated.
7. Urinalysis: For pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite (microscopic urinalysis). Additional urinalysis may be performed as clinically indicated.
8. Serum/Urine Pregnancy Test: For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on two occasions prior to commencing study therapy, once at the start of screening, once at the baseline visit, and immediately before investigational product administration. Pregnancy tests will be routinely repeated at every cycle during the active treatment period, at the end of study therapy, and additionally whenever a

menstrual cycle is missed, or when pregnancy is otherwise suspected. Additional pregnancy tests may be undertaken if requested by IRB/IECs, or if required by local regulations.

9. Triplicate 12-lead ECGs: At each time point 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval. ECGs will be collected as follows: a) at Screening; b) On Day-5, at pre-dose and 1, 4, and 24 hrs post-dose; c) On Cycle 1/Day 1, at pre-dose and 1 hr post-dose; d) On Cycle 1/Day 8 at 1 hr post-dose; e) On Cycle 1/Day 15 at 1 hr post-dose; f) On Cycle 1/Day 21, at pre-dose and 1, 2, 4, and 24 hours following the dose of PF-04449913; g) For every subsequent cycle on Day 1 at 1 hr post-dose and h) at the End of Treatment visit. Refer to PK/ECG collection time points**.**
10. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. 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. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
11. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration must be recorded on the CRF.
12. Drug Compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability on Day 1 of each cycle.
13. PF-04449913 Dosing: A single dose of PF-04449913 will be administered on Day -5 (lead-in period), and PF-04449913 will then be given continuously orally, once daily in 28- day cycles.
14. PF-04449913 PK: Blood samples for PF-04449913 PK will be collected a) during the lead-in Period on Day -5, at pre-dose and at 0.5, 1, 2, 4, 8, 24, 48, 72, and 120 hrs (±1 day) post-dose (i.e., pre-dose on Cycle 1/Day 1); b) On Cycle 1 on Day 1, Day 8 and Day 15, at pre-dose and 1 hr post-dose (matched with the ECG); c) On Cycle 1/ Day 21 at pre-dose and at 0.5, 1, 2, 4, 8, and 24 hrs post-dose; d) For Cycles 2, 3, and 4 on Day 1 at pre-dose and 1 hr post-dose (matched with the ECGs).
15. A bone marrow aspirate and/or biopsy (±5 days of nominal date) will be collected for local clinical staging.
    Time Points for Bone Marrow Sampling: For AML and CML AP (accelerated phase)/BC (blast crisis) patients these will be collected at a) screening, b) every even cycle on Day 1 and c) at End of Treatment and at investigators discretion. For all other diseases these will be collected at screening and Day 1 of Cycle 2, 6 and 10 (and every 4 cycles), End of Treatment and at investigators discretion. If a bone marrow aspirate and/or biopsy has been collected within 28 days (excluding the screening sample) it need not be repeated. For centralized biomarker assessments, bone marrow aspirate will be collected at a) screening; b) at End of Treatment/Withdrawal. With sponsor approval, the screening bone marrow need not be performed based on the patient characteristics (eg, dry tap or inevaluable) or a bone marrow performed prior to the screening period may be used for study inclusion.
16. Quantitative immunophenotyping and cytogenetics on blood and/or bone marrow will be conducted for all patients at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy as well as at screening (if a bone marrow is not performed the assessments should be performed using blood), End of Treatment, and at the investigator's discretion.
17. Blood samples for PD biomarkers: Blood will be collected a) on Cycle 1/Day 1 at pre-dose; b) on Cycle 1/Day 21 at pre-dose; c) at End of Treatment.
18. Follow-up Visit: At least 28 days, and no more than 35 days, after discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosupression) patients will return to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
19. A normal skin punch biopsy will be collected at screening and on Cycle 1/Day 21 (±7 days of nominal date). Both biopsies should be obtained from approximately the same area of the body.

20. For all CML patients, mutation analyses will be conducted on blood and/or bone marrow samples at screening only. Quantitative PCR for BCR-ABL will be conducted on blood and/or bone marrow samples at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy as well as at screening (if a bone marrow is not performed the assessments should be performed using blood), End of Treatment, and at the investigator's discretion.
21. For all non-CML patients mutation analysis is required within 6-months of start of the lead-in period. If not been performed within 6 months the mutation analysis must be performed on blood or bone marrow at screening.
22. CCI [redacted]

Table 2. Combination Cohort 1: PF-04449913 + LDAC in Unfit Patients with AML or High-Risk MDS

	Screening	Cycle 1 (28-day Cycle)					Even-Numbered Cycle*		Odd-Numbered Cycle*			
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day 1**	**Day 2**	**Day 3**	**Day 10**	**Day 21 (±2 day)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[23]**
Baseline documentation												
Informed Consent[1]	X											
Medical/Oncologic History[2]	X											
ECOG Performance Status[3]	X	X					X		X		X	
Safety Labs/Measurements												
Vital Signs (BP and pulse) **	X	X			X	X	X	X	X	X	X	
Physical Examination[4]**	X	X			X	X	X		X		X	
CBC (Complete Blood Count) with differential[5] **	X	X			X	X	X	X	X	X	X	
Blood Chemistry[6]**	X	X			X	X	X	X	X	X	X	
Urinalysis with micro[7] **	X	X					X		X		X	
PT/PTT (or aPTT)/INR**	X	X					X		X		X	
Pregnancy Test[8]	X	X					X		X		X	
Triplicate 12-lead ECG[9]	X	X		X	X	X	X		X		X	
Other Clinical Assessments												
Adverse Event (AE)[10]		X	X	X	X	X	X	X	X	X	X	X[23]
Prior/Concomitant Medications and Treatments[11]	X	X	X	X	X	X	X	X	X	X	X	X[23]
Recording of red blood cell and platelet transfusions[21]	X	X	X	X	X	X	X	X	X	X	X	
Drug Compliance[12]		X	X	X	X	X	X	X	X	X	X	
Survival Follow-up[13]												X[13]
Study Treatments												
PF-04449913 Dosing[14]				Days 3 to 28			Days 1 to 28		Days 1 to 28			
LDAC Dosing[15]		Days 1 to 10					Days 1 to 10		Days 1 to 10			
Special Laboratory Studies												
Blood samples for PF-04449913 PK[16]				X	X	X	X		X			
Blood samples for LDAC PK[17]			X		X							
Blood samples for PD biomarkers[18]		X	X			X					X	
Normal Skin Punch Biopsy[24] (± 7 day)	X					X						

	Screening	Cycle 1 (28-day Cycle)					Even-Numbered Cycle*		Odd-Numbered Cycle*			
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day 1**	**Day 2**	**Day 3**	**Day 10**	**Day 21 (±2 day)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[23]**
Bone marrow for clinical and pharmacodynamic (PD) analysis[19] (±7 days)	X						X (C6 and C12)		X (C3 and C9)		X	
Immunophenotyping and Cytogenetics[20]	X						X (C6 and C12)		X (C3 and C9)		X	
CCI [redacted]												

* For Cycles ≥7, only a Day 1 assessment is required
** If assessment obtained within 48 hours of Cycle 1/Day 1 and following scheduled time points, it need not be repeated.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Must be obtained additional Informed consent form for confirmation of patient's willingness to continue participation in the study at the end of Cycle 1.
2. Medical History: To be collected within 28 days prior to first dose. Includes oncology history, full history of AML/MDS prior therapy (include dosing and duration of therapy) with best response, FAB subtype at initial presentation (for AML only), cytogenetics, mutation history, and prior and concomitant illnesses.
3. ECOG performance scale is provided in Appendix 1.
4. Physical Examination includes examination of major body systems as well as measurement of spleen and liver size to assess extramedullary disease (EMD) Weight must be recorded at Screening and on Day 1 of each cycle. Height need not be recorded after the first measurement.
5. CBC (Complete Blood Count): WBC (White Blood Cell) with differential, hemoglobin and platelet count. These hematology tests may be repeated as clinically indicated. For patients with MDS only, all platelet, absolute neutrophil and hemoglobin values observed during the 28-day screening period should be captured in the CRF.
6. Blood Chemistry: Total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, magnesium, chloride, calcium, phosphorus, BUN or Urea, creatinine, uric acid, glucose, creatine kinase. These chemistry tests may be repeated as clinically indicated.
7. Microscopic urinalysis: For pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite. These urine tests may be repeated as clinically indicated.
8. Serum/Urine Pregnancy Test: For female patients of childbearing potential, a serum or urine pregnancy test, with a sensitivity of at least 25 mIU/mL will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
9. Triplicate 12-lead ECGs: At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: a) Screening; b) Cycle 1/Day 1 at pre-dose; c) Cycle 1/Day 3 at pre-dose, 1 and 4 hour post-dose; d) Cycle 1/Day 10 at pre-dose and 1, 2, and 4 hrs post-dose; e) Cycle 1/Day 21 at pre-dose and 1 and 4 hrs post-dose; f) In Cycles 2, 3, 4 and 5, on Day 1 at 1 hr post-dose and g) End of Treatment. Refer to PK/ECG collection time points.
10. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. 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. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

11. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration must be recorded on the CRF.
12. Drug compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability on Day 1 of each cycle.
13. Survival follow-up post treatment: All patients will be followed for survival by site visit, phone or letter, regardless of initiation of new cancer therapy.
14. PF-04449913 Dosing: For Cycle 1 only, PF-04449913 will start on Day 3, and will then be given continuously orally, once daily in 28-day cycles. All subsequent cycles of PF-04449913 will start on Day 1 of each cycle, and be dosed as above. PF-04449913 will be administered in the morning at approximately the same time as the first LDAC subcutaneous injection on days these agents are dosed together. On days that PF-04449913 is dosed alone, PF-04449913 will be administered in the morning at approximately the same time each day.
15. LDAC Dosing: LDAC will be administered at a dose of 20 mg SC BID (morning and evening; approximately 12 hrs apart) for 10 consecutive days, starting on Day 1 of each cycle.
16. Blood samples for PF-04449913 PK will be collected on: a) Cycle 1/Day 3 at pre-dose and 0.5 (30 min), 1, and 4 hrs post-dose; b) Cycle 1/Day 10 and Day 21 at pre-dose and 0.5 (30 min), 1, 2, 4, 6 and 24 hrs post-dose; c) In Cycles 2, 3, 4 and 5 on Day 1 at pre-dose and 1 hr post-dose. All samples will be collected relative to PF-04449913 dosing. Refer to PK/ECG collection time points.
17. Blood samples for LDAC PK will be collected on: a) Cycle 1/Day 2, at pre-dose and 0.25 (15 min), 0.5 (30 min), 1, 2, 4 and 6 hrs post-dose following the AM subcutaneous injection; b) On Cycle 1/Day 10, at pre-dose and 0.25 (15 min), 0.5 (30 min), 1, 2, 4 and 6 hrs post-dose following the AM subcutaneous injection. All samples will be collected relative to LDAC dosing. Refer to PK/ECG collection time points.
18. Blood samples for PD biomarkers will be collected on: a) Cycle 1/Day 1 at pre-LDAC dose; b) Cycle 1/Day 2 at 1 hr post LDAC-dose; c) Cycle 1/Day 21 at pre PF-04449913-dose and d) End of Treatment
19. **Type of Bone Marrow Sample:** For all patients, a bone marrow aspirate and/or a biopsy sample is required and will be used for local clinical staging. **Only aspirates are required from all patients, and biopsies are optional unless required for clinical staging (e.g., dry tap).** All aspirate collections are mandatory unless in the clinical judgment of the investigator, aspirate collection is inappropriate in which case following discussion with the sponsor collection may not be required.
Time Points for Bone Marrow Sampling: Bone marrow evaluations are required within 14 days of screening period (maximum window allowed is -42 days from study entry), and on Cycle 3/Day 1 (±7 days) and every third cycle (Cycle 6/Day 1, Cycle 9/Day 1, Cycle 12/Day 1), **and within 14 days of achieving initial hematologic recovery in the peripheral blood (defined as ANC>1000/µL and platelets≥100,000/µL)**, End of Treatment and at investigators discretion.If hematologic recovery bone marrow has been performed within 14 days of next scheduled bone marrow evaluation, then it does not need to be repeated. For centralized biomarker assessments, bone marrow aspirate will be collected at a) screening; b) at End of Treatment/Withdrawal.
20. Quantitative immunophenotyping (to include MDR-1 [CD243] and ABCG-2 [CDw338] where possible) and cytogenetics will be conducted for all patients using any scheduled or unscheduled bone marrow samples collected during study participation.
21. All red blood cell and platelet transfusions, including date of each transfusion and the number of red blood cell units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded. For patients with high-risk MDS, the transfusion history must be provided for 8-weeks prior to the start of study treatment.
22. CCI [redacted]
23. Follow-up Visit: At least 28 days, and no more than 35 days following discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosupression) patients require review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

24. A normal skin punch biopsy will be collected at screening and on Cycle 1/Day 21 (±7 days of nominal date). Both biopsies should be obtained from approximately the same area of the body.

Table 3. Expansion Cohort of LDAC combination for efficacy: PF-04449913 + LDAC in Unfit Patients with AML or High-Risk MDS

	Screening	Cycle 1 (28-day Cycle)					Even-Numbered Cycle*		Odd-Numbered Cycle*			
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day 1**	**Day 2**	**Day 3**	**Day 10**	**Day 21 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal[22]**	**Post-Txt Follow-Up[23]**
Baseline documentation												
Informed Consent[1]	X											
Medical/Oncologic History[2]	X											
ECOG Performance Status[3]	X	X										
Safety Labs/Measurements												
Vital Signs (BP and pulse)**	X	X			X	X	According to local clinical practice					
Physical Examination[4]**	X	X			X	X	According to local clinical practice					
CBC (Complete Blood Count) with differential[5]**	X	X			X	X	According to local clinical practice					
Blood Chemistry[6]**	X	X			X	X	According to local clinical practice					
Urinalysis with micro[7]**	X	X					According to local clinical practice					
PT/PTT (or aPTT)/INR**	X	X					According to local clinical practice					
Pregnancy Test[8]	X	X					X		X		X	
Triplicate 12-lead ECG[9]	X	X			X		According to local clinical practice					
Other Clinical Assessments												
Adverse Event (AE)[10]		X	X	X	X	X	X	X	X	X	X	X[23]
Prior/Concomitant Medications and Treatments[11]	X	X	X	X	X	X	X	X	X	X	X	X[23]
Recording of red blood cell and platelet transfusions[12]	X	X	X	X	X	X						
Drug Compliance[13]		X	X	X	X	X	X	X	X	X	X	
Disease progression post treatment[14]												
New anti-cancer therapies since discontinuation of study treatment[14]												
Survival Assessment[14]												
Study Treatments												
PF-04449913 Dosing[15]		Days 1 to 28					Days 1 to 28		Days 1 to 28			

Protocol Activity	Screening	Cycle 1 (28-day Cycle)					Even-Numbered Cycle*		Odd-Numbered Cycle*			
	Within 28 Days Prior to Study Entry	Day 1	Day 2	Day 3	Day 10	Day 21 (±2 days)	Day 1 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)	Day 15 (±2 days)	End of Txt/ Withdrawal[22]	Post-Txt Follow-Up[23]
LDAC Dosing[16]		Days 1 to 10					Days 1 to 10		Days 1 to 10			
Special Laboratory Studies												
Blood samples for PF-04449913 PK[17]							X (C6)		X (C3)			
Blood samples for PD biomarkers[18]		X	X			X						
Bone marrow for clinical and pharmacodynamic (PD) analysis[19] (±7 days)	X						According to local clinical practice (at least every 6 months)					
Immunophenotyping and Cytogenetics[20]	X											
CCI [redacted]	[redacted]											

* For Cycles ≥7, only a Day 1 assessment is required.
** If assessment obtained within 48 hours of Cycle 1/Day 1 and following scheduled time points, it need not be repeated.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures.
2. Medical History: To be collected within 28 days prior to first dose. Includes oncology history, full history of AML/MDS prior therapy (include dosing and duration of therapy) with best response, FAB subtype at initial presentation (for AML only), cytogenetics, mutation history, and prior and concomitant illnesses.
3. ECOG performance scale is provided in Appendix 1. This assessment is not required after Protocol Amendment 8.
4. Physical Examination includes examination of major body systems as well as measurement of spleen and liver size to assess extramedullary disease (EMD). Weight must be recorded at Screening and on Day 1 of each cycle. Height need not be recorded after the first measurement. After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).
5. CBC (Complete Blood Count): WBC (White Blood Cell) with differential, hemoglobin and platelet count. These hematology tests may be repeated as clinically indicated. For patients with MDS only, all platelet, absolute neutrophil and hemoglobin values observed during the 28-day screening period should be captured in the CRF. After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).
6. Blood Chemistry: Total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, magnesium, chloride, calcium, phosphorus, BUN or Urea, creatinine, uric acid, glucose, creatine kinase. These chemistry tests may be repeated as clinically indicated. After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).
7. Microscopic urinalysis: For pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite. These urine tests may be repeated as clinically indicated. After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).
8. Serum/Urine Pregnancy Test: For female patients of childbearing potential, a serum or urine pregnancy test, with a sensitivity of at least 25 mIU/mL will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual

cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment may be performed at a local clinic. Local laboratory reference ranges and lab accreditation need to be collected. Records of local laboratory tests and lab accreditation should be retrieved and kept in the site medical records and relevant data from the local clinic entered in the CRF.

9. Triplicate 12-lead ECGs: At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: a) Screening; b) Cycle 1/Day 1 at pre-dose, 1 and 4 hour post-dose; c) Cycle 1/Day 10 at 1 and 4 hour post-dose; d) In Cycles 2 and 3, on Day 1 at 1 hour post-dose and e) End of Treatment. Refer to PK/ECG collection time points. After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).
10. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. 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 study drug are to be reported to the Sponsor. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment should be conducted by phone or video contact and based on the test results from a local clinic if applicable.
11. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) must be reviewed. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review should be conducted by phone or video contact. After Protocol Amendment 8, these data are not required to be recorded on the CRF.
12. All red blood cell and platelet transfusions, including date of each transfusion and the number of red blood cell units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded. For patients with high-risk MDS, the transfusion history must be provided for 8-weeks prior to the start of study treatment. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review should be conducted by phone or video contact. After Protocol Amendment 8, these data are not required to be recorded on the CRF.
13. Drug compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability on Day 1 of each cycle. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review of dosing compliance should be conducted by phone or video contact.
14. Disease progression post treatment, new anti-cancer therapies since discontinuation of study treatment and Survival Assessment: All patients will be followed every 8 weeks starting from the last dose of study medication to confirm survival status and collect information on any new anti-cancer therapies initiated. All patients will be followed for survival every 8 weeks up to 2 years from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy. For patients refusing to return to the site, a telephone follow-up call is acceptable. Post-treatment disease progression including the data for disease assessment recorded in the source documents will be collected until initiation of new anti-cancer therapies. For patients in DMR, disease assessment and corresponding lab data (neutrophil counts, platelets and peripheral/bone marrow blasts %) will be collected if available from the source documents. After Protocol Amendment 8, these follow-up assessments are not required.
15. PF-04449913 Dosing: PF-04449913 will start on Day 1 of each cycle, and be given continuously orally, once daily in 28-day cycles. PF-04449913 will be administered in the morning at approximately the same time as the first LDAC subcutaneous injection on days these agents are dosed together. On days that PF-04449913 is dosed alone, PF-04449913 will be administered in the morning at approximately the same time each day.
16. LDAC Dosing: LDAC will be administered at a dose of 20 mg SC BID (morning and evening; approximately 12 hrs apart) for 10 consecutive days, starting on Day 1 of each cycle. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, LDAC administration may be skipped only once. In such case, the safety assessments should be performed by phone or video contact, and/or by utilizing the test results from a local clinic if applicable. If 2 or more consecutive skips are required, the investigator and the Sponsor should have a consultation to determine the necessity of the study treatment discontinuation.

17. Blood samples for PF-04449913 PK will be collected on: a) Cycle 3/Day 1 at pre-dose and b) Cycle 6/Day 1 at pre-dose (i.e. the same dates as bone marrow aspirates for biomarker assessments).
18. Blood samples for PD biomarkers will be collected on: a) Cycle 1/Day 1 at pre LDAC-dose; b) Cycle 1/Day 2 at 1 hr post LDAC-dose; c) Cycle 1/Day 21 at pre PF-04449913-dose and d) End of Treatment. After Protocol Amendment 8, these assessments are not required.
19. **Type of Bone Marrow Sample:** For all patients, a bone marrow aspirate and/or a biopsy sample is required and will be used for local clinical staging. **Only aspirates are required from all patients, and biopsies are optional unless required for clinical staging (e.g., dry tap).** All aspirate collections are mandatory unless in the clinical judgment of the investigator, aspirate collection is inappropriate in which case following discussion with the sponsor collection may not be required.
    Time Points for Bone Marrow Sampling: Bone marrow evaluations are required within 14 days of screening period (maximum window allowed is -42 days from study entry), and on Cycle 3/Day 1 (±7 days) and every third cycle (Cycle 6/Day 1, Cycle 9/Day 1, Cycle 12/Day 1, etc.), **and within 14 days of achieving initial hematologic recovery in the peripheral blood (defined as ANC>1000/µL and platelets≥100,000/µL)**, End of Treatment and at investigators discretion. If hematologic recovery bone marrow has been performed within 14 days of next scheduled bone marrow evaluation, then it does not need to be repeated. For centralized biomarker assessments, bone marrow aspirate will be collected at the timing of bone marrow assessment for disease assessment (after consent obtained). After Protocol Amendment 8, bone marrow evaluation for clinical assessment will be conducted according to local clinical practice (at least every 6 months) but bone marrow samples are not required to be submitted for centralized biomarker assessments.
20. Quantitative immunophenotyping (to include MDR-1 [CD243] and ABCG-2 [CDw338] where possible) and cytogenetics will be conducted for all patients using any scheduled or unscheduled bone marrow samples collected during study participation. After Protocol Amendment 8, these assessments are not required.
21. CCI [redacted]
22. End of Treatment: Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression).
23. Follow-up Visit: At least 28 days, and no more than 35 days following discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosuppression) patients require review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Table 4. Combination Cohort 2: PF-04449913 + Cytarabine/Daunorubicin in Fit Patients with AML or High-Risk MDS

	Screening	Induction					Consolidation				Maintenance		
		Lead-in (first cycle only)	Up to 2 Induction Cycles (28-day cycle)				2-4 Consolidation Cycles (28-day cycle)***				Maximum of 6 Maintenance Cycles (28-day cycle)		
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day -3 ***	**Day 1**	**Day 3**	**Day 10 (±1 days)**	**Day 21 (±2 days)**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21 (±2 days)**	**Day 1 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[24]**
Baseline documentation													
Informed Consent[1]	X												
Medical/Oncologic History[2]	X												
ECOG Performance Status[3]	X	X	X				X				X	X	
Safety Labs/Measurements													
Vital Signs (BP and pulse) **	X	X	X				X				X	X	
Physical Examination[4]**	X	X	X		X	X	X	X		X	X	X	
CBC (Complete blood count) with differential[5] **	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry[6] **	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis with micro[7] **	X	X	X				X				X	X	
PT/PTT (or aPTT)/INR**	X	X	X				X				X	X	
Pregnancy test[8]	X	X					X				X	X	
Triplicate 12-lead ECG[9]	X	X			X		X				X	X	
ECHO or MUGA scan[21]	X												
Other Clinical Assessments													
Adverse Event (AE)[10]		X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications and Treatments[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Recording of red blood cell and platelet transfusions[22]	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Compliance[12]		X	X	X	X	X	X	X	X	X	X	X	

	Screening	Induction					Consolidation				Maintenance		
		Lead-in (first cycle only)	Up to 2 Induction Cycles (28-day cycle)				2-4 Consolidation Cycles (28-day cycle)***				Maximum of 6 Maintenance Cycles (28-day cycle)		
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day -3 ***	**Day 1**	**Day 3**	**Day 10 (±1 days)**	**Day 21 (±2 days)**	**Day 1**	**Day 5**	**Day 10 (±1 days)**	**Day 21 (±2 days)**	**Day 1 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow-Up[24]**
Study Treatments													
PF-04449913 Dosing[13]		Days -3 to 28					Days 1 to 28				Days 1 to 28		
Daunorubicin Dosing[14]			Days 1 to 3										
Cytarabine Dosing[15]			Days 1 to 7				Days 1, 3, and 5						
Special Laboratory Studies													
Blood samples for PF-04449913 PK[16]		X		X	X		X				X		
Blood samples for Daunorubicin PK[17]				X									
Blood samples for Cytarabine PK[17]				X									
Blood samples for PD biomarkers[18]		X		X	X		X		X			X	
Normal Skin Punch Biopsy[25](± 7day)	X					X							
Bone marrow for clinical staging and for PD biomarker analysis (±7 days)[19]	X					X				X	X	X	
Immunophenotyping and Cytogenetics[20]	X					X				X	X	X	
CCI [redacted]													

* There is no Day 0.
** If assessment obtained within 48 hours of Cycle 1/Day 1 and following scheduled time points, it need not be repeated.
***Patients with CR/CRi must receive a minimum of 2 consolidation cycles, but no more than 4 consolidation cycles, to be eligible for maintenance therapy.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Must be obtained additional Informed consent form for confirmation of patient's willingness to continue participation in the study at the end of Induction Cycle 1.
2. Medical History: To be collected within 28 days prior to first dose. Includes oncology history, full history of AML/MDS prior therapy (include dosing and duration of therapy) with best response, FAB subtype at initial presentation (for AML only), cytogenetics and mutation history and prior and concomitant illnesses.
3. ECOG performance scale is provided in Appendix 1.

4. Physical Examination includes examination of major body systems as well as measurement of spleen and liver size to assess extra-medullary disease (EMD). Weight must be recorded at Screening and Day 1 of each cycle. Height need not be recorded after the first measurement.
5. CBC (Complete blood count): WBC (White blood cell) with differential, hemoglobin and platelet count. Additional hematology tests may be performed as clinically indicated. For patients with MDS only, all platelet, absolute neutrophil and hemoglobin values observed during the 28-day screening period should be captured in the CRF.
6. Blood Chemistry: Total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, magnesium, chloride, calcium, phosphorus, BUN or Urea, creatinine, uric acid, glucose, creatine kinase. These chemistry tests may be repeated as clinically indicated.
7. Microscopic urinalysis: For pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite. These urine tests may be repeated as clinically indicated.
8. Serum/Urine Pregnancy Test: For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on two occasions prior to starting study therapy once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
9. Triplicate 12-lead ECGs: At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected at:
   a) Screening; b) Induction Cycle 1 Lead-in Day -3 at pre-dose and 1 hr post PF-04449913 dose; c) Induction Cycle 1/Day 10 at 1 and 4 hrs post-PF-04449913 dose; d) If a second induction cycle is administered, then ECG should be collected on Day 1 and Day 10 at 1 hr post-dose; e) Consolidation cycles on Day 1 at 1 hr post-PF-04449913 dose in first 2 cycles; f) Maintenance cycles on Day 1 at 1 hr post-PF-04449913 dosing in first 2 cycles and g) End of Treatment. Refer to PK/ECG collection time points.
10. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient be commenced on another anti-cancer therapy in the meantime. 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. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
11. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration must be recorded on the CRF.
12. Drug compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability on Day 1 of each cycle.
13. PF-04449913 Dosing: PF-04449913 will be started at Day-3 for the first cycle of induction only, and given <u>continuously</u> from Day -3 onwards as described below. For all other cycles, PF-04449913 will start on Day 1 of each cycle and will be given orally once daily in the morning at approximately the same time of day for all 3 phases (induction, consolidation and maintenance) in 28-day cycles. Where possible, PF-04449913 will be administered together with daunorubicin IV injection during induction and the morning cytarabine IV infusion start during consolidation.
14. Daunorubicin Dosing (Induction only): Daunorubicin will be given at a dose of 60 mg/m^2 as an IV in combination with cytarabine and PF-04449913, on Days 1-3 of induction Cycle 1. Induction chemotherapy may be repeated for one additional cycle if an unsatisfactory clinical response is observed and there are no signs of cardiac toxicity. If clinical signs of cardiac dysfunction are observed, a repeat MUGA/ECHO should be performed, and must demonstrate a LVEF ≥45% to receive a second course of induction chemotherapy. If a second cycle of induction therapy is required, it may start prior to Day 28 of induction Cycle 1 but not earlier than Cycle 1/Day 21. Dose must be recalculated if the weight changes by >10%.
15. Cytarabine Dosing: Separate cytarabine dosing and schedules will be used for Induction and Consolidation and administered using institutional guidelines:
    Induction: Cytarabine will be administered (in parallel to daunorubicin) at a dose of 100 mg/m^2 by continuous IV infusion for 7 days on Days 1-7 of induction Cycle 1.

If a second cycle of induction therapy is indicated by the treating physician and the patient does not have resistant disease, it may start prior to Day 28 of induction Cycle 1 but no earlier than Cycle 1/Day 21. Dose must be recalculated if the weight changes by >10%.
Consolidation: Single-agent cytarabine will be administered at a dose of 1g/m^2 IV infused over 3 hours, given Q12 hours (morning and evening) on Days 1, 3 and 5. Consolidation cytarabine will be repeated every 28 days for 4 cycles unless the patient relapses, unacceptable toxicity or patient withdrawal. Dose must be recalculated if the weight changes by >10%.

16. Blood samples for PF-04449913 PK will be collected on:
a) Induction Cycle 1 Lead-in Day -3 at pre-dose and 1 hr post-PF-04449913 dose; b) Induction Cycle 1/Day 3 at pre-dose, 0.5 (30 min), 1, 6, and 24 hrs post-PF-04449913 dose; c) Induction Cycle 1/Day 10 at pre-dose, 0.5 (30 min), 1, 4, 6, and 24 hrs post-PF-04449913 dose; d) Consolidation cycles on Day 1 at 1 hr post-PF-04449913 dose in first 2 cycles; e) Maintenance cycles on Day 1 at 1 hr post-dose in first 2 cycles. All samples will be collected relative to PF-04449913 dosing. Refer to PK/ECG collection time points.
17. Blood samples for Cytarabine and Daunorubicin PK**:**
Daunorubicin: Day 3 (Induction Cycle 1 only) at pre-dose, 0.25 (15 min, mid-infusion), 0.5 (30 min, immediately prior to the end of infusion), 1, 4, 6, 24 hrs post administration of daunorubicin. All samples will be collected relative to daunorubicin dosing. Refer to PK/ECG collection time points.
Cytarabine: Day 3 (Induction Cycle 1 only), at pre-dose, 6 and 24 hours after the start of cytarabine infusion. All samples will be collected relative to cytarabine dosing. Refer to PK/ECG collection time points.
18. Blood samples for PD biomarkers will be collected on: a) Day -3 of first induction cycle at pre-dose; b) Day 3 of first induction cycle at 1 hr post-dose; c) Day 10 of first induction cycle at 1 hr post-dose; d) Day 1 of first consolidation cycle at 1 hr post-dose; e) Day 10 of first consolidation cycle at pre-dose and f) End of Treatment. All collections are relative to PF-04449913 dosing.
19. **Type of Bone Marrow Sample:** For all patients a bone marrow aspirate and/or a biopsy sample is required and will be used for local clinical staging. **Only aspirates are required of all patients, and biopsies are optional unless required for clinical staging (e.g., dry tap).** All aspirate collections are mandatory unless in the clinical judgment of the investigator, aspirate collection is inappropriate in which case following discussion with the sponsor collection may not be required.
Time Points for Bone Marrow Sampling: For screening: An aspirate and biopsy obtained within 14 days of screening period (maximum window allowed is -42 days from study entry) is acceptable for patient eligibility and PD biomarker assessment, but if not available it will need to be obtained as part of the screening procedures.
    - **Induction:** the bone marrow samples will be collected during both Induction cycles. There is only an allowed window of +7 days (i.e., Day 21-Day 28). Bone marrow evaluations may be repeated at Investigator discretion as required for clinical staging anytime prior to next cycle of chemotherapy.
    - **Consolidation:** If a patient enters consolidation with a CRi (post-induction), the bone marrow evaluation must be repeated **within 14 days if initial hematologic recovery is achieved in the peripheral blood (defined as ANC>1000/µL and platelets≥100,000/µL)**. Bone marrow evaluation is required D21 (±7 days) of the final cycle of consolidation. If hematologic recovery bone marrow has been performed within 14 days of next scheduled bone marrow evaluation it need not be repeated. Additional bone marrow evaluations may be repeated at Investigator discretion as required for clinical staging anytime prior to next cycle of chemotherapy.
    - **Maintenance:** A bone marrow is required on Day 1 (±7 days) every third cycle from start of maintenance therapy (i.e., Cycles 3 and 6 of the maintenance cycle).

    For centralized biomarker assessments, bone marrow aspirate will be collected at a) screening; b) at End of Treatment/Withdrawal.
20. Quantitative immunophenotyping (to include MDR-1 [CD243] and ABCG-2 [CDw338] where possible) and cytogenetics will be conducted locally for all patients using any scheduled or unscheduled bone marrow samples collected during study participation.
21. Should be repeated before Induction Cycle 2 if signs of cardiac toxicity are observed and as clinically indicated thereafter.
22. All red blood cell and platelet transfusions, including date of **each** transfusion and number of red blood cell units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded. For patients with high-risk MDS, the transfusion history is required to be provided for 8-weeks prior to start of study treatment.
23. CCI [redacted]
24. Follow-up Visit: At least 28 days, and no more than 35 days, after discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosupression) patients require review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing

to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

25. A normal skin punch biopsy will be collected at screening and on Cycle 1/Day 21 (±7 days of nominal date). Both biopsies should be obtained from approximately the same area of the body.

Table 5. Combination Cohort 3: PF-04449913 + Azacitidine in Patients with previously untreated AML who are eligible for non-intensive chemotherapy

	Screening	Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)		Cycles ≥3 (28-day cycles)	End of Txt/ Withdrawal[25]	Post-Txt Follow-Up[26]
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day 1**	**Day 2**	**Day 7**	**Day 21**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**		
Baseline documentation										
Informed Consent[1]	X									
Medical History[2]	X									
ECOG Performance Status[3]	X	X				X		X	X	
Disease Classification[4]	X									
Safety Labs/Measurements										
Vital Sign (BP and pulse)**	X	X				X		X	X	
Physical Examination[5]**	X	X				X		X	X	
CBC (Complete Blood Count) with differential [6]**	X	X		X	X	X	X	X	X	
Blood Chemistry[7]**	X	X		X	X	X	X	X	X	
Urinalysis[8]**	X	X				X		X	X	
Coagulation[9]**	X	X			X	X	X	X	X	
Pregnancy test[10]	X	X				X		X	X	
Triplicate 12 - lead ECG[11]	X	X	X	X	X	X		X	X	
Study Treatment										
PF-04449913 Dosing[12]			Oral Daily Continuous Dosing (For Cycle 1 only PF-04449913 dosing will start on Day 2)							
Azacitidine Dosing[13]		SC injection or IV Days 1-7 (After Cycle 1, ±3 days window applicable to each dose)								
Drug Compliance[14]		X	X	X	X	X	X	X	X	
Clinical Staging										
Bone Marrow[15]	X							X[15]	X	
Bone marrow immunophenotyping and Cytogenetics[16]	X							X	X	
Other Clinical Assessments										
Adverse Event Monitoring[17]		X							X	X
Review Prior/Concomitant Treatments[18]	X	X							X	X
Recording of red blood cell and platelet transfusions[19]	X	X							X	

	Screening	Cycle 1 (28-day cycle)				Cycle 2 (28-day cycle)		Cycles ≥3 (28-day cycles)	End of Txt/ Withdrawal[25]	Post-Txt Follow-Up[26]
Protocol Activity	**Within 28 Days Prior to Study Entry**	**Day 1**	**Day 2**	**Day 7**	**Day 21**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**		
Disease progression post treatment[20]										X
New anti cancer therapies since discontinuation of study treatment[20]										X
Survival Assessment[20]										X
PK Sampling										
Blood Samples for PK evaluation[21]		X	X	X	X			X		
Biomarker Assessments										
Blood samples for biomarkers[22]		X				X			X	
Bone marrow aspirate for biomarker analysis[23]	X							X (Cycle 4 only)	X	
CCI [redacted]										

** If assessment obtained within 3 days of Cycle 1/Day 1 and following scheduled time points, it need not be repeated.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Must be obtained additional Informed consent form for confirmation of patient's willingness to continue participation in the study at the end of Cycle 1.

2. Medical History: Includes oncology history, full history of AML prior therapy (include dosing and duration of therapy) with best response, FAB subtype at initial presentation, cytogenetics and mutation history and prior and concomitant illnesses.
3. ECOG: See Appendix 1.
4. Disease Classification: AML by WHO. Prognostic system using 2017 European Leukemia Net (ELN) criteria.
5. Physical Examination: Examination of major body systems as well as measurement of spleen and liver size to assess extra-medullary disease (EMD). Weight must be recorded at Screening and Day 1 of each cycle. Height need not be recorded after the first measurement at screening.
6. CBC (Complete Blood Count): WBC (White Blood Cell) with differential, hemoglobin and platelet count. These hematology tests may be repeated as clinically indicated. The list of required laboratory tests is provided in Secton 7.1.3.
7. Blood Chemistry: The list of required laboratory tests is provided in Section 7.1.3.
8. Urinalysis: The list of required laboratory tests is provided in Section 7.1.3.
9. Coagulation: The list of required laboratory tests is provided in Section7.1.3.

10. Pregnancy Tests: For female patients of childbearing potential, a serum or urine pregnancy test, with a sensitivity of at least 25 mIU/mL will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations.
11. ECG: See Table 11 for detailed ECG Schedule.
12. PF-04449913 Dosing: Treatment will be administered in 28-day cycles (cycle duration may be extended to allow for toxicity resolution). PF-04449913 will be administered once daily continuously, in the morning at approximately the same time each day. For Cycle 1 only PF-04449913 dosing will start on Day 2 to accommodate PK samples collection for DDI assessment. In all subsequent cycles PF-04449913 administration will start on Day 1.
13. Azacitidine Dosing: Azacitidine will be administered subcutaneously or IV on Days 1-7 of each 28-day cycle (After Cycle 1, ±3 days window applicable to each dose). The next cycle start can be delayed to allow for toxicity resolution.
14. Drug Compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.
15. Bone Marrow Assessments for Clinical Staging.
    - Type of Bone Marrow Sample: For all patients, a bone marrow aspirate and/or a biopsy sample are required at screening and will be used for clinical staging. For screening, samples taken prior to consent but within the 28-day window prior to fist dose can be used and need not be repeated. **Only bone marrow aspirates are performed for disease evaluation and biopsies are optional unless required for clinical staging (eg, dry tap)**. All aspirate collections are mandatory unless in the clinical judgment of the investigator, aspirate collection is inappropriate in which case following discussion with the sponsor collection may not be required.
    - Timepoints for Bone Marrow Sampling:
      Bone marrow assessment must be completed at screening (within 28 days of first dose). However, if progression is suspected during the screening period an additional BM sample should be collected prior first dose of study drug to confirm eligibility. Subsequent BM samples to be collected on C4D1 (±7 days), and every 3 cycles afterwards (C7D1, C10D1, C13D1 and so on ±7 days), at the EOT, and as clinically indicated. If hematologic recovery bone marrow has been performed within 14 days of next scheduled bone marrow evaluation it need not be repeated.
16. Bone Marrow Immunophenotyping and Cytogenetics: Quantitative immunophenotyping (to include MDR-1 [CD243] and ABCG-2 [CDw338] where possible) and cytogenetics will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Please see Footnote 15 for details on bone marrow samples collection schedule.
17. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. 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. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.
18. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration must be recorded on the CRF.
19. Red Blood Cells and Platelets Transfusion Recording: Transfusion history up to 8 weeks prior to the start of study treatment should be recorded. All red blood cell and platelet transfusions, including date of each transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units, not number of bags, must be recorded.

20. Disease progression post treatment, new anti-cancer therapies since discontinuation of study treatment and Survival Assessment: All patients will be followed every 12 weeks starting from the last dose of study medication to confirm survival status and collect information on any new anti-cancer therapies initiated. All patients will be followed for survival every 12 weeks up to 3 years from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy. For patients refusing to return to the site, a telephone follow-up call is acceptable. Post-treatment disease progression including the data for disease assessment recorded in the source documents will be collected until initiation of new anti-cancer therapies. For patients in remission, disease assessment and corresponding lab data (neutrophil counts, platelets and peripheral/bone marrow blasts %) will be collected if available from the source documents.
21. Blood samples for PK Evaluation: See detailed information in Table 11 for PK timepoints.
22. Blood samples for Biomarker Profiling: Blood samples for biomarkers profiling will be collected on C1D1 (pre-dose), C2D1 (pre-dose), and EOT.
23. Bone Marrow Aspirates for Biomarker Analysis: A bone marrow aspirate for biomarker assessments must be collected at screening, C4D1, and EOT. All bone marrow aspirate collections are mandatory unless in the clinical judgment of the Investigator aspirate collection is inappropriate in which case following discussion with the Sponsor collection may not be required. Collection of an aspirate BM sample for biomarker analysis should also occur when the BM for clinical response assessment is repeated. Samples will be analyzed centrally.

CCI [redacted]

25. End of Treatment: Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression).
26. Follow-up Visit: At least 28 days, and no more than 35 days following discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosupression) patients require review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Table 6. Continuation Cohort (Monotherapy Cohort): Single-Agent PF-04449913 in Myelofibrosis Patient

	Screening	Cycle 1 (28-day Cycle)	Cycles 4, 7, 10 and thereafter every 3 cycles		
Protocol Activity	**Within 28 Days Prior to Cycle 1 Day 1**	**Day 1**	**Day 1 (±2 days)**	**End of Txt/ Withdrawal**	**Post-Txt Follow- Up[12]**
Baseline documentation					
Informed Consent [1]	X				
Medical/Oncologic History [2]	X				
Safety Labs/Measurements					
Height and Weight[3]***	X		X	X	
CBC (Complete Blood Count) with differential[4]***		X	X	X	
Pregnancy Test [5]		X	X	X	
Triplicate 12-lead ECG[6]		X	X	X	
Others (ex. Vital signs, ECOG Performance Status, Blood Chemistry, Coagulation, Urinalysis)	According to local clinical practice				
Other Clinical Assessments					
Adverse Event (AE) [7]	X				
Concomitant Medications and Treatments[8]	X				
Recording of red blood cell and platelet transfusions[9]	X				
Drug Compliance[10]		X	X	X	
Study Treatment					
PF-04449913 Dosing[11]		X	X		

*** If assessment obtained within 48 hours of scheduled time points, it need not be repeated.
In the event that the in-clinic study visits cannot be conducted due to COVID-19-related reasons, the study visits every 3 cycles may be skipped only once. In such case, the safety assessments should be performed by phone or video contact, and/or by utilizing the test results from a local clinic if applicable. If 2 or more consecutive skips are required, the investigator and the Sponsor should have a consultation to determine the necessity of the study treatment discontinuation.

1. Informed Consent: Must be obtained prior to undergoing any study-specific procedures.
2. Medical History: Includes oncology history, prior and concomitant illnesses. Ongoing adverse events which had occurred in the previous study and any new or worsened conditions since baseline during study treatment should be reported on the Adverse Event CRF.
3. Weight and Hight: Weight must be recorded at Baseline, thereafter on Day 1 of every 3 cycles and at End of Treatment. Height must be recorded at Baseline only. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, weight tests may be performed at a local clinic. Local laboratory reference ranges and lab accreditation need to be collected. Records of local laboratory tests and lab accreditation should be retrieved and kept in the site medical records and relevant data from the local clinic entered in the CRF.

4. CBC (Complete Blood Count): To be collected at Cycle 1 Day 1 (pre-treatment), thereafter on Day 1 of every 3 cycles and at the End of Treatment. Refer to Section 7.1.3 for a list of assessments. Additional hematology tests may be performed as clinically indicated. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment may be performed at a local clinic. Local laboratory reference ranges and lab accreditation need to be collected. Records of local laboratory tests and lab accreditation should be retrieved and kept in the site medical records and relevant data from the local clinic entered in the CRF.
5. Serum/Urine Pregnancy Test: Pregnancy tests will be collected at Cycle 1 Day 1 (pre-treatment), thereafter routinely repeated at every cycle during the active treatment period, at End of Treatment, and additionally whenever a menstrual cycle is missed, or when pregnancy is otherwise suspected. Additional pregnancy tests may be undertaken if requested by IRB/IECs, or if required by local regulations. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment may be performed at a local clinic. Local laboratory reference ranges and lab accreditation need to be collected. Records of local laboratory tests and lab accreditation should be retrieved and kept in the site medical records and relevant data from the local clinic entered in the CRF.
6. Triplicate 12-lead ECGs: At each time point 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval. ECGs will be collected as follows: On Cycle 1/Day 1 at pre-dose and thereafter on Day 1 at 1 hr post-dose of every 3 cycles and at the End of Treatment. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment may be performed at a local clinic. Local laboratory reference ranges and lab accreditation need to be collected. Records of local laboratory tests and lab accreditation should be retrieved and kept in the site medical records and relevant data from the local clinic entered in the CRF.
7. Adverse Event (AE) Assessments: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.0. Ongoing events which had occurred in the previous study and any new or worsened conditions since baseline during study treatment should be reported on the Adverse Event CRF. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. 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. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this assessment should be conducted by phone or video contact and based on the test results from a local clinic if applicable.
8. Concomitant Medications and Treatments: Every concomitant medication and treatment required by the patient within 28 days prior to Cycle 1 Day 1 and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration must be recorded on the CRF. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review should be conducted by phone or video contact.
9. All red blood cell and platelet transfusions, including date of each transfusion and the number of red blood cell units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review should be conducted by phone or video contact.
10. Drug compliance: All PF-04449913 bottles including any unused tablets and patient dosing diaries will be returned for assessing compliance and drug accountability on Day 1 of each cycle. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review of dosing compliance should be conducted by phone or video contact.
11. PF-04449913 Dosing: PF-04449913 will be given continuously orally, once daily in 28-day cycles. The starting dose will be the same as the dose at the time the patient discontinued from Study B1371013.
12. Follow-up Visit: At least 28 days, and no more than 35 days following discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosupression) patients require review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

PK/ECG collection time points:

Table 7. Monotherapy Cohort: Single-Agent PF-04449913 in Select Hematologic Malignancies

	PK Lead-in Period									Cycle 1					
Study Days	**Day -5**						**Day -4**	**Day -3**	**Day -2**	**Day 1 (±1)**		**Day 8 (±1)**		**Day 15 (±1)**	
PF-04449913 Dosing	✓									✓		✓		✓	
Hour	0 (pre-dose)	0.5	1	2	4	8	24	48	72	120[a]	1	0 (pre-dose)	1	0 (pre-dose)	1
Blood samples for PF-04449913 PK	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Triplicate 12-lead ECG	✓		✓		✓		✓			✓	✓		✓		✓

a. The 120 hr time point is also the pre-dose (0 hour) time point for Cycle 1/Day 1.
Patients should be hospitalized on Day -5 and Day -4 in PK Lead-in Period for full PK sample collection.

	Cycle 1							Cycle 2-4	
Study Days	**Day 21 (±1)**						**Day 22**	**Day 1 (±2)**	
PF-04449913 Dosing	✓						✓	✓	
Hour	0 (pre-dose)	0.5	1	2	4	8	24 [a]	0 (pre-dose)	1
Blood samples for PF-04449913 PK	✓	✓	✓	✓	✓	✓	✓	✓	✓
Triplicate 12-lead ECG[b]	✓		✓	✓	✓		✓		✓

a. The 24 hr time point for Cycle 1/Day 21 is the pre-dose time point on Cycle 1/Day 22.
b. After Cycle 4, for every subsequent cycle on Day 1 at 1 hr post-dose.
Patients should be hospitalized on Cycle 1/Day 21 and Day 22 for full PK sample collection.

Table 8. Combination cohort 1: PF-04449913 + LDAC in Unfit Patients with AML or High-Risk MDS

	Cycle 1 (28 day Cycle)														
Study Days	**Day 1**				**Day 2**							**Day 3**			
PF-04449913 Dosing												✓			
LDAC Dosing	✓				✓							✓			
Hour	0 (pre-dose)	0.5	1	4	0 (pre-dose)	0.25	0.5	1	2	4	6	0	0.5	1	4
Blood samples for PF-04449913 PK[a]												✓	✓	✓	✓
Blood samples for LDAC PK[b]					✓	✓	✓	✓	✓	✓	✓				
Triplicate 12-lead ECG	✓											✓		✓	✓

a. All samples will be collected relative to PF-04449913 dosing.
b. All samples will be collected relative to LDAC dosing.

	Cycle 1 (28 day Cycle)														Cycle 2-5	
Study Days	**Day 10**							**Day 11**	**Day 21 (±2)**					**Day 22**	**Day 1 (±2)**	
PF-04449913 Dosing	✓							✓	✓					✓	✓	
LDAC Dosing	✓														✓	
Hour	0 (pre-dose)	0.25	0.5	1	2	4	6	24[a]	0 (pre-dose)	0.5	1	2	4	6	24[a]	0 (pre-dose)	1
Blood samples for PF-04449913 PK[b]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood samples for LDAC PK[c]	✓	✓	✓	✓	✓	✓	✓										
Triplicate 12-lead ECG	✓			✓	✓	✓			✓		✓		✓				✓

a. The 24 hr time point for Cycle 1/Day 10 is the pre-dose time point on Cycle 1/Day 11 and the 24 hr time point for Cycle 1/Day 21 is the pre-dose time point on Cycle 1/Day 22.
b. All samples will be collected relative to PF-04449913 dosing.
c. All samples will be collected relative to LDAC dosing.
Patients should be hospitalized on Cycle 1/Day 2 and 3, Cycle 1/Day 10 and 11, and Cycle 2/Day 21 and 22 for full PK sample collection.

Table 9. Expansion Cohort of LDAC combination for efficacy: PF-04449913 + LDAC in Unfit Patients with AML or High-Risk MDS

	Cycle 1 (28 day Cycle)					Cycle ≥2 (28 day Cycle)	
Study Days	**Day 1**			**Day 10**		**Day 1 (±2)**	
PF-04449913 Dosing	✓			✓		✓	
LDAC Dosing	✓			✓		✓	
Hour	0 (pre-dose)	1	4	1	4	0 (pre-dose)	1
Blood samples for PF-04449913 PK[a]						✓ (C3 and C6 only)	
Triplicate 12-lead ECG[b]	✓	✓	✓	✓	✓		✓ (C2-3 only)

a. Blood samples for PF-04449913 PK will be collected on the same days as the collection of bone marrow aspirates for biomarker assessments.
b. Triplicate 12-lead ECGs: At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the appropriate time. All ECG timepoints are in reference to dosing of PF-04449913.

Table 10. Combination cohort 2: PF-04449913 + Cytarabine/Daunorubicin in Fit Patients with AML or High-Risk MDS

	Induction																**Consolidation**	**Maintenace**
	Cycle 1 (28 day Cycle)																**First 2 cycle**	**First 2 cycle**
Study Days	**Day -3**		**Day 3**						**Day 4**	**Day 10**						**Day 11**	**Day 1**	**Day 1**
PF-04449913 Dosing	✓		✓						✓	✓						✓	✓	✓
Daunorubicin Dosing			✓															
Cytarabine Dosing			✓						✓								✓	
Hour	0 (pre-dose	1	0 (pre-dose	0.25	0.5	1	4	6	24[a]	0 (pre-dose	0.25	0.5	1	2	4	6	24[a]	1	1
Blood samples for PF-04449913 PK[b]	✓	✓	✓		✓	✓		✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Blood samples for Daunorubicin PK[c]			✓	✓	✓	✓	✓	✓	✓										
Blood samples for Cytarabine PK			✓					✓	✓										
Triplicate 12-lead ECG[d]	✓	✓											✓		✓			✓	✓

a. The 24 hr time point for Cycle 1/Day 3 is the pre-dose time point on Cycle 1/Day 4 and the 24 hr time point for Cycle 1/Day 10 is the pre-dose time point on Cycle 1/Day 11.
b. All samples will be collected relative to PF-04449913 dosing.
c. All samples will be collected relative to daunorubicin dosing. Cycle 1/Day 3: 0 hour (pre-dose), 0.25 hour (mid-infusion), 0.5 hour (immediately prior to the end of infusion).
d. If a second induction cycle is administered, then ECG should be collected on Day 1 and Day 10 at 1 hr post-dose.
Patients should be hospitalized on Cycle 1/Day 3 and 4, and Cycle 1/Day 10 and 11 for full PK sample collection.

Table 11. Combination cohort 3: PF-04449913 + Azacitidine in Patients with previously untreated AML who are eligible for non-intensive chemotherapy

Study Days	Screening	Cycle 1, Day 1						Cycle 1 Day 2		Cycle 1, Day 7&21 (azacitidine samples taken only on C1D7)								Cycle ≥2 Day 1 (PK samples taken only on C3D1 and C5D1)			EOT
Hour[a]		0[a]	0.25	0.5	1	2	6	1	4	0[a,c]	0.25	0.5	1	2	4	6	24	0[a]	1	4	0
PF-04449913 PK Samples								X	X	X	X		X		X	X	X	X	X	X	
Azacitidine PK Samples			X	X	X	X	X			X	X	X	X	X		X					
Triplicate 12-lead ECG[b]	X	X						X	X				X		X			X[d]	X	X[d]	X

a. PK sample collection: In all instances, "0 hour" represents a pre-dose collection. The PK sample should be collected within 30 minutes prior to the first dose administration and within 15 minutes prior to the subsequent dose administrations. Patients should be reminded not to take their study drug prior to arriving at the clinic on protocol scheduled visits. The PK time points for each compound (Azacitidine and PF-04449913) are in reference to their respective dosing times.

b. Triplicate 12 lead ECGs: At each time point, 3 consecutive supine 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the appropriate time. All ECG timepoints are in reference to dosing of PF-04449913.

c. The 24 hr time points for Cycle 1/Day 7 and Cycle 1/Day 21 are the pre-dose time points on Cycle 1/Day 8 and Cycle 1/Day 22, respectively.

d. For patients without any medical history of cardiac disease or cardiac observation during the study, ECGs at 0 and 4 hours on Day 1 of Cycle 7 and thereafter may be omitted. However, if a moderate/strong CYP3A4/5 inhibitor or TdP drug will be initiated, the guidance provided in Section 7.1.5 requiring additional ECG monitoring before and after starting the medication must be followed for all patients.

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APPENDICES

1. INTRODUCTION

PF-04449913 is a novel small molecule inhibitor of the Sonic Hedgehog (Hh) signaling pathway being developed for the treatment of hematologic malignancies and solid tumors. This Phase 1 study is designed to evaluate the safety, tolerability, efficacy, PK and PD of PF-04449913 administered orally as a single agent in Japanese patients with select advanced hematologic malignancies, in combination with intensive chemotherapy (cytarabine and daunorubicin) or low-dose cytarabine (LDAC) in patients with previously untreated AML or high-risk MDS, or in combination with azacitidine in previously untreated AML patients who are eligible for non-intensive chemotherapy. PF-04449913 is administered as a single agent in 1 Japanese MF patient who has been treated in Study B1371013. Forty-nine patients will be enrolled in this study at maximum.

1.1. Indication

Hematologic malignancies, including acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS).

1.2. Background and Rationale

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

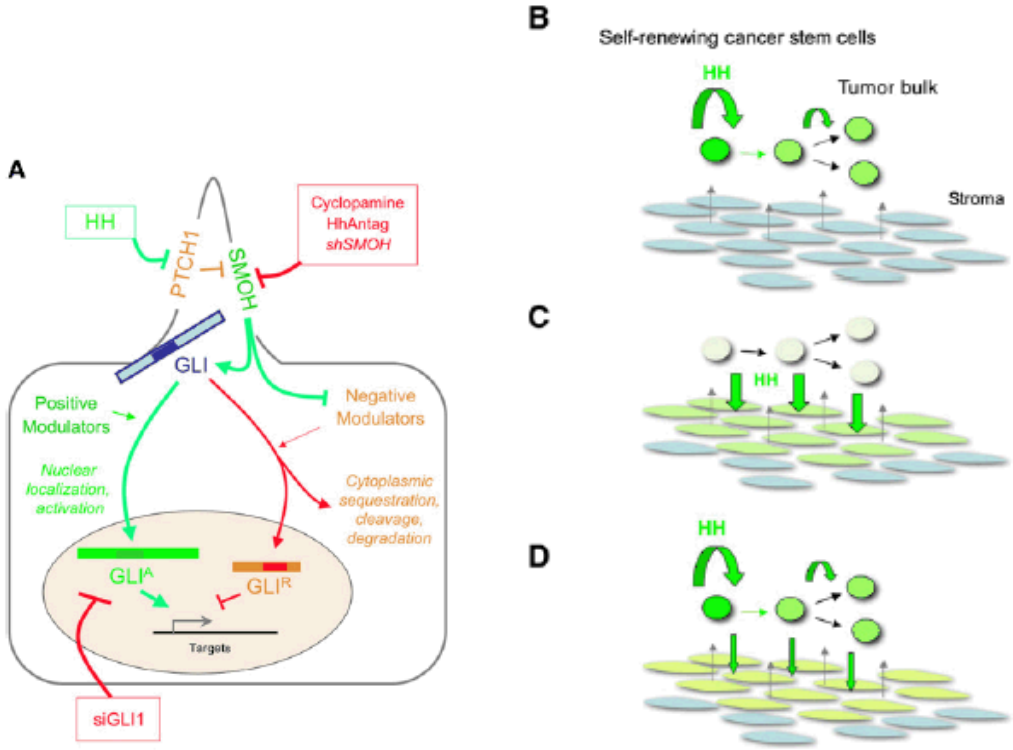
A milestone in understanding cancer as a developmental problem is the identification of cancer stem cells that self-renew, reinitiate tumor development, and give rise to tumor bulk. This may ultimately contribute to tumor resistance and metastatic spread, and impact overall survival. Standard chemotherapy, radiotherapy, and a range of targeted therapies can reduce tumor bulk, but are less effective at targeting cancer stem cells. The key challenge has been to identify the molecular mechanisms that maintain and support cancer stem cell self-renewal and survival.

Hh and Gli signaling (Hh-Gli) are critical pathways in animal patterning and cell terminal differentiation during embryogenesis, and may play a key role in human malignancies when aberrantly activated. After birth, the Hh pathway is repressed in the majority of cells but is activated during tissue repair and in self-renewing populations. Hh signaling is initiated when Hh binds to the Patched (PTCH) transmembrane protein and inactivates its function, which in the absence of Hh, is to inhibit SMO signal transduction. Following deactivation of PTCH in response to the binding of Hh ligand, the seven-transmembrane protein Smoothened (SMO), which is normally held in an inactive state by PTCH, is released and activates a signaling cascade that regulates the Gli family of transcription factors (Figure 2). The Gli family of genes encodes proteins that act either as transcriptional repressors (in the absence of Hh), or as transcriptional activators (in the presence of Hh) of genes controlled by the Hh pathway. Several proteins modulate the ratio of Gli activator (GliA) to Gli repressor (GliR) activity and in so doing determine the level of active cellular Hh ligand (Figure 2).

Since its original description, the Hh pathway has received increasing attention as a pleiotropic oncogenic pathway, and its aberrant activity has been implicated in both hematopoietic and solid tumor malignancies utilizing a range of different mechanisms, including direct cell cycle and anti-angiogenic effects (Thomas BJ, 2005; Straface G et al,

2008). [1, 2] Given that these cell types and mechanisms are unrelated in their developmental origin, site, and function, a common dependence of cancer stem cells on Hh-Gli signaling for survival and self-renewal, paralleling its roles in normal development and homeostasis, could underlie its widespread involvement in human cancers (Altaba AR, 2008). [3] An important caveat is that the Hh signaling pathway is dispensable for adult hematopoetic stem cell function (Gao J et al, 2009). [4]

Figure 2. Mechanism of Hh Signaling



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1.2.2. The Role of Hh in Myeloid Malignancies

Aberrant Hh signaling has been described in a variety of different human lymphoid and myeloid leukemias, and leukemia stem cells. The expression levels of PTCH, SMO and GLI1 were found to be elevated in several leukemic cell lines (Bai LY et al, 2008) [5]. PTCH and SMO were found to be expressed in Jurkat T-ALL cells, and Shh and GLI1 expression were identified in human promyelocytic leukemia (HL-60) and KG-1 cell lines (Kobune M et al, 2009). [6] Patient-derived AML samples have been shown to express Gli-1 in proportion to the number of CD34+ blast cells (Jamieson C et al, 2011). [7] In addition, Hh signaling is up-regulated in several subtypes of human AML cells, including primary CD34+ leukemic cells and cytokine-responsive CD34+ cell lines such as Kasumi-1, Kasumi-3, and TF-1. Inhibition of Hh signaling induced apoptosis following 48 h of exposure, although these CD34+ cell lines exhibited resistance to cytarabine. These data were confirmed by reverse transcription-

polymerase chain reaction (RT-PCR) for Hh pathway components, and a GLI-responsive reporter assay (Kobune M et al, 2009). [6] Finally, upregulation of Hh pathway components has been observed in chemoresistant AML cell lines in vitro, and pharmacological inhibition of the Hh pathway resulted in decreased multi-drug resistance (MDR-1) or P-glycoprotein (P-gp) expression in these cells (Queiroz KCS et al, 2010). [8]

Given the central role of Hh signaling in cell differentiation, Hh inhibition represents a mechanistically novel approach, with the potential to eliminate the leukemia stem cells (LSC) population and to abrogate tumor proliferation in at least a subset of CD34+ lymphoid and myeloid hematopoietic malignancies.

1.2.3. Role of Hh Pathway Activation in Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

MDS and AML comprise a group of myeloid neoplasms, whose common feature is a stem-cell-derived clonal myelopoiesis with altered proliferation and differentiation. AML is generally a disease of older individuals, and is uncommon prior to the age of 40. The average age of diagnosis of AML is 67 years. It is estimated that there will be 12,950 new cases and 9,050 deaths from AML in the United States in 2011 (American Cancer Society: Cancer Facts and Figures 2011). [9] It is estimated that there will be 3,400 new cases of AML in Japan (Mattson-Jack Epi data 2012). Similarly, the onset of MDS before age 50 is rare, and the estimated annual incidence of MDS is similar for different regions; United States (3.3 per 100,000 persons), England and Wales (3.6 per 100,000), Germany (4.1 per 100,000) and France (3.2 per 100,000) (Rollison DE et al, 2008). [10] It is estimated that annual incidence rate of MDS is 2.7 per 100,000 in Japan (Investigation by Japan Ministry of Health, Labour and Welfare). Genetic and functional studies have demonstrated that AML and MDS develop as a result of the acquisition of genetic and epigenetic alterations resulting in abnormal cell differentiation and dysregulated self-renewal.

In 2001, the WHO (World Health Organization) committee modified the FAB (French-American-British) system (Appendix 2) by lowering the level of myeloblasts required for the diagnosis of AML to >20%. The revised MDS 2008 WHO criteria (Appendix 3) made additional adjustments, classifying adult-onset primary MDS into six subcategories including RAEB-2 (defined as 5-19% circulating peripheral blasts or 10-19% bone marrow blasts). The estimated risk of leukemic transformation from RAEB-2 (also referred to as high-risk MDS) to AML is more than 50%; thus most patients with MDS RAEB-2 are treated with AML-type therapies (Tefferi A et al, 2009). [11]

In addition to the evidence described in Section 1.2.2, further data supporting the importance of aberrant Hh pathway activation in leukemia is derived from patients enrolled in the completed SMO inhibitor monotherapy hematology trial (B1371001). Preliminary data from this study suggests that the mechanism of action of Hh inhibition in leukemia may involve the mobilization of blast cells from the bone marrow to the peripheral blood, with subsequent expansion and differentiation to leukemia stem cells (Jamieson C et al, 2011). [7] Fiedler W et al (ASH 2011) [12] examined untreated AML patient samples and identified GLI2 gene expression as a negative prognostic indicator that correlated with *FLT3* mutation status. In

addition, the clinical outcome of patients correlated with Hh pathway expression, suggesting that aberrant Hh pathway activity may be a relevant therapeutic target.

Given the central role that Hh signaling plays in cell differentiation through impacting both the LSC population and the surrounding stromal microenvironment or niche supporting these cells, Hh inhibition in combination with chemotherapy represents a mechanistically attractive approach to assist with the elimination of the residual LSC population in AML and MDS that persists following standard chemotherapy regimens, and is likely to contribute to recurrence.

1.2.4. Rationale for Combination Therapy of PF-04449913 in Patients with AML and MDS

Patients with AML and MDS have few treatment options yielding durable remissions, especially in older patients. Although treatment regimens and outcomes for patients with AML may differ between younger and older adults, induction chemotherapy with cytarabine and an anthracycline has been a standard treatment for newly diagnosed AML over the past 20 years. Complete remissions can be achieved in 50-80% of adult patients <60 years old with de novo AML, when treated with continuous infusion cytarabine and anthracycline, depending on the patient's prognostic factors. However, only 20-40% of patients who achieve a remission have prolonged leukemia-free survival (Stone RM et al, 1993; Bishop JF, 1997; Mayer RJ, 1994). [13, 14, 15]

While there is no clear dividing line when considering age in AML, in many studies, 'older adults" have been defined as >60 years of age. Outcomes for AML patients worsen with age, as overall survival rates decrease as age increases (Schiller G et al, 1997). [16] Most trials of older patients with newly diagnosed AML have reported CR (complete remission) rates of between 40 and 60 percent (Applebaum FR et al, 2006; Juliusson G et al, 2009; Lowenberg B et al, 2009; Lowenberg B et al, 1998; Estey E et al, 2007; Ferrara F et al, 1998; Leoni F et al, 1997; Juliusson G et al, 2003; Vey N et al, 2004; Gardin C et al 2007). [17, 18, 19, 20, 21, 22, 23, 24, 25, 26] This may in part be due to the fact that older patients are often ineligible for intensive chemotherapy due to co-morbidities, and thus are treated with less aggressive approaches that result in lower frequencies of durable response rates. These patients also more commonly have adverse prognostic factors including central nervous system involvement of the leukemia, systemic infection at diagnosis, elevated white blood cell count (>100,000/mm^3), treatment-induced AML, a history of MDS or another antecedent hematological disease (AHD), or express the progenitor cell antigen CD34 and/or the P-glycoprotein (*MDR1* gene product), both of which result in a more unfavorable outcome (Myint H et al, 1992; Geller RB et al, 1990; Campos L et al, 1992). [27, 28, 29] Taken together these data indicate that therapeutic options for these patients are limited, and less toxic therapies with more durable responses are urgently required.

One option for these patients may be to combine with an agent that targets the residual cancer stem cells which may persist following standard chemotherapy. Given the central role of Hh signaling in cell differentiation through modulating the LSC population and surrounding stromal microenvironment supporting and nourishing these cells, Hh inhibition in combination with chemotherapy represents a mechanistically attractive approach to eliminate the LSC population in MDS and AML. In addition, it has been demonstrated that Hh

signaling maintains chemo-resistance in myeloid leukemia cells (Queiroz KCS et al, 2010).[8] Finally, the clinical activity observed with PF-04449913 monotherapy in AML and MDS (Section 1.2.8.1) suggests that these diseases may be Hh pathway dependent. Thus, the rationale for this combination, is that patients with previously untreated AML and MDS will have increased efficacy with acceptable accompanying safety profiles when PF-04449913 is added to standard 7:3 induction chemotherapy (fit patients), or used in combination with LDAC in patients unable to tolerate intensive chemotherapy.

1.2.4.1. Rationale for Intensive Chemotherapy Combinations with PF-04449913

Fit patients are defined as those having an ECOG (Eastern Cooperative Oncology Group) performance status less than 2 and having a lack of specific co-morbidities (Kantarjian H et al, 2006).[30] For these patients, standard intensive induction therapy is often a reasonable option, resulting in CR rates averaging 50% and rates of death from aplasia or indeterminate causes below 15% (Applebaum FR et al, 2006; Estey E, 2007).[31, 21] Induction therapy generally comprises 3 days of an anthracycline (eg, daunorubicin 45-60 mg/m^2 or an alternative anthracycline at equivalent dose) and 7 days of cytarabine (100-200 mg/m^2 continuous IV). Both American (Rowe JM et al, 2004; Anderson JE et al, 2002)[32, 33] and European (Gardin C et al, 2007)[26] cooperative group studies have found that the choice of anthracycline (daunorubicin or idarubicin) is of little consequence, assuming equitoxic doses are administered. In addition, protocols that have substituted other anthracyclines, evaluated increased doses of cytarabine or daunorubicin, or added a third or fourth drug, have not shown significantly improved response rates. Specifically, attempts to improve responses with potentially non-cross-resistant drugs have not been successful (eg, fludarabine, etoposide, topotecan, thioguanine, mitoxantrone) (Arlin Z et al, 1990; MacCallum PK et al, 1993; Buchner T et al, 1999; Ho AD et al, 1998; Feldman EJ et al, 1993; Estey EH et al, 2001; Russo et al, 2005; Bishop JF et al, 1990; Hann IM et al, 1997).[34, 35, 36, 37, 38, 39, 40, 41 ,42] As such, there is no conclusive evidence to recommend one "7+3" regimen over another (Kolitz JE et al, 2006).[43] Depending on dose, schedule, and patient selection criteria, most regimens evaluated have similar response rates and share common toxicities (Atallah E et al, 2007; Mandelli F et al, 2009; Lowenberg B et al, 2009).[44, 45, 19] Thus, a reasonable induction regimen for patients who are medically fit is seven days of continuous infusion of cytarabine (Ara-C, 100 mg/m^2 per day) plus three days of daunorubicin (60 mg/m^2 per day) (Larson R et al, 2011).[46]

The AML 14 trial is being used in this study as a reference for intensive chemotherapy response rates (Burnett AK et al, 2009).[47] The Burnett trial enrolled 1273 patients, predominantly aged over 60 years (although younger patients were allowed) with AML and High-risk MDS. The overall response rate across all arms was 62% (complete remission 54%, complete remission without platelet/neutrophils recovery 8%); 5-year survival was 12%, and no benefits were observed in either dose escalation schedule.

To determine whether the addition of an Hh inhibitor can increase intensive chemotherapy response rates with an accompanying acceptable safety profile, PF-04449913 will be administered once daily and continuously starting on Day -3, prior to the commencement of cytotoxic therapy. This schedule is consistent with other mobilizing/cytotoxic combination

studies, and will allow cells time to transit from the marrow to the peripheral blood compartment (Fierro FA et al, 2009).[48]

1.2.4.2. Rationale for LDAC and PF-04449913 Combinations

Less aggressive therapies are often required for unfit older patients with poor performance status (as defined by Kantarjian H et al, 2006). [30] Low-dose Ara-C (LDAC) is commonly used in this patient population (Dohner H et al, 2010). [49] Data obtained from a large trial comparing LDAC (given at the dose of 20 mg twice daily for 10 days on a 28-day cycle) to hydroxyurea, showed LDAC CR rates of 18% with an OS of 6 months (Burnett AK et al, 2007). [50] Based on the above data, LDAC offers significant therapeutic advantages over best supportive care in patients who cannot tolerate intensive chemotherapy and have few clinical options. For the purposes of this trial and in order to maintain consistency with the above data, LDAC will be given at a dose of 20 mg administered SC twice daily for 10 days every 28 days. PF-04449913 will be added to these agents to determine if the combination regimen is adequately tolerated and can improve on the efficacy response rates and survival of stand-alone LDAC chemotherapy.

1.2.4.3. Rationale for azacitidine and PF-04449913 Combinations

In a randomised Phase 3 trial to compare azacitidine with standard therapy in untreated non-Japanese elderly AML patients (>30% bone marrow blast), azacitidine showed a clinically meaningful prolongation of OS [mOS: 10.4 mo (95%CI (confidential interval): 8.0, 12.7) vs 6.5 mo (95%CI: 5.0, 8.6), HR (hazard ratio): 0.85 (95%CI: 0.69, 1.03), log-rank p-value (one-side) = 0.1009], although it did not reach the statistically significant difference. CR/CRi (CR with incomplete blood count recovery) rate were 27.8% for azacitidine and 25.1% for standard therapy. [51] Based on this study result, azacitidine has been approved in Europe for the indication of AML in addition to MDS. [52] Also, in National Comprehensive Cancer Network (NCCN) Guidelines, Ver. 2 (2016) [53] azacitidine is recommended as a standard medication for treatment of elderly patients with AML not indicated for intensive chemotherapy, and is also positioned as a standard treatment in the United States. In Japan, azacitidine has been approved as a drug for treatment of MDS in the FAB classification [including AML accompanying multilineage dysplasia by the WHO classification (AML-MLD)], and the safety profile thereof in Japanese patients with AML-MLD (499 subjects, 13.70%) was confirmed to be not notably different from that of non-Japanese patients in a drug use investigation of azacitidine conducted in 3642 subjects. [54] Furthermore, the regimens used in the standard treatment group of the above-mentioned phase 3 study comparing azacitidine monotherapy and standard therapy were also a standard therapy for treatment of AML in Japan, and compared to those regimens, azacitidine demonstrated a clinically-meaningful improvement, and thus, should also be appropriate as a control drug to be used in Japan.

1.2.4.4. Rationale for Assessment of the Drug-Drug Interaction (DDI) Potential between PF-04449913 and Coadministered Drugs

PF-04449913 is extensively metabolized by CYP3A4 (99.8%) in human liver microsomes and hepatocytes. Cytarabine is metabolized to a uracil derivative, arabinofuranosyl uracil in the liver and kidneys. Daunorubicin hydrochloride is extensively metabolized in the liver

and other tissues, producing daunorubicinol, the major metabolite which has anti-neoplastic activity. For azacitidine, the exact route of elimination and metabolic fate is not known in humans. One of the pathways of elimination for azacitidine appears to be deamination by cytidine deaminase principally located in the liver but also in granulocytes, the intestinal epithelium, and whole blood (Vidaza® USPI [US Prescribing Information]). The potential for a DDI is considered low for each of these agents, as enzyme systems other than CYP3A4 may be involved in the metabolism of these drugs. Since it is required to assess the DDI potential in humans when drugs are dosed in combination, a DDI assessment has been implemented for cytarabine and daunorubicin in the ongoing global Phase 1B/2 study (B1371003) and for azacitidine in the global Phase 1b/2 study (B1371012) with the Western population. In this study, potential DDI in Japanese patients will be evaluated.

1.2.5. Summary of Product Profile

1.2.5.1. Properties of PF-04449913

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

In the PTCH/P53 medulloblastoma mouse model of Hh pathway-driven tumors, PF-04449913 inhibited pathway activation (Gli1 expression) and produced rapid and complete tumor regression. Preclinical PK/PD modeling using this model suggests a target human dose of 15 mg/day is projected to yield at least 50% of tumor Gli1 mRNA inhibition from baseline levels and approximately 20% of skin Gli1 mRNA suppression.

PF-04449913 has been shown pre-clinically to have activity in imatinib-resistant CML blast crisis disease. Patient derived CD34+ imatinib resistant blast crisis CML cells xenotransplanted into immunocompromised mice treated with PF-04449913 alone or in combination with dasatinib reduced primary leukemic tumor burden. In addition, treatment with PF-04449913 reduced leukemic tumor formation in secondary recipients, suggesting that PF-04449913 is able to inhibit the LSC population that supports tumor propagation. Importantly, this was verified in CML T315I mutants, which are resistant to treatment with standard TKI therapy such as Imatinib. Similar studies are currently on-going in AML patient derived samples.

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

1.2.5.2. Properties of Cytarabine (Cytosine Arabinoside, Ara-C)

Cytarabine (1-β-D-Arabinofuranosylcytosine) is an anti-neoplastic synthetic nucleoside which differs from the normal nucleosides cytidine and deoxycytidine in that the sugar moiety is arabinose rather than ribose or deoxyribose. It is approved for use in combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults and children.

Common side effects of cytarabine include bone marrow suppression, Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise) and infections. Additional side effects include anorexia, nausea, vomiting, diarrhea, oral or anal ulcerations, hepatic dysfunction, fever, rash, bleeding and thrombophlebitis. At high doses it may cause neurological disorders. For details of the safety of cytarabine, please refer to the Japanese Package Inserts.

For induction therapy of acute non-lymphocytic leukemia and high-risk MDS, the usual cytarabine dose in combination with other anticancer drugs (including daunorubicin, see below) is 100-200 mg/m^2/day on Days 1-7 by continuous IV infusion. Cytarabine is then given at higher doses for consolidation therapy (1-3 g/m^2) Q12 hours on Days 1, 3 and 5 for 2-4 cycles.[63, 64, 65] It is also commonly used at low-doses (LDAC) as single-agent in patients unfit for intensive chemotherapy.

1.2.5.3. Properties of Daunorubicin

Daunorubicin has anti-mitotic and cytotoxic activity through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA (deoxyribonucleic acid) by intercalation between base pairs inhibiting topoisomerase II activity, therefore inhibiting polymerase activity and altering regulation of gene expression, as well as producing free radical damage to DNA. Daunorubicin hydrochloride in combination with other approved anticancer drugs (including cytarabine) is indicated for remission induction in acute non-lymphocytic leukemia (myelogenous, monocytic, erythroid) of adults. In the treatment of adult acute non-lymphocytic leukemia, daunorubicin hydrochloride, used as a single-agent, has produced complete remission rates of 40-50%, and in combination with cytarabine, has produced complete remission rates of 53-65%.

Side effects of daunorubicin include local tissue necrosis if there is extravasation during administration. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. In adult patients, the incidence of myocardial toxicity increases after a total cumulative dose is administered exceeding 400 to 550 mg/m^2. Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage. Other side effects include reversible alopecia, contact dermatitis and urticaria. For patients with AML and high-risk MDS, induction chemotherapy consisting of 1 or 2 cycles of daunorubicin hydrochloride 45-90 mg/m^2/day IV on Days 1, 2, and 3 in combination with cytosine arabinoside (see above) is commonly given. For details of the safety of daunorubicin, please refer to the Japanese Package Inserts.

1.2.5.4. Properties of Azacitidine

Azacitidine is a chemical analogue of the cytosine nucleoside whose mechanism of action involves inhibition of DNA methyltransferase at low doses, causing hypomethylation of DNA, and direct cytotoxicity in abnormal hematopoietic cells in the bone marrow through its incorporation into DNA and ribonucleic acid (RNA) at high doses, resulting in cell death. Azacitidine was approved for the treatment of all subtypes of MDS according to the FAB classification in Japan.

Main adverse reactions associated with azacitidine treatment include neutropenia (including febrile neutropenia), thrombocytopenia, leukopenia , haemoglobin decreased, constipation, erythropenia, injection site reaction (including erythemas, rash, pruritus, induration), haematocrit decreased, lymphopenia, malaise, pyrexia, alanine aminotransferase (ALT) increased, anorexia, ALP increased, aspartate aminotransferase (AST) increased, blood albumin decreased. For details of the safety of azacitidine, please refer to the Japanese Package Inserts.

1.2.6. PF-04449913 Preclinical Safety Data

In the 1-month rat toxicity study, the primary target organs included the kidney and bone (epiphyseal growth plate); the no observed adverse effect level (NOAEL) was 10 mg/kg/day (Day 29, male and female combined, free C_{max} of 97 ng/mL and free Cave of 40 ng/mL). In the 1-month dog toxicity study, the primary target organ was the kidney; the NOAEL was 1 mg/kg/day (Day 29, free C_{max} of 28 and 14 ng/mL and free Cave of 6 and 2.5 ng/mL, in males and females, respectively).

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

In the rat 10-day study, kidney injury was dose-dependent. Microscopically, severe hyaline droplet deposition along with degeneration/necrosis, karyomegaly and vacuolation was observed in the kidneys of all animals given 500 mg/kg/day. Similar changes of lower severity were observed microscopically at 50 mg/kg/day, without clinical evidence.

In the 1-month rat toxicity study, the microscopic changes were similar to those reported in the 10-day rat study and were also dose dependent. Regeneration of tubule cells in the cortical region was moderate in 1/10 males and 8/10 females, with the remaining animals in the 50 mg/kg/day group exhibiting minimal to slight regenerative changes. These microscopic changes correlated with significant increases in serum creatinine levels, a decrease in urinary pH and the presence of inflammatory cells and granular casts in the urine.

Evidence from both the rat and dog 1-month toxicity study suggested that the kidney changes are reversible as determined by histological examination.

Bone Effects: Bone changes were limited to the 50 mg/kg/day group in the 1-month rat toxicity study. Changes in femur and sternum were characterized by slight to moderate epiphysis alterations and decreased medullary trabeculae. The epiphyseal chondrocytes were decreased in number and disorganized in appearance. These changes persisted throughout

the 1-month recovery phase. The changes in the epiphyseal growth plate are consistent with inhibiting the Hh pathway in growing bone (Kimura H et al, 2008) [55] and chondrogenesis (Amando K et al, 2008). [56]

Cardiovascular Effects: The hERG (human ether- à -go-go-related gene) binding IC_{50} for PF-04449913 was 3.1 uM. PF-04449913 produced dose related changes in electrocardiogram parameters in a single dose cardiovascular safety pharmacology study in dogs at 5 and 30 mg/kg. At 5 mg/kg, a small (5 msec) but statistically significant increase in QT measurement corrected by heart rate (QTc) occurred 7 to 14 hour post-dose, where the peak free plasma concentration was 276 ng/mL. At 30 mg/kg, statistically significant increases in heart rate (10 bpm) and QRS, QT and QTc were observed. Of note, the statistically significant increases in heart rate at 30 mg/kg coincided with episodes of emesis, and therefore were most likely due to the emetic effect. There were no statistical or remarkable changes in cardiovascular parameters in dogs treated with 1 mg/kg PF-04449913.

Other Findings:

- Hematologic

There were no histopathologic correlates suggestive of changes in normal bone marrow.

- Gastrointestinal

In a 7-day repeat dose toxicity study in dogs up to 100 mg/kg/day there were observations of emesis and liquid stool. In the 1-month toxicity study in dogs, vomiting and discolored/liquid feces was observed at 5 mg/kg.

- Phototoxic

PF-04449913 absorbs light with a peak absorbance observed at 204 and 280 nm. For the UVA-UVB/visible range important for phototoxic potential (290 nm-700 nm), PF-04449913 absorbs light at 290 nm; the tail of the large absorbance peak at 280 nm. The molar extinction coefficient for PF-04449913 at 290 nm is 9,622 L/mol/cm.

Impact of preclinical safety findings on patient management:

Based on the pre-clinical safety studies, the kidney could be a target organ of toxicity in humans. However, given the ability to monitor for changes in kidney function and reversibility of the effects in both animal species this suggests that this is a manageable risk for PF-04449913. Renal function and potentially related adverse events have been closely monitored in the B1371001 and B1371002 studies, and no gross adverse renal effects have been identified in patients to date.

The pre-clinical data suggest there is a potential for PF-04449913 to induce QT prolongation in humans. Electrocardiograms (ECGs) and vital signs and potentially related adverse events are closely being monitored in the ongoing dose-escalation Phase 1 studies with PF-

04449913 administered as single-agent to patients with hematologic malignancies or solid tumors.

PF-04449913 has the potential to be phototoxic. Guidelines for the prevention of excessive sunlight exposure will be implemented in the study (Section 4.4).

Bone changes occurred only in the growth plate of the growing bone of the rat and did not occur in the closed plate of the dog therefore these effects are not a risk for adult patients where the epiphyseal growth plate is also closed.

1.2.7. PF-04449913 Preclinical Pharmacokinetics Data

In humans, PF-04449913 has been projected to have an oral bioavailability of 55%, a steady state volume of distribution of 2.7 L/kg, a systemic plasma clearance of 1.03 mL/min/kg, and an elimination half-life of 30 hours. PF-04449913 exhibited high plasma protein binding with a fraction unbound of 0.091 in humans. All primary metabolites observed *in-vitro* and *in-vivo* appeared to be formed via oxidative metabolism, indicating that this is likely the major route of clearance of PF-04449913. CYP3A4 appeared to be the major enzyme mediating PF-04449913 metabolism (~99.8%). The contributions from the other ten P450s evaluated in the metabolism of PF-04449913 were negligible. In rats, 6.88% and 10.7% of the administered dose was eliminated unchanged from urine and bile, respectively.

In-vitro data indicate that PF-04449913 has minimal potential to inhibit all the major human CYP enzymes with IC_{50} values greater than 30 μM (11,232 ng/mL) for CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. PF-04449913 does not inhibit the metabolic activity of CYP3A in a time dependent manner. PF-04449913 was evaluated in-vitro to determine if it is a substrate for human P-glycoprotein (P-gp) in monolayer Madine-Darby Canine Kidney cells transfected with human Multi-drug Resistance gene. The resulting polarized efflux ratio was 14.9. In the presence of a combination of P-gp inhibitors, the efflux ratio reduced to unity. These data collectively suggest the involvement of P-gp in attenuating the absorptive transport of PF-04449913.

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

1.2.8. Summary of Safety, Efficacy and PK data in Patients with Selected Myeloid Malignancies and Solid Tumors

As of 29 January 2020, 7 clinical studies have been conducted in cancer patients. Four (4) studies in cancer patients have completed (B1371001, B1371002, B1371003 and B1371013), and 3 studies are ongoing (B1371005, B1371012 and B1371019).

- B1371001: A Phase 1 dose-escalation, single-agent study in patients with select advanced hematologic malignancies. Forty-seven patients were dosed. This study has completed.

- B1371002: A Phase 1 dose-escalation, single-agent study in patients with advanced solid tumors. Twenty-three patients were dosed. This study has completed.

- B1371003: A Phase 1b/2 study of glasdegib in combination with low-dose cytarabine (Ara-C), decitabine, or intensive chemotherapy (cytarabine/daunorubicin), in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome. Two hundred fourty six (246) patients were dosed. This study has completed.

- B1371005: A Phase 1 dose-finding study of single-agent glasdegib in Japanese patients with select advanced hematologic malignancies, or glasdegib in combination with intensive chemotherapy (cytarabine and daunorubicin), low-dose cytarabine (LDAC) or azacitidine in patients with previously untreated AML or high-risk MDS. Fourty five (45) patients have been enrolled and treated in this ongoing study.

- B1371012: A Phase 1b/2 study of glasdegib in combination with azacitidine versus p in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20% to 30% blasts and multi-lineage dysplasia, and CMML. Seventy-two (72) patients have been enrolled and treated in this ongoing study.

- B1371013: A Phase 2 study of single-agent glasdegib versus placebo in patients with primary or secondary myelofibrosis who have been previously treated with a Janus kinase inhibitor. Twenty-one (21) patients were enrolled and treated. This study has completed.

- B1371019: A Phase 3 study of glasdegib versus placebo in combination with intensive chemotherapy (cytarabine/daunorubicin) or azacitidine, in patients with previously untreated acute myeloid leukemia. Seven hundred seventeen (717) patients have been enrolled and treated in this ongoing study. Following planned interim analyses for the Non-Intensive and Intensive study cohorts, Pfizer accepted the External Data Monitoring Committee's (EDMC) conclusion of futility that in this trial the combination arms (azacitidine + glasdegib and cytarabine/daunorubicin + glasdegib, respectively) would not meet the primary objective of improving overall survival with respect to azacitidine and cytarabine/daunorubicin alone.

1.2.8.1. Safety and Efficacy Summary in Patients with Select Myeloid Malignancies and Solid Tumors

1.2.8.1.1. B1371001: Patients with Select Myeloid Malignancies

A total of 47 patients were screened and assigned to treatment. All treated patients were analyzed for PK and safety. All treated patients except 1 patient in the 80 mg group were included in the efficacy analysis. The majority (28/47 patients, 59.6%) of patients were male. The mean age was 69 years (range from 25 to 89 years). The diagnoses of enrolled patients included: AML (28 patients, 59.6%), CML (5 patients, 10.6%), CMML (1 patient, 2.1%), MDS (6 patients, 12.8%), and MF (7 patients, 14.9%). The median duration of treatment with PF-04449913 for AML patients, CML patients, CMML patients, MDS patients, and MF patients was 64.5 days (range: 5-261 days), 36.0 days (range: 1-280 days), 54.0 days (range: 54-54 days), 153.0 days (range: 36-537 days), and 182.0 days (range: 44-371 days) respectively.

Out of the 41 DLT evaluable patients, 2 patients (1 patient each in the 80 mg and the 600 mg groups) experienced DLTs during Cycle 1. One patient in the 80 mg group experienced non-hematologic DLTs of hypoxia and pleural effusion. In response to the hypoxia, which was also considered as a Serious Adverse Event (SAE), dosing with the study drug was interrupted temporarily, and the dose reduced. The patient also received a blood transfusion. One patient in the 600 mg group experienced a non-hematologic DLT of peripheral oedema which was also considered an SAE. In response to the SAE, the study drug was stopped temporarily. All the 3 DLTs experienced by the 2 patients were Grade 3 in severity and considered to be related to the study drug. Six patients were not evaluable for DLTs as they took less than 80% of the planned dose in Cycle 1 for reasons other than study drug related non-hematologic and hematologic toxicities (except prolonged myelosuppression), including 1 patient who received the lead in dose but developed CNS (central nervous system) disease progression during the lead-in period, and thus did not start the Cycle 1/Day 1 dose.

The majority of treatment-related adverse events (AEs) reported were Grades 1 to 3 in severity. The most frequently reported treatment-related AE was dysgeusia (27.7%).Treatment-related Grade 3 events included: decreased appetite (n = 5), weight decreased (n = 2), nausea, vomiting, fatigue, mucosal inflammation (n = 1 each). The only treatment related Grade 3 AE reported in >2 patients included decreased appetite (5 patients). Three treatment-related Grade 4 AEs were reported. No treatment-related Grade 5 AEs were reported. One Grade 1 and 4 Grade 2 treatment-related AEs of prolonged ECG QT were reported.

Grade 3 laboratory test results independent of causality included: lymphocytes (n = 16), platelets (n = 8), WBCs (n = 8), haemoglobin (n = 10), neutrophils (n = 3), ALT (n = 1), alkaline phosphatase (n = 2), total bilirubin, hypokalemia, hyponatremia (n = 4 each), hyperglycemia (n = 3), hypoalbuminemia, hypocalcemia and hypophosphatemia (n = 1 each). Grade 4 laboratory test results independent of causality included: platelets (n = 33), neutrophils (n = 26), WBCs (n = 15), lymphocytes (n = 6), hemoglobin (n = 4), bicarbonate (n = 1).

QTc AEs were observed in the B1371001 study. Three patients (1 patient in the 400 mg group and 2 patients in the 600 mg group) had a post-baseline maximum QTcF interval (QTc interval using Fridericia's correction formula) of ≥500 msec and 6 patients (1 from the 5 mg group and 5 from the 600 mg group) had a maximum QTcF increase from baseline of ≥60 msec. All these events were non-symptomatic in nature.

Although the evaluation of efficacy was not the primary objective of this study, patients were evaluated for disease specific efficacy endpoints and the best overall responses, duration of response, TTP and PFS were derived. A total of 4 MDS/CMML patients (4/7 patients: 3/6 MDS patients and 1/1 CMML patient, 57.1%) achieved stable disease or better, among whom 2 patients (2/7 patients, 28.6%) showed hematologic improvement. For the 7 MF patients, 2 patients achieved clinical improvement. For patients with AML (28 patients), 1 patient (3.6%) had morphologic complete remission with incomplete blood count recovery, 4 patients (14.3%) had partial remission with incomplete blood count recovery, and 4 patients (14.3%) had minor response. Treatment failures occurred in 7 patients (25%) due to resistant

disease. Clinical benefit (CR + CRi+ PR + PRi+ stable disease + MR) was shown in 16 patients (57.1%), including 7 patients (25%) with stable disease. Among the 2 patients with CML-AP/BC, 1 patient had a partial cytogenetic response. None of the patients with CML-CP had a cytogenetic response. Out of the 46 patients evaluated for efficacy, 2 out of 7 MDS/CMML patients (28.6%), 2 out of 7 MF patients (28.6%) and 9 out of 28 AML patients (32.1%) had an OR. No CML patients had an OR.

1.2.8.1.2. B1371002: Patients with Solid Tumors

A total of 23 patients were screened and received study treatment. Nine (39.1%) females and 14 (60.9%) males were assigned to study treatment; the majority of the patients were white (18/23, 78.3%). The median age was 61.0 years, ranging from 27 to 76 years. The diagnoses of enrolled patients included: adenocarcinoma of the cervix, basal cell carcinoma, chondrosarcoma, malignant hepatic neoplasm, leiomyosarcoma, malignant fibrous histiocytoma, metastatic malignant melanoma, small cell lung cancer, malignant tongue neoplasm, dermatofibrosarcoma, signet-ring cell carcinoma, primitive neuroectodermal tumour (PNET), non-small cell lung cancer and desmoplastic small round cell tumour (DSRCT) (1/23 each, 4.3%); extraskeletal chondrosarcoma (2/23, 8.7%); and pancreatic carcinoma [7/23 (including pancreatic carcinoma, metastatic pancreatic carcinoma and adenocarcinoma pancreas), 30.4%].

Four patients each were assigned to PF-04449913 80 mg and 160 mg treatment, respectively. One patient in PF-04449913 160 mg cohort did not receive 80% of the planned PF-04449913 dose during Cycle 1 for reasons other than safety problems, therefore was not evaluable for assessment of DLT and was thus replaced. No patients in PF-04449913 80 mg and 160 mg cohorts experienced DLTs. A total of 7 patients were assigned to PF-04449913 320 mg treatment, among whom, 1 patient was not evaluable for DLT. A total of 8 patients were assigned to PF-04449913 640 mg treatment, among whom, 2 patients were not evaluable for assessment of DLT. Of the first 3 DLT-evaluable patients treated at 640 mg QD, 1 patient developed a DLT and thus the cohort was expanded to include 3 additional patients, of whom another patient developed a DLT. Thus the maximum administered dose was achieved at 640 mg QD and the MTD was estimated at 320 mg QD.

All patients experienced at least 1 Treatment-Emergent Adverse Events (TEAE during) the study, and 87% of the patients reported treatment-related TEAEs. The most frequently reported treatment-related AEs were dysgeusia (65.2%), fatigue (52.2%), decreased appetite (34.8%), nausea (34.8%) and dizziness (30.4%). The majority of treatment-related AEs reported were Grade 1 and 2 in severity. No Grade 3 treatment-related AEs were reported in ≥2 patients. Grade 3 treatment-related AEs included fatigue, increased ALT, increased AST, decreased appetite, dehydration, hyponatraemia, hypophosphataemia, dizziness and syncope reported in 1 patient each. No Grades 4 and 5 treatment-related AEs were reported in the study.

Grade 3 laboratory test results independent of causality included: lymphopenia (n = 3), hyponatremia (n = 5), increased AST and hypophosphatemia (n = 2 each), and hypocalcemia, hyperglycemia, increased ALT, increased total bilirubin and increased alkaline phosphatase

(n = 1 each). Grade 4 laboratory test results independent of causality included: lymphopenia , hypokalemia, hypocalcemia and hyperglycemia (n = 1 each).

Although the evaluation of efficacy was not the primary objective of this study, patients were evaluated for best overall response according to RECIST version 1.1. Of the 23 patients enrolled, 8 (34.8%) patients had a best overall response of objective disease progression and 8 (34.8%) achieved disease stabilization. Among the 8 patients with disease stabilization, 3 had stable disease lasting more than 6 months (1 patient with DSRCT, 1 patient with pancreatic cancer and 1 patient with extraskeletal myxoid chondrosarcoma). No patients achieved a complete response or partial response.

In summary, PF-04449913 appears to be safe and well-tolerated to date, with signs of clinical efficacy observed in all the hematologic malignancies studied (AML, MDS, CML and MF), with the exception of CMML. Several patients with aggressive malignancies remained on trial for prolonged durations; some exhibited cellular differentiation as determined by flow cytometry. On-target AEs (including alopecia and dysgeusia) were observed at multiple dose levels in both studies. Taken together, the data support testing PF-04449913 as a combination therapy in patients with AML and MDS for whom there are limited available therapeutic options.

1.2.8.1.3. B1371003: Patients with AML or high-risk MDS

As of July 2015, B1371003 Phase 1b enrollment of AML or High-Risk MDS patients for Arms A and B (unfit) and Arm C (fit) was completed and 52 patients were enrolled in this portion. In this portion, the median age was 70.0 (27-85 years). The majority of the patients were White (82.7%). The diagnoses included AML in 45 patients (Arm A = 20; Arm B = 5; Arm C = 20) and MDS in 7 patients (Arm A = 3; Arm B = 2; Arm C = 2).

In Arm A (LDAC + PF-04449913), twenty three patients were enrolled. Seventeen (17) patients received a starting PF-04449913 dose of 100 mg and 6 patients of 200 mg QD. No DLTs were observed. The most frequently reported treatment-related AEs in patients who received LDAC + PF-04449913 100 mg included nausea (35.3%), diarrhoea and neutropenia (29.4% each), and muscle spasms and dysgeusia (23.5% each). Grade 3 treatment-related TEAEs reported were anaemia (17.6%), fatigue (11.8%) and diarrhoea, stomatitis, abdominal pain, enterocolitis, impaired gastric emptying, oral disorder, febrile neutropenia, thrombocytopenia, backpain, pneumonia and hyperuricaemia (5.9% each). Grade 4 treatment-related TEAEs reported were neutropenia (29.4%), febrile neutropenia and thrombocytopenia (11.8% each), cardiac failure congestive (5.9%). Two on-study deaths were reported, one due to acute respiratory distress syndrome and one to acute myocardial infarction; both deaths were considered not related to PF-04449913 as per Sponsor assessment.

In Arm B (Decitabine + PF-04449913) 7 patients were enrolled. Four (4) patients received PF-04449913 100 mg and 3 patients received PF-04449913 200 mg. No DLTs were reported. The most frequently reported treatment-related AEs in patients who received Decitabine + PF-04449913 100 mg were nausea (75.0%), diarrhoea, thrombocytopenia, and neutropenia (50.0% each). No Grade 3 treatment-related TEAEs were reported. Grade 4

treatment related TEAEs were neutropenia and thrombocytopenia (50.0% each). No treatment-related deaths have been reported. This arm will not be evaluated in the Phase 2 portion of Study B1371003.

In Arm C (Cytarabine/Daunorubicin + PF-04449913), 22 fit patients were enrolled. Sixteen patients received a starting PF-04449913 dose of 100 mg QD and 6 patients of 200 mg. The most frequently reported treatment-related AEs in patients who received Cytarabine/Daunorubicin + PF-04449913 100 mg included nausea (81.3%), diarrhoea, febrile neutropenia and muscle spasms (43.8% each), dysgeusia (37.5%), stomatitis, headache, fatigue and pyrexia (31.3% each), constipation, dyspepsia, vomiting, anaemia, neutropenia, white blood cell count decreased, hypocalcaemia, hypokalaemia and alopecia (25% each). Grade 3 treatment-related TEAEs reported in more than 1 patient were febrile neutropenia (43.8%), anaemia (25.0%) and pyrexia (12.5%). Grade 4 treatment-related TEAEs reported in more than 1 patient were white blood cell count decreased (25.0%), thrombocytopenia and leukopenia (12.5% each). No treatment-related deaths have been reported. A DLT of Grade 4 polyneuropathy was reported at the 100 mg dose level and treatment was permanently discontinued.

Phase 2 consists of 2 components: Phase 2 randomized component in unfit patients (P2 Unfit) enrolled to receive either LDAC in combination with PF-04449913 or LDAC alone, and Phase 2 single arm component in fit patients (P2 Fit) who received PF-04449913 in combination with cytarabine/daunorubicin. As of Jan 2017, data were available for 132 patients in the P2 Unfit randomized portion of the study, and 71 patients in the P2 Fit arm.

The primary analysis of OS was conducted after 92 OS events observed. As a result, statistically and clinically significant improvement of OS prolongation in LDAC + PF-04449913 arm was observed (mOS for LDAC + PF-04449913 was 8.3 months vs 4.9 months for LDAC alone; stratified HR of 0.537 [80% CI: 0.407, 0.708]; 1-sided stratified log-rank p-value 0.0017) (data cut off: 13 Apr 2016). This result was consistent with the updated analysis in the CSR (mOS 8.8 months vs 4.9 months; stratified HR=0.513 (80% CI: 0.394, 0.666; stratified p=0.0004) (data cut off, hereafter: 3 Jan 2017). CR and DMR[a] rates based on derived response for PF-04449913 + LDAC were 17.0% (15/88) and 34.1% (30/88) versus 2.3% (1/44) and 6.8% (3/44) for LDAC alone, respectively. The safety profile of PF-04449913 100 mg combined with LDAC and LDAC alone was tolerable and manageable: The most commonly-reported AEs in the PF-04449913 100 mg+LDAC arm were cytopenia and gastrointestinal disorder. Cytopenias were not accompanied by higher rates of infections or bleeding as compared to the LDAC alone arm. SAEs of febrile neutropenia (28.6% versus 17.1%) and pneumonia (22.6% versus 17.1%) were more frequent in the PF-04449913 100 mg+LDAC arm than in the LDAC alone arm. In contrast, SAE of

[a] Disease Modifying Response (DMR) rate includes Complete Remission (CR), CR with incomplete blood count recovery (CRi), Morphologic Leukemia-Free State (MLFS), marrow CR (mCR) and Partial Remission (PR) (Appendix 5 and Appendix 8).

sepsis (3.6% versus 12.2%) was less frequently reported for the PF-04449913+LDAC arm versus the LDAC alone arm.

In P2 Fit arm (cytarabine/daunorubicin + PF-04449913), the primary analyses were planned for patients age ≥55 years old. For the primary endpoint, 22 (36.7%) patients achieved CR based on derived response for patients ≥55 years old. For OS of the secondary endpoint, the estimated mOS was 14.7 months for patients ≥55 years old. The safety profile of PF-04449913 100 mg combined with cytarabine/daunorubicin for patients in the P2 Fit arm was tolerable and manageable. The most frequently reported AEs (≥50%) in the P2 Fit arm were diarrhoea, febrile neutropenia, nausea and hypokalaemia.

1.2.8.1.4. Phase 1b/2 to Evaluate the Safety and Tolerability of PF-04449913 in Combination with Azacitidine in Patients with Previously Untreated Intermediate-2 or High-Risk Myelodysplastic Syndrome, Acute Myeloid Leukaemia with 20%-30% Blasts and Multi-Lineage Dysplasia, and Chronic Myelomonocytic Leukaemia (B1371012)

As of 2 September 2015, 10 patients have received 100 mg QD PF-04449913 + azacitidine 75 mg/m^2 day given subcutaneously for 7 consecutive days every 28 days. The primary diagnosis was MDS (n = 6), AML (n = 3) and CMML (n = 1). As of the time of reporting (15 July 2015), only 6 patients had received study treatment. The most frequently reported treatment-related TEAEs in ≥20% patients were fatigue (50.0%) and constipation (33.3%). The Grade 3 treatment-related TEAEs were hypophosphataemia, anaemia and febrile neutropenia (16.7% each). Grade 4 treatment-related TEAEs reported were neutropenia and thrombocytopenia (16.7% each). No Grade 5 treatment-related TEAEs were reported.

For additional details on the safety, tolerability and efficacy of PF-04449913 please refer to the current IB.

1.2.8.2. Clinical PK Summary

1.2.8.2.1. B1371001: Patients with Selected Myeloid Malignancies

Data following single and multiple dosing of PF-04449913 from study B1371001 in patients with selected hematologic malignancies are summarized for all cohorts tested (5, 10, 20, 40, 80, 120, 180, 270, 400, and 600 mg QD).

PF-04449913 was rapidly absorbed following oral dosing with a median T_{max} of PF-04449913 ranged from 1-2 hours following a single dose and 1-4 hours following multiple dosing. The geometric mean $t_{½}$ for PF-04449913 ranged from 17.4 to 34.3 hours (Table 12) across the various dose levels; however, at most dose levels, the half-life was ~ 24 hours. The geometric mean CL/F ranged from 5.63 to 12.7 L/hour following a single dose and 5.33 to 13.3 L/hour following multiple dosing. PF-04449913 accumulated following repeated dosing with a median R_{ac} ranging from 1.2 to 2.5. This was consistent with the observed $t_{½}$, as the predicted R_{ac} is in agreement with the estimated R_{ac}. The median linearity ratio (R_{ss}) ranged from 0.76 to 2.1, with the ratio being close to unity for most of the tested dose levels.

Table 12. Summary of Plasma Pharmacokinetic Parameters Following Single and Multiple Oral Doses of PF-04449913 in Select Hematological Malignancies (Study B1371001)

Parameter (Units)	Parameter Statistics by Dose Level									
	5 mg QD n=3	10 mg QD n=3	20 mg QD n=4	40 mg QD n=4	80 mg QD n=8	120 mg QD n=3	180 mg QD n=3	270 mg QD n=5	400 mg QD n=9	600 mg QD n=5
Cycle 1 Lead-in Day (Single Dose)										
N	3	3	4	4	8[a]	3	3	5	9[a]	5
C_{max} (ng/mL)	32.9 (3.0)	59.0 (21)	247 (47)	313 (51)	746 (56)	1418 (22)	1409 (79)	1534 (72)	3714 (30)	4527 (64)
T_{max} (hr)	2.0 (1.0-4.0)	2.0 (1.2-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	2.0 (1.0-4.0)	2.0 (1.3-4.0)	2.0 (1.1-4.0)	2.0 (1.0-4.1)	2.0 (1.3-4.5)	2.0 (1.1-4.0)
AUC_{inf} (ng•hr/mL)	657(19)	786 (23)	3548 (50)	3614 (38)	8755 (64)	14430 (35)	21280 (64)	25110 (109)	67720 (19)	86620 (58)
CL/F (L/hr)	7.61 (19)	12.7 (23)	5.63 (50)	11.1 (37)	9.13 (64)	8.33 (36)	8.48 (64)	10.8 (110)	5.90 (19)	6.93 (58)
Vz/F (L)	262 (32)	455 (41)	265 (62)	367 (38)	292 (71)	316 (52)	210 (92)	359 (143)	185 (50)	191 (78)
$t_{1/2}$ (hr)	25.1 (9.6)	25.1 (4.3)	34.3 (14)	23.3 (4.2)	23.3 (8.1)	26.5 (4.0)	17.4 (3.3)	23.6 (5.5)	23.9 (14)	19.6 (4.7)
Cycle 1/Day 21 (Multiple Dose)										
N	3	3	3	3	5	3	4[c]	2	6	4
C_{max} (ng/mL)	45.4 (12)	75.0 (30)	249 (35)	565 (83)	871 (35)	1621 (10)	2069 (41)	1504	4989 (7.0)	6413 (65)
T_{max} (hr)	2.2 (1.0-4.0)	1.0 (1.0-2.0)	0.92 (0.92-1.0)	1.0 (1.0-2.0)	1.3 (1.0-2.0)	2.2 (2.0-6.1)	1.1 (1.0-2.0)	3.1	4.0 (1.1-4.2)	3.2 (2.2-4.6)
AUC_{tau} [b](ng•hr/mL)	583 (10)	753 (27)	2566 (13)	6134 (61)	7482 (46)	22520 (13)	23060 (47)	22990	70430 (24)	71710 (51)
CL/F (L/hr)	8.57 (9.0)	13.3 (27)	7.79 (13)	6.52 (62)	10.7 (46)	5.33 (13)	7.81 (48)	11.8	5.68 (24)	8.36 (51)
C_{avg} (ng/mL)	24.3 (9.0)	31.4 (27)	107 (13)	256 (61)	312 (46)	940 (13)	961 (48)	960	2933 (24)	2986 (51)
C_{min} (ng/mL)	14.7 (15)	18.9 (14)	54.7 (46)	162 (107)	116 (48)	360 (115)	408 (42)	428	1113 (44)	1641 (59)
C_{trough} (ng/mL)[d]	15.1 (17)	18.9 (14)	67.8 (48)	170 (121)	120 (53)	495 (56)	485 (86)	428	1291 (42)	1871 (57)
R_{ac}	1.4 (1.3-1.7)	1.6 (1.1-1.8)	1.6 (1.6-1.9)	2.4 (2.3-3.0)	1.4 (1.1-2.2)	2.5 (1.5-3.4)	1.4 (0.8-2.0)	1.5	1.2 (1.0-2.8)	1.4 (1.1-1.6)
R_{ss}	0.91 (0.79-0.98)	1.1 (0.70-1.2)	0.76 (0.71-1.2)	1.6 (1.5-2.2)	0.97 (0.75-1.7)	2.1 (0.91-2.1)	1.0 (0.5-1.4)	1.0	0.86 (0.76-2.1)	0.97 (0.72-1.1)

Geometric mean (geometric %CV) for all except: median range for T_{max}, R_{ss} and R_{ac}, and arithmetic mean (SD) for t½. Geometric (%CV) not reported for n≤2.
Abbreviations: %CV = percent coefficient of variation, N/n = number of patients, PK = pharmacokinetic(s), QD = once daily, SD = standard deviation

a. For AUC_{inf}, t½., CL/F and Vz/F, the number of patients with PK parameters available on Cycle 1/Lead-in for the 80-mg and 400-mg dose groups were 7 and 8 respectively.
b. For Cycle 1/Day 21 (multiple dose), tau was 24 hours.
c. Patient 10011010 was dose reduced from 270 mg to 180 mg in Cycle 1. This patient's PK parameters are reported under 180 mg for Cycle 1/Day 21.
d. The number of patients with C_{trough} data at 20 mg, 400 mg and 600 mg were 4, 7, and 3 respectively.

1.2.8.2.2. B1371010: Food Effect and Drug Interaction Study

The effect of food on single dose PF-04449913 plasma PK and the effect of multiple dose ketoconazole on the single dose PF-04449913 plasma PK in healthy subjects were evaluated in study B1371010. The safety and tolerability of a single dose of PF-04449913 in healthy subjects when administered alone and with ketoconazole or with food were also assessed. Following PF-04449913 administration under fed conditions, PF-04449913 AUC_{inf} and C_{max} decreased ~13% and 34%, respectively, as compared to administration under overnight fasted conditions. Following administration of ketoconazole 400 mg once daily for 7 days, PF-04449913 AUC_{inf} and C_{max} increased by ~140% and 40%, respectively, as compared to PF-04449913 administered alone. Generally, a single dose of PF-04449913 200 mg was well tolerated when administered alone under fasted or fed conditions and with ketoconazole in healthy subjects.

1.2.8.2.3. B1371002: Patients with Solid Tumors

PF-04449913 exhibited similar PK properties in solid tumor patients as in those with hematological malignancies. PF-04449913 was rapidly absorbed following oral dosing with a median T_{max} of 1-2 hr after single and multiple dose administration. Following attainment of C_{max}, PF-04449913 plasma concentrations showed a bi-exponential decline. The mean terminal half-life (estimated following the Day 25 dose) ranged from 16 to 21 hours. In general, low to moderate inter-individual variability were observed in C_{max} and AUC following single and multiple dose administration.

Overall, PF-04449913 exhibited similar PK properties in both hematological and solid tumor patients with drug exposure increasing with dose both after single and multiple dosing.

1.2.8.3. Clinical PD Summary

Analysis of Hh pathway gene expression changes in surrogate tissue (skin) in samples collected from both the B1371001 and B1371002 studies indicated >80% down regulation of the expression of the Hh pathway gene *GLI1* at doses of 80 mg or higher. To investigate PD data at doses lower than 80 mg, lower dose levels (such as 25 mg) may be explored at any time during the B1371005 study. Evaluation of circulating cytokine modulation demonstrated a post-treatment decrease in IL-8 and IL-10 in one MF patient who responded to treatment in B1371001, although limited conclusions can be drawn due to the small number of samples available for analysis. No consistent changes in cytokine levels were identified in patients treated in the B1371002 trial.

1.2.9. Rationale for the Starting Dose and the Highest Dose of PF-04449913 in This Trial

The Phase 1 study of single-agent PF-04449913 in select hematologic malignancies (B1371001) in Western patients has been completed. A total of 47 patients were treated at doses ranging between 5-600 mg daily. This study has identified the MTD as 400 mg QD in Western patients, and it was decided that the appropriate recommended phase 2 dose (RP2D) for PF-0449913 would be 200 mg or less, based on the following factors:

- Doses of PF-04449913 up to 200 mg are safe and well-tolerated following prolonged administration (most patients tolerated study drug for a minimum of 3 cycles in the dose range of 5-180 mg). Three patients (1 patient in the 400 mg group and 2 patients in the 600 mg group) had a post-baseline maximum QTcF interval of ≥500 msec;

- The most commonly reported treatment-related AEs have been grade 1 and 2, suggesting that PF-04449913 is generally well-tolerated. Most frequently reported treatment-related AEs include gastrointestinal-related events (weight loss, nausea, and diarrhea), dysgeusia, and muscle cramps;

- Clinical responses have been observed in 16 patients (including 5 patients with AML) with doses of PF-04449913 as low as 10 mg QD, with the majority of responses observed at 80 mg QD;

- Linear dose-dependent PK have been observed at all doses of PF-04449913 for which data are available, suggesting that exposures of PF-04449913 are predictable;

- *GLI1* (a biomarker of Hh pathway signaling activation) expression is down-regulated by ≥80% at doses of 80 mg QD or more in surrogate (skin) tissue, suggesting that at the 100 mg dose, there will be adequate target modulation.

Following this, the healthy volunteer study to assess the effect of azoles on PF-04449913 exposures, indicated that there was up to a 140% increase in AUC_{inf}. For patients with AML who are frequently treated with azoles, the RP2D in Western patients was conservatively selected as 100 mg to accommodate the use of azoles given the plateau in Hh pathway modulation and the clinical signals observed over a wide dose range.

In this study, the starting dose has been established at 50 mg which is one-half of the Western RP2D (100 mg QD). And the highest dose level has been set at 100 mg QD which is the Western RP2D (100 mg QD).

Complete information for PF-04449913 may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure. For the purpose of this study, the Single Reference Safety Document for cytarabine, daunorubicin and azacitidine are the Japanese Package Inserts for each product.

1.2.10. Summary of Benefit-Risk Assessment

Based on the pre-clinical data available to date, the safety profile of PF-04449913 is characterized by manageable and reversible toxicities (mainly renal and effects on the QTc interval). PF-04449913 was well tolerated in the two phase 1 studies (B1371001, B1371002) with adverse events reported mostly as mild to moderate in severity. In the patients with hematological malignancies (B1371001), the most frequently reported treatment-related AE was dysgeusia (27.7%). In the patients with solid tumors (B1371002), the most frequently reported treatment-related AEs were dysgeusia (65.2%), fatigue (52.2%), decreased appetite (34.8%), nausea (34.8%) and dizziness (30.4%). The clinical activity observed with single-

agent PF-04449913 in AML and MDS patients suggests that there may be Hh signaling dependence in these diseases.

In the Phase 1b component of study B1371003, 7 patients have been treated with PF-04449913 in combination with the hypomethylating agents (HMA) decitabine. Overall, the combination appears to be safe and tolerable, suggesting that a combination of PF-04449913 with the HMA azacitidine will show similar safety and tolerability. Preliminary evidence of clinical activity of the decitabine/PF-04449913 combination has also been observed in 5 patients achieving a response; in particular 1 patient with AML and 1 patient with MDS achieved prolonged CR or marrow CR (mCR), respectively. [66] Furthermore, in the P2 Unfit Arm of this study, the primary anlysis of the primary endpoint OS, which was conducted after 92 OS events had been observed, showed a statistically and clinically significant prolongation of survival in the PF-04449913 + LDAC combination therapy arm than LDAC monotherapy arm (mOS: 8.3 months vs 4.9 months, stratified HR 0.537 [80% CI: 0.407, 0.708], one-sided p-value of 0.0017 by stratified log-rank test, data cutoff: 13 Apr 2016).

Based on the available clinical data, the safety profile of PF-04449913 as a single agent administered on a once daily continuous dosing regimen is characterized by manageable and potentially reversible toxicities that are generally mild to moderate in severity. The key observed toxicities in the clinical studies are dysgeusia, decreased appetite, and alopecia.

Small but significant increases in the QTc interval have been reported in animal and clinical studies with PF-04449913 so specific dosing requirements and additional monitoring may apply (refer to section 5.3.11 and Table 20). Concomitant administration of PF-04449913 with moderate/strong CYP3A4/5 inhibitors (Appendix 12) are not permitted and drugs with known risk of Torsade de Pointes (TdP) (Appendix 11) is not recommended due to the potential for drug-drug interaction to prolong the QTc interval.

The results of the nonclinical toxicity and safety pharmacology studies, together with the clinical experience obtained to date with PF-04449913 support the hypothesis that an Hh inhibitor in combination with chemotherapy may represent an attractive therapeutic approach to eliminate the leukemia stem cell population in MDS and AML.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This study includes six cohorts: 1) a monotherapy cohort to evaluate the tolerability and safety of PF-04449913 administered orally as a single agent to Japanese patients with select advanced hematologic malignancies, 2) two combination cohorts of Japanese patients with previously untreated AML or high-risk MDS assessing the tolerability and safety of the following two combination regimens: (i) LDAC plus PF-04449913 in the unfit patient population for patients who are unable to receive intensive chemotherapy (Combination Cohort 1, unfit patients), and (ii) cytarabine/daunorubicin (7:3) plus PF-04449913 in the fit patient population for patients who are able to receive intensive chemotherapy (Combination Cohort 2, fit patients), 3) expansion cohort of LDAC combination for efficacy in which

PF-04449913 is administered with LDAC in 15 Japanese patients with previously untreated AML or high-risk MDS, 4) one combination cohort to evaluate the tolerability and safety of PF-04449913 administered in combination with azacitidine to 6 Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy, and 5) a continuation cohort (monotherapy cohort) in which PF-04449913 is administered as a single agent in 1 Japanese MF patient who has been treated in Study B1371013. The study objectives for each cohort are outlined below. A total of up to 49 patients will be treated across all six cohorts.

Monotherapy Cohort:

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered as monotherapy in Japanese patients with select advanced hematologic malignancies.

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of PF-04449913 as monotherapy in Japanese patients with select advanced hematologic malignancies;
- To evaluate the pharmacodynamics (PD) of PF-04449913 as monotherapy in Japanese patients with select advanced hematologic malignancies;
- To assess preliminary evidence of clinical efficacy of PF-04449913 administered as monotherapy in Japanese patients with select advanced hematologic malignancies.

Combination Cohorts 1 and 2 (Unfit and Fit Patients):

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered in combination with Low-dose Ara-C (LDAC) (Combination Cohort 1, unfit patients), or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML, or high-risk MDS.

Secondary Objectives

- To evaluate the PK of PF-04449913 and potential drug-drug interaction (DDI) between PF-04449913 and LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) administered to Japanese patients with previously untreated AML or high-risk MDS;
- To evaluate the PD of PF-04449913 administered in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS;

- To assess preliminary evidence of clinical efficacy (including disease-specific measures) of PF-04449913 administered in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS.

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Primary Objective

- To evaluate the efficacy (DMR rate) of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS.

Secondary Objectives

- To evaluate the safety of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS;

- To evaluate the efficacy (including OS) of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS;

- To evaluate the PK and PD of PF-04449913 administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS.

Combination Cohort 3 (Azacitidine Combination):

Primary Objective

- To determine the safety and tolerability of PF-04449913 administered in combination with azacitidine in Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy.

Secondary Objectives

- To evaluate the PK of PF-04449913 and azacitidine when administered to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;

- To evaluate the PD of PF-04449913 administered in combination with azacitidine to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;

- To assess any preliminary evidence of clinical efficacy including OS of PF-04449913 administered in combination with azacitidine to Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy.

Continuation Cohort (Monotherapy Cohort):

- To assess the safety of PF-04449913 administered as monotherapy in the Japanese MF patient who has been treated with PF-04449913 in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013.

2.2. Endpoints

Monotherapy Cohort:

Primary Endpoint

- First-cycle dose-limiting toxicities (DLTs); Type, incidence, severity [graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0], timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913;
- Potential biomarkers of target modulation, response or resistance to PF-04449913 in Japanese patients with advanced hematologic malignancies;
- Objective disease response as assessed using the response criteria for the hemotologic disease under study.

Combination Cohorts 1 and 2 (Unfit and Fit Patients):

Primary Endpoint

- First-cycle DLTs; Type, incidence, severity (graded by NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913 with: (i) LDAC, and (ii) cytarabine/daunorubicin (7:3) combinations;
- Potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with chemotherapy in Japanese patients with previously untreated AML or high-risk MDS;
- Objective disease response, as assessed using the appropriate response criteria for AML or MDS.

- Survival status (only Combination Cohort 1)

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Primary Endpoint

- DMR rate

Secondary Endpoints

- Type, incidence, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities;
- OS;
- Objective disease response, as assessed using the appropriate response criteria for AML or MDS; complete remission (CR) rate; duration of response; time to response;
- PK and potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with LDAC in Japanese patients with previously untreated AML or high-risk MDS.

Combination Cohort 3 (Azacitidine Combination):

Primary Endpoint

- First-cycle DLTs; Type, incidence, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; vital signs and laboratory test abnormalities.

Secondary Endpoints

- PK parameters of PF-04449913 and azacitidine;
- OS;
- Potential biomarkers of target modulation, response or resistance to PF-04449913 in combination with azacitidine in Japanese patients with previously untreated AML who are eligible for non-intensive chemotherapy;
- Objective disease response, as assessed using the appropriate response criteria for AML; duration of response; time to response

Continuation Cohort (Monotherapy Cohort):

- Type, severity (graded by NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of adverse events; laboratory test abnormalities.

Efficacy-related data will not be collected in this cohort.

3. STUDY DESIGN

3.1. Study Overview

This is an open-label, multi-center, Phase 1 study of PF-04449913 in Japanese patients. PF-04449913 will be administered orally as a single agent in up to 15 patients with select advanced hematologic malignancies (Monotherapy Cohort), or in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine and daunorubicin (7:3) (Combination Cohort 2, fit patients) in up to 12 previously untreated patients with AML or high-risk MDS. PF-04449913 will be administered in combination with LDAC in a total of 15 patients with previously untreated AML or high-risk MDS (Expansion Cohort of LDAC combination for efficacy, unfit patients). PF-04449913 will be also administered in combination with azacitidine in a total of 6 patients with previously untreated AML who are eligible for non-intensive chemotherapy (Combination Cohort 3, Azacitidine Combination). PF-04449913 wii be administered as a single agent in 1 Japanese MF patient who has been treated in Study B1371013 and on the study treatment at the time of the study discontinuation [Continuation Cohort (Monotherapy Cohort)].

3.1.1. Monotherapy Cohort

The monotherapy cohort will evaluate the safety and tolerability of PF-04449913 administered as a single agent once daily continuously. Cycle 1 will be preceded by a single lead-in dose of PF-04449913 administered on Day -5 (lead-in period) in order to characterize the single-dose PK of PF-04449913 prior to initiation of continuous dosing in the first cycle of treatment. From Cycle 1/Day 1 onwards, PF-04449913 will be administered continuously once daily, in 28-day cycles.

A standard 3+3 dose escalation design will be used to evaluate the tolerability of PF-04449913 with 3-6 patients per dose level. Two dose levels of PF-04449913 (Dose Level 1: 50 mg QD and Dose Level 2: 100 mg QD) will, in the first instance, be investigated in sequential cohorts of patients. Intermediate (such as 80 mg QD) or lower dose levels (such as 25 mg) may be explored at any time during the study if this is clinically and scientifically warranted. Study centers will receive a notification if additional dose levels are explored.

The DLT evaluation period includes the PK lead-in period, and the first cycle of treatment. Dose escalation to the 100 mg QD dose level will occur if <1/3 or <2/6 patients at the 50 mg QD dose level experience dose-limiting toxicities (DLT) during the first cycle of treatment. If ≤1 patient experiences a DLT event in the first 3 patients, an additional 3 patients will be enrolled to give a total of 6 patients in the 100 mg QD cohort. If ≤1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the 100 mg QD dose level in the monotherapy cohort will be deemed confirmed, and the study will proceed to the combination cohort. If 2 or more of the 6 patients treated at 100 mg QD in the monotherapy cohort experience a DLT by the end of Cycle 1, an intermediate dose level (80 mg QD) may be explored in the monotherapy cohort prior to proceeding with the combination cohort. If two or more of the 3 or 6 patients treated at 50 mg QD in the monotherapy cohort

experiences a DLT by the end of Cycle 1, the dose escalation will be terminated, and a lower dose may be explored.

As of 7 August 2014, it was decided by the study team that a lower dose level (25 mg QD) will be explored in the study, since evaluation of PD data at the 25 mg QD dose is scientifically warranted. Up to 3 patients will be enrolled at the 25 mg dose level. DLT evaluation will be performed on this dose level, however, it will not be used for the dose escalation decision, or for the determination of whether or not to proceed with the combination cohort. The Sponsor will discuss with the Investigator to confirm that there is no safety issue for patients enrolled at this dose level.

Treatment with PF-04449913 may continue for up to 12 cycles or until disease progression or relapse, patient withdrawal, or unacceptable toxicity occurs (whichever is first). Patients who complete 12 cycles of treatment will be deemed to have completed the study. However, patients who complete 12 cycles of study treatment who demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving the study treatment, may be given the opportunity to do so following agreement between the Investigator and Sponsor, and pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed as per Table 1 (See Schedule of Activities).

The study may at any time evaluate additional dose levels of single-agent PF-04449913 based upon the emerging data from the ongoing pre-clinical and clinical studies, following discussion between the Investigators and the Sponsor.

3.1.2. Combination Cohorts

The combination cohorts will evaluate the safety and tolerability of PF-04449913 at the starting dose of 100 mg once daily continuously administered in combination with 3 different chemotherapy regimens.

Combination Cohort 1 (Unfit Patients):

In this cohort, patients who are “unfit for intensive chemotherapy” based on predefined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with LDAC over 28 day cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. The DLT evaluation period includes the first cycle of treatment. If ≤ 1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the combination will be deemed confirmed. If 2 or more of the 6 patients experience a DLT by the end of Cycle 1, additional lower dose levels may be tested, applying identical criteria to those outlined above with respect to DLT events.

Treatment with PF-04449913 in combination with LDAC may continue for up to 12 cycles or until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever is first). Unfit patients who complete 12 cycles of study treatment will be deemed to have completed the study. However, patients who complete the 12 cycles of study

treatment and demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving the study treatment (monotherapy of PF-04449913 or combination therapy), may be given the opportunity to do so following agreement between the Investigator and Sponsor, and pending study drug availability. If treatment continues beyond 12 cycles, study procedures should continue to be performed as listed in Table 2 (Schedule of Activities). This cohort includes survival follow-up.

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

In this cohort, patients who are "unfit for intensive chemotherapy" based on predefined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with LDAC over 28-day cycles.

A total of 15 patients will be treated in this cohort and DMR rate will be evaluated. Treatment with PF-04449913 in combination with LDAC may continue until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever is first). All patients will be followed for survival every 8 weeks up to 2 years from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy (follow-up on survival status will no longer be required after Protocol Amendment 8).

Combination Cohort 2 (Fit Patients):

In this cohort, patients defined as "fit for intensive chemotherapy" based on pre-defined criteria (See Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with daunorubicin and cytarabine during induction and consolidation. For the first induction cycle only, PF-04449913 will commence on Day -3 and will then be given once daily continuously for the duration of treatment. Following completion of induction and consolidation, single-agent PF-04449913 may be given to eligible patients as maintenance therapy for a maximum of 6 cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. If ≤1 of the 6 patients experiences a DLT event by the end of Induction Cycle 1, the tolerability of the combination will be confirmed. If 2 or more of the 6 patients experience a DLT by the end of Induction Cycle 1, additional lower dose levels may be tested using identical criteria to those outlined above with respect to DLT events.

Treatment will continue until disease progression or relapse, patient refusal, or unacceptable toxicity (whichever is first). Fit patients who complete induction, consolidation and 6 cycles of maintenance with PF-04449913 will be deemed to have completed the study treatment. However, patients who complete the 6 cycles of maintenance and demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving single-agent PF-04449913, may be given the opportunity to do so following agreement between the Investigator and Sponsor, and pending study drug availability. If treatment continues beyond 6 cycles of maintenance, study procedures should continue to be performed as listed in Table 4 (Schedule of Activities).

Combination Cohort 3 (Azacitidine Combination):

In this cohort, patients with previously untreated AML and eligible for non-intensive chemotherapy will receive PF-04449913 once daily continuously at the starting dose of 100 mg in combination with azacitidine over 28 day cycles.

A total of 6 patients will be treated in this cohort and followed up for DLT evaluation. The DLT evaluation period includes the first cycle of treatment. If ≤1 of the 6 patients experiences a DLT by the end of Cycle 1, the tolerability of the combination will be deemed confirmed. If 2 or more of the 6 patients experience a DLT by the end of Cycle 1, the investigator and the sponsor will review all available safety data and discuss the next steps.

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until death, unacceptable toxicity, or patient refusal (whichever is first). If documentation of disease progression occurs within the first 6 cycles of study treatment, the patient **SHOULD NOT** be withdrawn from study treatment following agreement between the Investigator and Sponsor if, in the Investigator's judgment, the patient is still likely to receive clinical benefit.

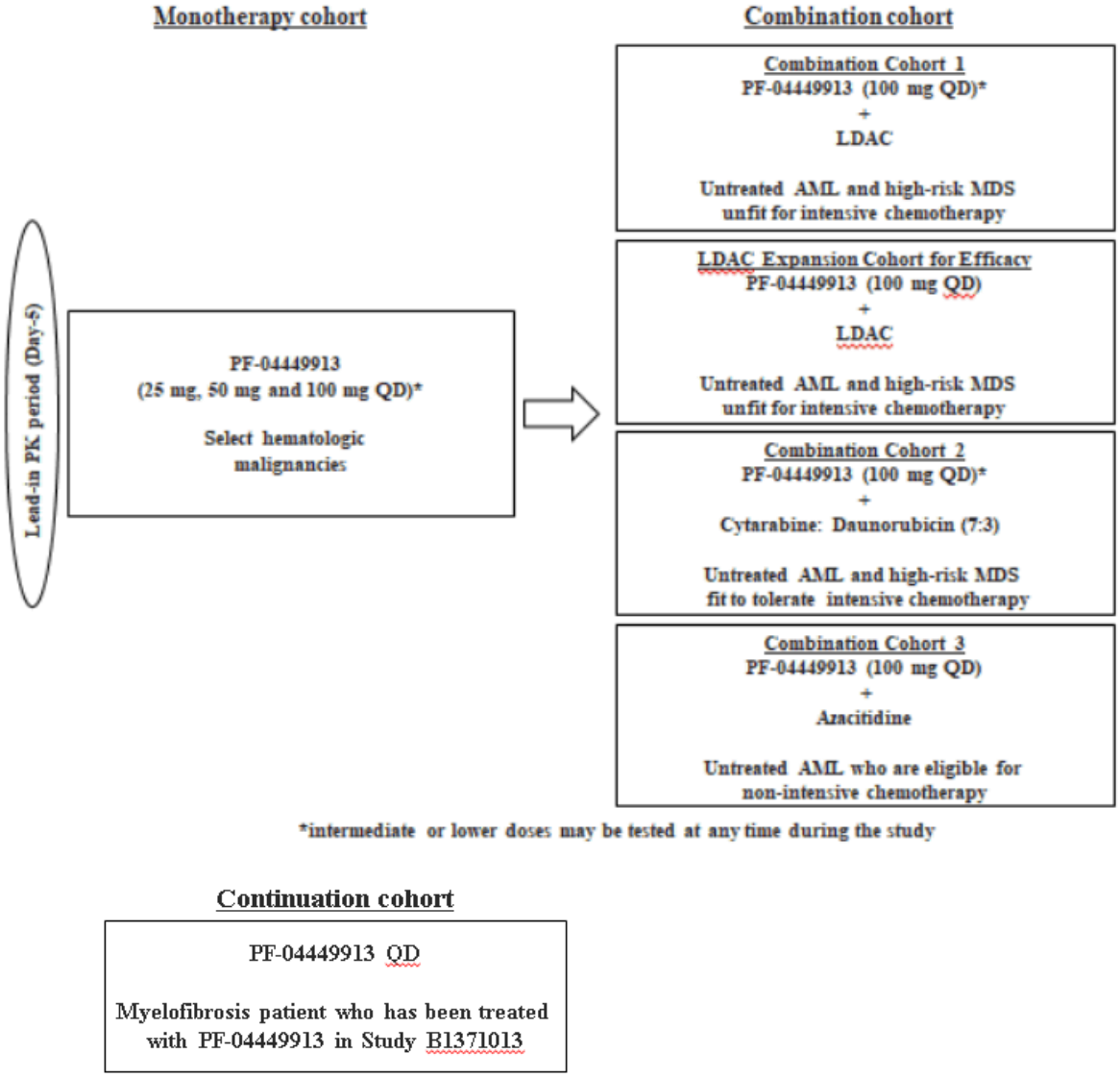
Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse (unless according to the Investigator there is reasonable evidence of clinical benefit, eg, HI [hematologic imiprovement], to justify continuation on treatment following agreement between the Investigator and Sponsor), death, unacceptable toxicity, or patient refusal (whichever is first). All patients will be followed for survival up to 3 years from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy.

3.1.3. Continuation Cohort (Monotherapy Cohort)

PF-04449913 at the same dose as the patient was taking in Study B1371013 will be orally administered once daily continuously as a single agent over 28 day cycles in 1 Japanese MF patient who has been treated in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013.

In this cohort, the patient receiving PF-04449913 will continue to receive study treatment until the time of disease progression, unacceptable toxicity, death, withdrawal of consent or termination of the study by Sponsor, whichever comes first. The patient may continue PF-04449913 treatment after objective progression of disease has been determined if the patient continues to experience clinical benefit, in the opinion of the investigator, and following discussion with the Sponsor. Refer to Appendix 7 for the definition of disease progression.

Figure 3 Schematic of Study Design



3.2. DLT Definition

DLTs will be classified according to CTCAE version 4.0.

In the Monotherapy Cohort, the DLT observation period will be from Day -5 to Day 28 of Cycle 1.

In Combination Cohort 1 (combination with LDAC, unfit patients) and Combination Cohort 3 (combination with azacitidine) the DLT observation period will be from Day 1 to Day 28 of Cycle 1;

In Combination Cohort 2 (combination with daunorubicin and cytarabine, fit patients) the DLT observation period will be from Day -3 to Day 21 or to Day 28 of the first induction cycle depending on when the next chemotherapy cycle is started (ie, anytime between Days 21 and 28).

Any of the following adverse events will be a DLT if considered by the Investigator to be possibly related to single-agent PF-04449913 (monotherapy cohort), to PF-04449913 in combination with chemotherapy (Combination Cohorts 1 and 2), or PF-04449913 in combination with azacitidine (Combination Cohorts 3):

1. Grade ≥3 non-hematologic toxicity (uncontrolled despite optimal medical management [eg, nausea, vomiting, and diarrhea]), excluding Grade ≥3 infection, fever (including febrile neutropenia), infusion related adverse events, electrolyte abnormalities and ALT/AST elevation that returns to Grade ≤1 or baseline within 7 days. Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT unless considered possibly related to PF-04449913.

- In an asymptomatic patient, Grade ≥3 QTc prolongation (QTc ≥ 501 msec) will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities, concomitant medications that may cause QTc prolongation, or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 prolongation persists, then the event should be considered a DLT.

2. Prolonged myelosuppression that lasts longer than 42 days from the point of detection, defined as absolute neutrophil count (ANC) <500/μL or platelet count <10 x 10^9/L with a normal bone marrow (<5% blasts and no evidence of disease or dysplasia).

3. Inability to deliver at least 80% of the planned study doses for all agents in a combination due to non-hematologic toxicities.

4. Delay of >28 days in receiving the next scheduled cycle due to persisting non-hematologic toxicities.

Patient replacement

Patients who receive less than 80% of the planned dose of any of the study drugs in the first cycle of treatment for reasons other than treatment-related toxicities are not evaluable for DLT, and should be replaced to adequately assess the safety of study treatments. At the time of dose escalation and when proceeding to the next cohort, Sponsor will discuss with Investigator to confirm there is no safety issue of patients who are not evaluable for DLT and replaced.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered

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

4.1. Inclusion Criteria

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

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

4.1.1. Monotherapy Cohort

1. Patients with selected advanced hematologic malignancies who are refractory, resistant or intolerant to prior therapies. Eligible patients are limited to 1. Myelodysplastic Syndrome (any MDS International Prognostic Scoring System or IPSS score), 2. Myleofibrosis, 3. Chronic Myelomonocytic Leukemia (CMML)**,** 4. CML T315I mutants, 5. CML in whom the T315I mutation is not present (any phase; must have received at least one prior treatment), 6. Acute Myeloid Leukemia (AML).

2. Patients with CML:

    a. Must have a confirmed diagnosis as evidenced by the presence of the BCR-ABL translocation [t(9;22)] by fluorescence in situ hybridization (FISH), cytogenetics, or quantitative polymerase chain reaction (QPCR) for chronic myeloid leukemia in either chronic, accelerated or blast phase.

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

    c. May be resistant or intolerant as defined by:

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

        - Secondary resistance is defined as a loss of CHR (defined by leukocytosis confirmed with at least one WBC>15K not felt to be due to a secondary cause); loss of a MCyR (defined by ≥30% increase in the number of metaphases); or disease progression to AP or BP;

        - In CML-AP or CML-BP, resistance is defined as the failure to achieve a hematologic response, an increasing WBC, or an overt disease progression.

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

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

- To be considered in chronic phase, all the following must be met:

  - <15% blasts in peripheral blood and bone marrow;

  - <30% blasts and promyelocytes in peripheral blood or bone marrow;

  - <20% basophils in peripheral blood;

  - Platelets ≥100 x 10^9/L;

  - No EMD other than spleen or liver.

- To be considered in accelerated phase, one or more of the following must be met:

  - ≥15% blasts in peripheral blood;

  - ≥30% blasts + promyelocytes in peripheral blood;

  - ≥20% basophils in peripheral blood;

  - Platelet count ≤100 x 10^9/L unrelated to therapy;

  - Clonal evolution.

- To be considered in blast phase, either one of the following criteria must be met:

  - ≥30% blasts in peripheral blood or bone marrow, or

  - Extramedullary disease.

3. All anti-cancer treatments should be discontinued as follows:

   - Anagrelide should be discontinued 7 days prior to first dose of investigational product;

- Dasatinib should be discontinued from 1 day (24 hrs) prior to first dose of investigational product;
- Nilotinib should be discontinued from 3 days (72 hrs) prior to first dose of investigational product;
- Imatinib should be discontinued from 4 days (96 hrs) prior to first dose of investigational product;
- Bosutinib should be discontinued from 4 days (96 hrs) prior to the first dose of investigational product;
- Ponatinib should be discontinued from 7 days (168 hrs) prior to the first dose of investigational product;
- All other anti-cancer treatments should be discontinued ≥2 weeks from first dose of investigational product, e.g., chemotherapy (including intrathecal), radiotherapy, cytokines, investigational agents, or hormones.

4. Age ≥20 years old.

5. ECOG performance status of 0, 1, or 2.

6. Patients who have previously received an autologous stem cell transplant are eligible provided that the transplant occurred more than 30 days prior to study entry and if the patient has recovered from transplant associated toxicities prior to study entry.

7. Patients with a history of allogeneic stem cell transplant are eligible for study participation provided that the transplant was greater than 60 days prior to first dose of investigational product and the patient has recovered from transplant-associated toxicities prior to first dose of investigational product.

8. Adequate organ function as defined by the following criteria:

   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy;
   - Total serum bilirubin ≤2 x ULN (except patients with documented Gilbert's syndrome);
   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution.

9. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose).

Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. Female patients are of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. Female patients with permanent sterilization or post-menopausal are not considered as childbearing potential. (Post-menopausal is defined medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative physiological causes.) Male patients are of childbearing potential if, in the opinion of the investigator, he is biologically capable of having children and is sexually active.

10. Evidence of a personally signed and dated informed consent document indicating that the patient (or legal representative) has been informed of all pertinent aspects of the study.

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

4.1.2. Combination Cohort 1, Expansion Cohort of LDAC combination for efficacy and Combination Cohort 2 (Unfit and Fit Patients)

1. Patients with AML or RAEB-2 High-Risk MDS who are newly diagnosed according to the WHO 2008 Classification and previously untreated. Eligible patients with MDS, as well as eligible patients with AML arising from an antecedent hematologic disease (AHD) or MDS may have had **one** prior regimen with commercially-available agent(s) (eg, azacitidine or decitabine) for the treatment of their prior hematologic disease. The patients may not have had any prior therapy for their AML.

2. AML patients include de-novo AML, AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation (secondary AML).

   - For a diagnosis of AML, a bone marrow blast count of 20% or more is required.

   - For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia the proportion of bone marrow blasts may be <20%.

   - In AML FAB M6a (erythroid leukemia) ≥20% of non-erythroid cells in the bone marrow must be leukemic blasts and ≥50% of the cells are erythroid precursors.

   - In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents.

3. For a diagnosis of high-risk Myelodysplastic Syndrome RAEB-2 the patient must have 10-19% bone marrow blasts.

4. Age:

   - ≥20 years old for patients enrolled in Combination Cohort 2 (Fit Patients);

- ≥55 years old for patients enrolled in Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy (Unfit Patients).

5. ECOG Performance Status 0, 1, or 2.

6. Patients with AML or High-Risk MDS who have **one or more** of the criteria below are considered unfit for intensive chemotherapy and are eligible for Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

   - Age ≥75 years;
   - ECOG Performance Status of 2;
   - Serum creatinine >1.3 mg/dL;
   - Severe cardiac disease (eg, LVEF <45% by multi-gated acquisition [MUGA] or echocardiography [ECHO] at screening).

7. Patients with AML or high-risk MDS and have **none** of the following criteria are considered fit for intensive chemotherapy and are only eligible for Combination Cohort 2 (Fit Patients):

   - Age ≥75 years;
   - ECOG Performance Status of 2;
   - Serum creatinine >1.3 mg/dL;
   - Severe cardiac disease (eg, LVEF <45% by MUGA or ECHO at screening).

8. Adequate Organ Function as defined by the following:

   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy;
   - Total serum bilirubin ≤2 x ULN (except patients with documented Gilbert's syndrome);
   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution.

9. All anti-cancer treatments (unless specified) should be discontinued ≥2 weeks from first dose of investigational product, for example: targeted chemotherapy, radiotherapy, investigational agents, hormones, anagrelide or cytokines.

- For control of rapidly progressing leukemia, hydroxyurea or leukopheresis may be used before and for up to 1 week after first dose of PF-04449913;

- Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving intrathecal (IT) therapy at study entry are considered eligible, and will continue to receive IT therapy.

10. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for AEs not constituting a safety risk by investigator judgement.

11. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose).

    Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. Female patients are of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. Female patients with permanent sterilization or post-menopausal are not considered as childbearing potential. (Post-menopausal is defined medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative physiological causes.) Male patients are of childbearing potential if, in the opinion of the investigator, he is biologically capable of having children and is sexually active.

12. Evidence of a personally signed and dated informed consent document indicating that the patient (or legal representative) has been informed of all pertinent aspects of the study.

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

4.1.3. Combination Cohort 3 (Azacitidine Combination)

1. Patients with AML who are newly diagnosed according to the WHO 2008 Classification and previously untreated. Eligible patients with AML arising from an antecedent hematologic disease (AHD) may have had **one** prior regimen with commercially-available agent(s) (eg, azacitidine or decitabine) for the treatment of their prior hematologic disease. The patients may not have had any prior therapy for their AML.

2. AML patients include de-novo AML, AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation (secondary AML).

    - For a diagnosis of AML, a bone marrow blast count of 20% or more is required.

    - For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia the proportion of bone marrow blasts may be <20%.

- In AML FAB M6a (erythroid leukemia) ≥20% of non-erythroid cells in the bone marrow must be leukemic blasts and ≥50% of the cells are erythroid precursors.

- In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents.

3. AML patients who are eligible for non-intensive chemotherapy per investigator's judgement.

4. ≥20 years old.

5. ECOG Performance Status 0, 1, or 2.

6. Adequate Organ Function as defined by the following:

   - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤3 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy;

   - Total serum bilirubin ≤2 x ULN (except patients with documented Gilbert's syndrome);

   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

7. All anti-cancer treatments (unless specified) should be discontinued ≥2 weeks from first dose of investigational product, for example: targeted chemotherapy, radiotherapy, investigational agents, hormones, anagrelide or cytokines.

   - For control of rapidly progressing leukemia, hydroxyurea or leukopheresis may be used before and for up to 1 week after first dose of PF-04449913

   - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving intrathecal (IT) therapy at study entry are considered eligible, and will continue to receive IT therapy.

8. Resolved acute effects of any prior therapy to baseline severity or Grade ≤1 CTCAE except for AEs not constituting a safety risk by investigator's judgement.

9. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose).

   Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. Female patients are of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. Female patients with permanent sterilization or post-menopausal are not considered as

childbearing potential. (Post-menopausal is defined medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative physiological causes.) Male patients are of childbearing potential if, in the opinion of the investigator, he is biologically capable of having children and is sexually active.

10. Evidence of a personally signed and dated informed consent document indicating that the patient (or legal representative) has been informed of all pertinent aspects of the study.

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

4.1.4. Continuation Cohort (Monotherapy Cohort)

1. Patient receiving the study treatment with PF-04449913 in Study B1371013 without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013.

2. Patient tolerating the study drug.

3. Serum/urine pregnancy test (for females of childbearing potential) that is negative immediately prior to initiation of treatment (first dose).

   Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. Female patients are of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. Female patients with permanent sterilization or post-menopausal are not considered as childbearing potential. (Post-menopausal is defined medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months with no alternative physiological causes.) Male patients are of childbearing potential if, in the opinion of the investigator, he is biologically capable of having children and is sexually active.

4. Evidence of a personally signed and dated informed consent document indicating that the patient (or legal representative) has been informed of all pertinent aspects of the study.

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

4.2. Exclusion Criteria

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

4.2.1. Monotherapy Cohort

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

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

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

    - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving IT therapy at first dose of investigational product are considered eligible, and will continue to receive IT therapy.

4. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes or clinically significant ventricular arrhythmias.

5. QTc interval >470 msec using Fridericia's correction formula (QTcF).

6. Patient has an active, life threatening, or clinically significant uncontrolled systemic infection.

7. Patients with active central nervous system (CNS) involvement of the leukemia.

8. Active graft-versus-host disease, other than Grade 1 skin involvement.

9. Patients taking immunosuppressants for GVHD or any other medical conditions (including but not limited to: steroids, cyclosporine, tacrolimus, methotrexate or mycophenolate mofetil) within 14 days prior to first dose of investigational product.

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

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

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

13. Concurrent administration of herbal preparations.

14. Current use or anticipated need for food or drugs that are strong/moderate CYP3A4/5 inhibitors, including their administration within 7 days prior to first dose of investigational product.

15. Current use or anticipated need for drugs that are known strong/moderate CYP3A4/5 inducers, including their administration within 7 days prior to first dose of investigational product.

16. Current use or anticipated need for drugs that are P-glycoprotein inhibitors/inducers, including their administration within 7 days prior to first dose of investigational product.

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

18. Current drug or alcohol abuse.

19. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, 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.

20. 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.

21. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 180 days after last dose of investigational product.

4.2.2. Combination Cohort 1, Expansion Cohort of LDAC combination for efficacy and Combination Cohort 2 (UnFit and Fit Patients)

1. Acute Promyelocytic Leukemia (APL) patients with t(15;17) or patients with a t(9;22) cytogenetic translocation for any component of the study.

2. Hyperleukocytosis (leukocytes $\geq 30 \times 10^9$/L) at study entry. These patients may be treated with hydroxyurea or receive leukopheresis treatment according to routine practice, and enrolled in the study when the leukocyte count falls below 30×10^9/L.

3. Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.

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

    - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving IT therapy at first dose of investigational product are considered eligible, and will continue to receive IT therapy.

5. For Combination Cohort 2 (Fit Patients):

    - LVEF <45% by ECHO or MUGA scan;

    - Cumulative anthracycline dose equivalent of ≥190 mg/m^2 of doxorubicin. (Refer to Appendix 10)

6. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes or clinically significant ventricular arrhythmias.

7. QTc interval >470 msec using Fridericia's correction formula (QTcF).

8. Patients with an active, life threatening or clinically significant uncontrolled systemic infection.

9. Patients with known active uncontrolled central nervous system (CNS) leukemia.

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

11. Known malabsorption syndrome or other condition that may impair absorption of study medication (eg, gastrectomy or lap band).

12. Major surgery or radiation within 4 weeks of starting the study treatment.

13. Prior treatment with:

    - a Hh inhibitor at any time;

    - an investigational agent for the treatment of an antecedent hematologic disease (AHD).

14. Prior treatment with cytarabine (Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy, Unfit Patients only).

15. The presence of hypersensitivity to cytarabine (not including drug fever or exanthema) and daunorubicin (Combination Cohort 2, Fit Patients only).

16. Concurrent treatment with any investigational or approved oncology agents (unless specified in the protocol).

17. Concurrent administration of herbal preparations.

18. Current use or anticipated need for food or drugs that are strong/moderate CYP3A4/5 inhibitors, including their administration within 7 days prior to first dose of investigational product.

19. Current use or anticipated need for drugs that are known strong/moderate CYP3A4/5 inducers, including their administration within 7 days prior to first dose of investigational product.

20. Current use or anticipated need for drugs that are P-glycoprotein inhibitors/inducers, including their administration within 7 days prior to first dose of investigational product.

21. Current drug or alcohol abuse.

22. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, 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.

23. 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.

24. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 180 days after last dose of investigational product.

4.2.3. Combination Cohort 3 (Azacitidine Combination)

1. Acute Promyelocytic Leukemia (APL) patients with t(15;17) or patients with a t(9;22) cytogenetic translocation for any component of the study.

2. Hyperleukocytosis (leukocytes $\geq 30 \times 10^9$/L) at study entry. These patients may be treated with hydroxyurea or receive leukopheresis treatment according to routine practice, and enrolled in the study when the leukocyte count falls below 30×10^9/L.

3. Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.

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

    - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving IT therapy at first dose of investigational product are considered eligible, and will continue to receive IT therapy.

5. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes or clinically significant ventricular arrhythmias.

6. QTc interval >470 msec using the Fridericia correction (QTcF).

7. Patients with an active, life threatening or clinically significant uncontrolled systemic infection.

8. Patients with known active uncontrolled CNS leukemia.

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

10. Known malabsorption syndrome or other condition that may impair absorption of study medication (eg, gastrectomy or lap band) and inability or unwillingness to swallow tablets or capsules.

11. Major surgery or radiation within 4 weeks of starting the study treatment.

12. Prior treatment with:

    - A Hh inhibitor at any time;

    - An investigational agent for the treatment of an antecedent hematologic disease (AHD).

13. The presence of hypersensitivity to azacitidine or mannitol.

14. Concurrent administration of herbal preparations.

15. Current use or anticipated need for food or drugs that are strong/moderate CYP3A4/5 inhibitors, including their administration within 7 days prior to first dose of investigational product.

16. Current use or anticipated need for drugs that are known strong/moderate CYP3A4/5 inducers, including their administration within 7 days prior to first dose of investigational product.

17. Current use or anticipated need for drugs that are P-glycoprotein inhibitors/inducers, including their administration within 7 days prior to first dose of investigational product.

18. Current drug or alcohol abuse.

19. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, 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.

20. 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.

21. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 180 days after last dose of investigational product.

4.2.4. Continuation Cohort (Monotherapy Cohort)

1. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use two (2) highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 180 days after last dose of investigational product.

4.3. Life Style Guidelines

All male and female patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use two (2) highly effective methods of contraception consistently and correctly for the duration of the active treatment period and for at least 180 days after the last dose of investigational product. The investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in their consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, this review of contraception methods should be conducted by phone or video contact. In addition, the investigator will instruct the patient to call immediately if the selected birth control methods are discontinued or if pregnancy is known or suspected.

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

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

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

3. Male condom or female condom used WITH a spermicide* (ie, foam, gel, film, cream, suppository).

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

5. Bilateral tubal ligation or bilateral salpingectomy.

*Not commercially available in Japan

4.4. Sunlight Exposure

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

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the team SharePoint site.

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 number, contact information for the investigational site and contact details for a help desk 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 patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used 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 study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Treatment allocation will be performed centrally by the Sponsor for all patient cohorts. Following full assessment and determination that the patient meets all eligibility criteria, the investigator or designee will fax or email a complete Registration Form to the designated Sponsor study team member. For the combination cohorts, attribution to the fit or unfit patient category will be based on the patient's characteristics by the Investigator and confirmed by the Sponsor. The Sponsor will assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient and fax of email to the site.

No patient shall receive study drug until the Investigator or designee has received the following information from the Sponsor: confirmation of the patient's enrollment.

5.2. Drug Supplies

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

Commercially available cytarabine and daunorubicin will be used in the study and sourced by the sites.

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

5.2.1. Dosage Form(s) and Packaging

5.2.1.1. PF-04449913

PF-04449913 is formulated in tablets containing 10 mg, 25 mg, and 100 mg of study medication. Supplies will be labeled according to local regulatory requirements. The tablets are packaged in high-density polyethylene (HDPE) bottles, with protection from moisture and should be handled with care. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers.

5.2.1.2. Daunorubicin

Commercially available daunorubicin will be used. Refer to the local package insert or Institutional Guidelines for detailed formulation, preparation and dispensing information.

5.2.1.3. Cytarabine

Commercially available cytarabine will be used. Refer to the local package insert or Institutional Guidelines for detailed formulation, preparation and dispensing information.

5.2.1.4. Azacitidine

Upon site activation, Pfizer will provide a supply of azacitidine for clinical use. Refer to the local package insert for detailed formulation, preparation and dispensing information.

5.2.2. Preparation and Dispensing

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. Administration

5.3.1. General Guidelines

In the monotherapy cohort, PF-04449913 administered as a single agent will be evaluated. In the combination cohort, three different PF-04449913 combinations (with LDAC for the unfit patient population, with cytarabine/daunorubicin for the fit patient population, and with azacitidine for the azacitidine patient population) will be evaluated. In the Continuation

Cohort, PF-04449913 continuously administered as a single agent will be evaluated for safety. Patients should be instructed to take their medication at approximately the same time each day and to not take more than the prescribed dose at any time.

Study drugs are administered in cycles. Bone marrow evaluations are performed at specified times to determine clinical response and treatment progression decisions within the trial (except for the Continuation Cohort).

5.3.1.1. In the combination cohorts, all patients should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of cytarabine, daunorubicin required, or azacitidine for dose preparation. Decision to recalculate cytarabine, daunorubicin, or azacitidine dose based on the weight obtained at each cycle can be in accordance with institutional practice for changes in weight of 10% or less; however, if the patient experienced either a weight loss or gain of >10%, the amount of cytarabine, daunorubicin, or azacitidine required for study drug preparation and administration must be recalculated using this most recent weight obtained.Study Treatment Duration in the Monotherapy Cohort

Treatment with PF-04449913 may continue for up to 12 cycles or until disease progression or relapse, patient withdrawal, or unacceptable toxicity occurs (whichever comes first). However, patients who complete 12 cycles of study treatment demonstrating clinical benefit with manageable toxicity, and are willing to continue receiving the study treatment, may be given the opportunity to do so upon agreement between Investigator and Sponsor and pending study drug availability.

5.3.1.2. Study Treatment Duration in the Combination Cohorts

Combination Cohort 1 (Unfit Patients):

Study treatment (LDAC plus PF-04449913) may continue for up to 12 cycles or until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever comes first). However, patients who complete 12 cycles of study treatment, demonstrate clinical benefit with manageable toxicity, and are willing to continue receiving the treatment (monotherapy of PF-04449913 or combination therapy), may be given the opportunity to do so following discussion and agreement between the Investigator and Sponsor, and pending confirmation of study drug availability.

Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Study treatment (LDAC plus PF-04449913) may continue until disease progression or relapse, patient refusal, or unacceptable toxicity occurs (whichever comes first).

Combination Cohort 2 (Fit Patients):

Study treatment may continue until patient refusal, or the patient develops unacceptable toxicity or demonstrates either resistant disease during induction (ie, the bone marrow blast

count is greater than or equal to the screening bone marrow blast count), or disease progression/relapse after induction but before maintenance (see Appendix 5 and Appendix 8)

- Patients with residual disease following the first induction (ie, persistent leukemia on bone marrow exam [ie, lower blast counts than the screening bone marrow but still >5% blasts and not meeting a complete response]) are candidates for a second cycle of induction if re-induction criteria are met;

- In addition, following completion of the induction and consolidation, PF-04449913 single agent may be given to eligible patients as maintenance treatment for a maximum of 6 cycles. However, patients who complete the maintenance treatment period and who demonstrate clinical benefit with manageable toxicity, and who are willing to continue receiving PF-04449913 single agent, may be given the opportunity to do so following agreement between Investigator and Sponsor, and pending confirmation of study drug availability.

Combination Cohort 3 (Azacitidine Combination):

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until death, unacceptable toxicity, or patient refusal (whichever is first). If documentation of disease progression occurs within the first 6 cycles of study treatment, the patient **SHOULD NOT** be withdrawn from study treatment following agreement between the Investigator and Sponsor if, in the Investigator's judgment, the patient is still likely to receive clinical benefit.

Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse (unless according to the Investigator there is reasonable evidence of clinical benefit, eg, HI [hematologic improvement], to justify continuation on treatment following agreement between the Investigator and Sponsor), death, unacceptable toxicity, or patient refusal (whichever is first).

5.3.1.3. Study Treatment Duration in the Continuation Cohort (Monotherapy Cohort)

In this cohort, the patient receiving PF-04449913 will continue to receive study treatment until the time of disease progression, unacceptable toxicity, death, withdrawal of consent or termination of the study by Sponsor, whichever comes first. The patient may continue PF-04449913 treatment after objective progression of disease has been determined if the patient continues to experience clinical benefit, in the opinion of the investigator, and following discussion with the Sponsor. Refer to Appendix 7 for the definition of disease progression.

5.3.2. PF-04449913 Administration

PF-04449913 will be administered once daily and orally on a continuous basis for all patients. A cycle is defined as 28 days unless the cycle is prolonged due to toxicity per Section 5.3.9 and Section 5.3.10. PF-04449913 will be administered without adjustment for body size and with plenty of water. Tablets must not be crushed or cut; they must be swallowed whole and not chewed. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more

than the prescribed dose at any time. The patient will be reminded not to take their dose at home on clinic days but to bring their bottle into clinic so that PF-04449913 may be administered as described in the schedule of activities.

If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits anytime after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of PF-04449913.

If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, arrangements to send investigational product and dosing diary to patient's home via the third courier may be implemented. Participants must provide verbal consent for providing the contact details for shipping purposes. The verbal consent should be documented in the source document. Tracking record including temperature logs of shipments (eg. Lot number, receipt record by the participant and/or study drug status at the time of receipt, etc.) and the chain of custody of the study medication must be kept in the Investigational Product Accountability Log (IPAL) and/or the participant's medical records.

Patients should return all unused or partially used bottles of investigational product and dosing diaries at the next in-clinic visit.

5.3.3. PF-04449913 in Combination with LDAC (Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy: Unfit Patients)

- PF-04449913 will be commenced on Day 3 of Cycle 1 for PK assessment purposes (for Combination Cohort 1) or Day 1 of Cycle 1 (for Expansion Cohort) and thereafter given once daily and continuously for 28-day cycles (starting on Day 1 for all other cycles);

- PF-04449913 will be administered in the morning at approximately the same time as the first LDAC subcutaneous injection on days these agents are dosed together. On days that PF-04449913 is dosed alone, PF-04449913 will be administered in the morning at approximately the same time each day;

- LDAC will be given at a dose of 20 mg (not adjusted for the patients weight) subcutaneously (SC) twice daily (morning and evening; approximately 12 hrs apart) on Days 1-10 days of the 28 day cycles.

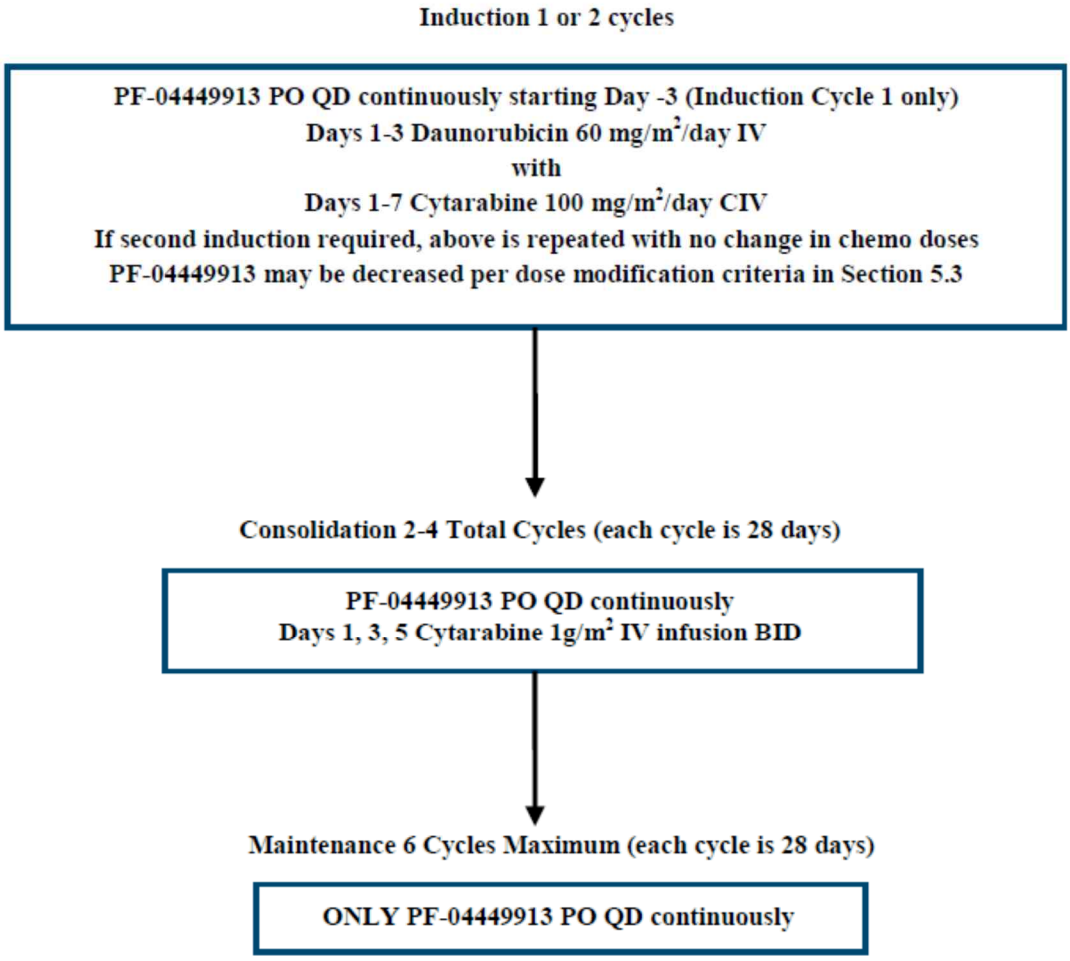
- If the in-clinic study visits cannot be conducted due to COVID-19-related reasons, LDAC administration may be skipped only once. In such case, the safety assessments should be performed by phone or video contact, and/or by utilizing the test results from a local clinic if applicable. If 2 or more consecutive skips are required, the investigator and the Sponsor should have a consultation to determine the necessity of the study treatment discontinuation.

5.3.4. PF-04449913 in Combination with Cytarabine/Daunorubicin (Combination Cohort 2: Fit Patients)

In this cohort, treatment consists of 3 distinct phases: induction, consolidation and maintenance. All patients must meet specific criteria to enter each phase and will be required to wait the full 28 days of each cycle before progressing (Figure 4). The only exception is for receiving the second cycle of induction which, if needed, can occur as early as Day 21 of induction Cycle 1.

Patients may require placement of a central venous catheter prior to initiation of therapy per institutional guidelines.

Figure 4. Overview of Combination Cohort 2 (Fit Patients) Treatment Plan



5.3.4.1. Induction

Patients will participate in their first induction therapy for a total of 28 days. However, if a patient requires a second cycle of induction therapy due to residual leukemia or investigator

opinion, this second course may start as soon as possible following the Cycle 1/Day 21 bone marrow evaluation. If the induction cycle(s) extends longer than 28 days, dosing with PF-04449913 should continue daily in the absence of PF-04449913-related toxicity that would prevent dosing.

The intensive chemotherapy doses will be unaltered for both induction cycles regardless of toxicity or response (see Section 5.3.1 for dose adjustments based on body weight changes). For the first induction cycle only, PF-04449913 will be started on Day -3 and will then be given once daily and continuously for the duration of the treatment. Daunorubicin will be given on Days 1 through 3 once daily at a dose of 60 mg/m^2/day by IV together with cytarabine on Days 1 through 7 at a dose of 100 mg/m^2/day by continuous intravenous infusion (CIV). Where possible, daunorubicin should be given as close as possible to the administration of PF-04449913. Daunorubicin and cytarabine should be administered per institutional guidelines.

The second induction cycle may be delayed up to an additional 28 days from Day 28 of the previous cycle to allow the patient to recover from any severe reversible hematologic or non-hematologic drug related toxicity. Treatment with PF-04449913 should continue during any delay before the start of the second cycle of induction in the absence of significant PF-04449913-related toxicity that would prevent dosing. The second cycle of induction should not be performed if the patient has clinically significant cardiotoxicity (LVEF <45%) and in this case the patient should be discontinued from treatment.

The bone marrow may be repeated at the Investigator's discretion as required for clinical staging at any time prior to the next cycle of chemotherapy.

The following rules apply for progression from induction to consolidation (Figure 5):

- Patients who successfully obtain a **CR** or **CRi** after induction are eligible to enter the consolidation phase of the trial 28 days from the start of the last induction cycle;
- Patients with **residual leukemia** at the end of induction Cycle 1 may be treated with a second cycle of induction therapy. If after the second cycle of induction the patient still shows signs of residual or resistant leukemia, they must be discontinued from treatment and followed as described in Section 5.3.7;
- Patients with **resistant leukemia** after the first and/or second course of induction will be discontinued from treatment and followed as described in Section 5.3.7.

5.3.4.2. Consolidation

Patients achieving a CR or CRi after the completion of induction therapy are eligible to begin consolidation. Post-remission therapy will consist of two to four courses of cytarabine at a dose of 1 g/m^2 administered as a 3 hour IV infusion Q12hrs (2 g/m^2/day) on Days 1, 3 and 5 of a 28-day cycle (see Section 5.3.1 for dose adjustments based on body weight changes). Cytarabine may be interrupted or delayed as clinically indicated. However, cytarabine may be dose reduced in the next cycle only, based on the worst toxicity experienced in the

previous cycle (Table 13 and Table 16). PF-04449913 will continue to be given once daily in the morning continuously in 28-day cycles, where possible at the same with chemotherapy infusion start.

Patients can remain on the study for a minimum of two, but not more than four, courses of consolidation if they do not progress during consolidation treatment. If a patient enters consolidation with a CRi (post induction) assessment but then achieves hematologic recovery in the peripheral blood (defined as ANC >1000/µL and platelets ≥100,000/µL), the bone marrow evaluation should be repeated within 14 days of the hematologic recovered blood counts observation. Bone marrow examinations may be performed at any time throughout consolidation as clinically indicated to confirm the patient has not relapsed. At a minimum a bone marrow evaluation is required Day 21 of the final consolidation cycle to confirm response before going on to maintenance therapy.

The start of subsequent consolidation cycles may be delayed from the end of the previous cycle to allow for recovery from reversible hematologic or non-hematologic drug-related toxicities. If the consolidation cycle(s) extends longer than 28 days, dosing with PF-04449913 should continue daily in the absence of PF-04449913-related toxicity that would prevent dosing.

The following rules apply for progression from consolidation to the maintenance treatment phase and will be based on the results of the bone marrow evaluation conducted during the last consolidation cycle:

- If a patient demonstrates a CR/CRi at the end of two or three consolidation cycles, and are not candidates for additional consolidation therapy, they are eligible to proceed to maintenance therapy;
- If a patient completes four cycles of consolidation and has a CR/CRi at the end of the 4th cycle, they are eligible to proceed to maintenance therapy;
- Patients who initially obtained a CR/CRi but no longer meet this definition may be eligible to continue with maintenance following consultation between Investigator and Sponsor;
- Patient requiring more than two dose reductions of cytarabine will be withdrawn from treatment unless otherwise agreed between the Investigator and the Sponsor.

5.3.4.3. Maintenance

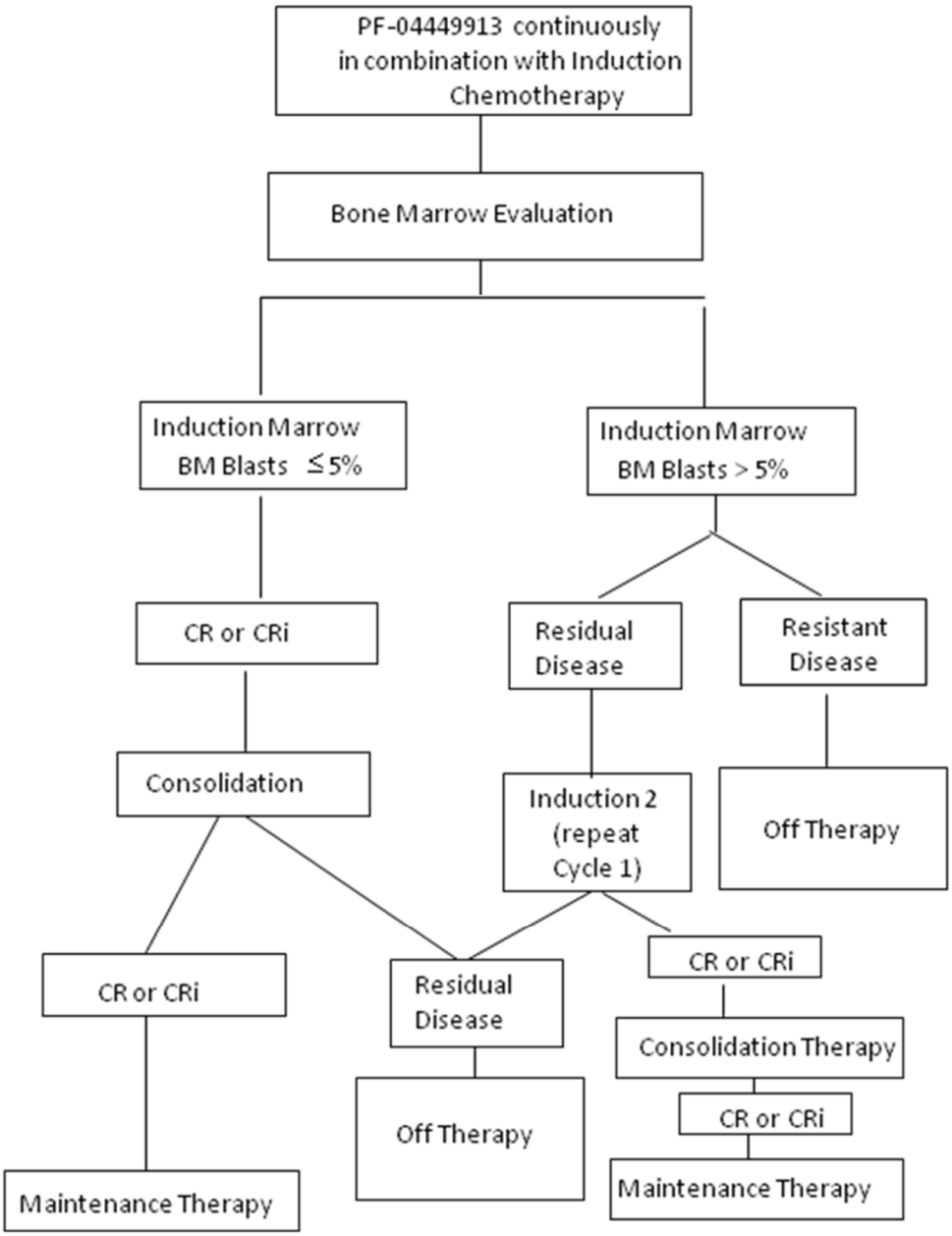
Patients are eligible for maintenance therapy if they have:

- Completed the induction phase;
- Completed at least 2, but not more than 4 cycles of consolidation;
- Maintained a CR/CRi through the end of consolidation;

- Maintenance begins at the end of consolidation (following Day 28 of the last consolidation cycle) and consists of PF-04449913 administered orally once daily continuously in the morning as monotherapy in 28-day cycles. Maintenance will continue for a maximum of six cycles after the completion of consolidation; thereafter, all patients will discontinue treatment (unless demonstrating clinical benefit and upon agreement between the Investigator and Sponsor).

Patients unable to maintain their CR/CRi while on maintenance may still be eligible to continue on maintenance therapy based on investigator Input and Sponsor approval. If a patient demonstrates unequivocal disease progression or unacceptable toxicity, they must be discontinued from treatment and followed as described in Section 5.3.7.

Figure 5. Treatment Flow Diagram for Combination Cohort 2 (Fit Patients)



5.3.5. PF-04449913 in Combination with Azacitidine (Combination Cohort 3)

- Azacitidine will be administered SC or IV daily at a dose of 75 mg/m^2/day on Days 1-7 of each 28-day cycle (After Cycle 1, ±3 days window applicable to each dose).
- PF-04449913 will be orally administered daily and continuously. In Cycle 1 only, administration of PF-04449913 will commence on Day 2 of the cycle (C1D2) to allow azacitidine alone PK sample collection. The starting dose will be 100 mg.

- Recommended dose modifications are discussed in Section 5.3.10.

5.3.6. Continuation Cohort (Monotherapy Cohort)

- PF-04449913 will be commenced on Day 1 of Cycle 1 and orally administered once daily and continuously in 28-day cycles. The starting dose will be the same as the dose at the time the patient discontinued from Study B1371013.

- Dose modifications are discussed in Section 5.3.9.

5.3.7. Post End-of-Treatment Follow-up

In all study cohorts, at least 28 days, and no more than 35 days, after discontinuation of treatment (up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosuppression) patients require review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. In Combination Cohort 1 (unfit patients), all patients will be followed for survival by site visit, phone or letter, regardless of initiation of new cancer therapy. In Expansion Cohort of LDAC combination for efficacy (unfit patients) and Combination Cohort 3 (Azacitidine Combination), all patients will be followed for survival every 8 weeks up to 2 years (for Expansion Cohort of LDAC combination for efficacy) or 12 weeks up to 3 years (for Combination Cohort 3) from the first dose of the last patient enrolled in the study, or until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy. For patients refusing to return to the site, a telephone follow-up call is acceptable. After Protocol Amendment 8, follow-up on survival status will no longer be required in Expansion Cohort of LDAC combination for efficacy (unfit patients).

5.3.8. Food Requirements

In all study cohorts, only in Cycle 1 PF-04449913 will be administered with plenty of water on an empty stomach ie, patients should refrain from food and beverages (except for water) where possible for at least two hours before and two hours after dosing throughout treatment administration. From Cycle 2 onwards, PF-04449913 can be administered with or without food. In the Expansion Cohort of LDAC combination for efficacy and Continuation Cohort, PF-04449913 may be administered with or without food in Cycle 1 and thereafter.

5.3.9. Recommended Dose Modifications [Monotherapy Cohort, Combination Cohort 1 and Expansion Cohort (Unfit Patients), Combination Cohort 2 (Fit Patients) and Continuation Cohort (Monotherapy Cohort)]

Every effort should be made to administer the study treatments at the planned dose and schedule.

In the event of study treatment related toxicity, dosing may be delayed and/or dose reduced as described below in Table 13. 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 three ways:

1. Within a cycle: dose interruption/reduction until adequate recovery during a given treatment cycle.

   - **PF-04449913 (All Cohorts)**:

     - Doses of PF-04449913 that are held or missed during any cycle due to PF-04449913-related toxicities will not be made up (eg. cycles will not be prolonged beyond the 28th calendar day in order to make up any missed PF-04449913 doses during the cycle);

     - PF-04449913 may be dose reduced during any cycle. However, for patients who are enrolled into the 25 mg dose level in the monotherapy cohort, PF-04449913 dose reduction is not allowed.

   - **Backbone chemotherapy (Combination Cohort 1, Expansion Cohort and Combination Cohort 2 only)**:

     - No dose-reductions are permitted in Cycle 1 for any of the backbone chemotherapeutic agents;

     - After Cycle 1, if a toxicity is attributed to the backbone chemotherapy and not to PF-04449913, chemotherapeutics may be delayed or reduced (see Table 13 and Table 15) (while PF-04449913 dosing should be continued);

     - Missed doses of backbone chemotherapy (LDAC, cytarabine/daunorubicin) can be made up if the Investigator considers it appropriate according to standard practice.

2. Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle.

     - A cycle may be extended to a maximum of 56 days for non-hematologic toxicity, or to a maximum of 70 days if due to hematologic toxicity. PF-04449913 dosing should continue if observed toxicity is not deemed related to PF-04449913;

     - If a treatment interruption continues beyond Day 28 of the current cycle for any agent, then the day when full treatment (all agents in the combination) is restarted will be counted as Day 1 of the next cycle for all agents.

3. In the next cycle: dose reduction based on worst toxicity in the previous cycle.

For all drug combinations:

A study treatment related continuous treatment interruption or delay of >28 days for non-hematologic toxicity OR >42 days for prolonged myelosuppression defined as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, will result in permanent discontinuation from treatment, unless the patient is demonstrating clinical benefit as agreed by the Investigator and Sponsor (Table 13).

Table 13. Recommended Dose Modification Criteria for Treatment-Related Toxicity [Monotherapy Cohort, Combination Cohort 1 and Expansion Cohort (Unfit Patients), Combination Cohort 2 (Fit Patients) and Continuation Cohort (Monotherapy Cohort)]

Drug	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
PF-04449913	Non Hematologic	Continue at the same dose level.	Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, 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 resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).	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. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).
PF-04449913	Hematologic - myelosuppression lasting **≤42 days**	If ANC <500/μL or platelet count <10 x10^9/L for ≤42 days in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, withhold dose until toxicity is grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.			
PF-04449913	Hematologic - prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
PF-04449913	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			

Drug	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
LDAC	Non Hematologic	Continue at the same dose level.	Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, 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 resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).	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. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).
LDAC	Hematologic - myelosuppression lasting **≤42 days**	If ANC <500/μL or platelet count <10 x10^9/L for **≤42 days** in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at same dose level or reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.			
LDAC	Hematologic - prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
LDAC	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			
Induction Cytarabine/Daunorubicin	Non Hematologic and Hematologic **≤42 days**	No dose modification permitted for either agent.			
Induction Cytarabine/Daunorubicin	Hematologic - prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
Induction Cytarabine/Daunorubicin	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			

Drug	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Consolidation Cytarabine	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 (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).	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. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).
Consolidation Cytarabine	Hematologic - prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
Consolidation Cytarabine	Hematologic - myelosuppression lasting **≤42 days**	If ANC <500/μL or platelet count <10 x10^9/L for **≤42 days** in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at same dose level or reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.			
Consolidation Cytarabine	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			

5.3.9.1. Additional Guidance for Intra-Patient Dose Modification [Monotherapy Cohort, Combination Cohort 1 and Expansion Cohort (Unfit Patients), Combination Cohort 2 (Fit Patients) and Continuation Cohort (Monotherapy Cohort)]

All dose reductions or interruptions will be at the discretion of the treating physician based on the known toxicities of each study drug. If no clear attribution can be determined, it is recommended to initially dose reduce PF-04449913 according to Table 14, followed by dose reduction of the chemotherapy as clinically indicated.

Once a patient has a dose reduction for a study drug-related toxicity, the dose will not be re-escalated. Patients requiring dose reductions exceeding the doses listed in Table 14-Table 16 will be withdrawn from treatment.

Recommended dose levels for individual agents are listed in below.

Table 14. PF-04449913 Dose Levels (All Cohorts)

Dose Level	PF-04449913 Dose Levels QD (mg)
1	100
-1	50
-2	25

Table 15. LDAC Dose Levels (Combination Cohort 1 and Expansion Cohort only)

Dose Level	LDAC Dose Levels Q12hrs (mg)
1	20 (starting dose level)
-1	15
-2	10

Table 16. Cytarabine Dose Levels in Consolidation Cycles (Combination Cohort 2 only)

Dose Level	Cytarabine Dose Levels Q12hrs (mg/m^2)
1	1000 (starting dose level)
-1	750
-2	500

No dose modification is permitted for Daunorubicin (Combination Cohort 2).

5.3.10. Recommended Dose Modifications [Combination Cohort 3 (Azacitidine Combination)]

Every effort should be made to administer the study drug treatment according to the planned dose and schedule. This section, package insert or institutional guideline for dose modification of azacitidine should be followed.

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

Dose modifications may occur in three ways:

- **Within a cycle**: Dosing interruption until adequate recovery followed by dose reduction (if required) of PF-04449913 during a given treatment cycle. Azacitidine dosing interruption is not allowed within a cycle unless there is an unexpected or unacceptable study drug combination related toxicity or ≥Grade 3 non-hematologic toxicity.

- **Between cycles:** The next treatment cycle may be delayed if toxicity from the preceding cycle persists. If a treatment interruption continues beyond Day 28 of the current cycle for any agent, then the day when full treatment (all agents in the combination) is restarted will be counted as Day 1 of the next cycle for all agents.

- **In the next cycle**: Dose reduction may be required based on toxicities experienced in the previous cycle.

A study treatment related continuous treatment interruption or delay of >28 days (21 days in case of azacitidine related) for non-hematologic toxicity OR >42 days for prolonged myelosuppression defined as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, will result in permanent discontinuation from treatment, unless the patient is demonstrating clinical benefit as agreed by the Investigator and Sponsor (Table 18 and Table 19).

5.3.10.1. Dose Interruptions for Azacitidine and PF-04449913 [Combination Cohort 3 (Azacitidine Combination)]

Azacitidine

Azacitidine dose interruption is not allowed within a cycle unless there is an unacceptable or unexpected study drug combination related toxicity or ≥Grade 3 non-hematologic toxicity. In this case azacitidine dosing may be resumed following the dose modifications listed in Table 18 and Table 19.

After Cycle1, each dose of azacitidine will be allowed to be shifted by a plus or minus 3 day window.

Patients experiencing ≥Grade 3 non-hematologic toxicities should have their azacitidine treatment interrupted regardless of when it occurs in the cycle until the toxicity returns to baseline. If the toxicity prolongs >21 days from when the next cycle is due to start or it becomes severe, azacitidine treatment will be discontinued permanently.

Appropriate follow up assessments should be implemented until adequate recovery occurs as assessed by the Investigator. The criteria that must be met prior to resuming treatment with azacitidine are outlined in Section 5.3.10.2.

Azacitidine administration should not be interrupted if PF-04449913 dosing is interrupted for toxicity.

PF-04449913

Patients experiencing ≥Grade 3 or persisting (at least 7 days not responding to optimal medical management) Grade 2 non-hematologic toxicities or myelosuppression defined as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia potentially attributable to PF-04449913 should have their PF-04449913 treatment interrupted regardless of when it occurs in the cycle until the toxicity recovers to Grade 1or less (for non-hematologic), Grade 2 or less (for hematologic) or baseline.

Appropriate follow-up assessments should be implemented until adequate recovery occurs. The criteria that must be met prior to resuming treatment with PF-04449913 are described in Section 5.3.10.2.

Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of PF-04449913 within the cycle. If the AE leading to treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. PF-04449913 doses omitted for toxicity will not be replaced within that cycle (eg, cycles will not be prolonged beyond the 28 days in order to make up for any missed PF-04449913 doses during that cycle).

The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in Section 5.3.10.3, unless specifically agreed otherwise following discussion between the Investigator and the Sponsor.

5.3.10.2. Dose Delays for Azacitidine and PF-04449913 [Combination Cohort 3 (Azacitidine Combination)]

Azacitidine

Hematologic toxicitity is defined as below:

- Patients without reduced baseline counts (defined as an absolute neutrophil count (ANC) ≥1,500/μL, white blood cells ≥3,000/μL and platelets ≥75,000/μL prior to the first cycle):
  - Hematologic toxicitity is defined as: the lowest count for the previous cycle showed ANC <1,000/μL or platelets <50,000/μL.
- Patients with reduced baseline counts (defined as ANC <1,500/μL, white blood cells <3,000/μL or platelets <75,000/μL prior to the first cycle):
  - Hematologic toxicitity is defined as: any parameters of ANC, white blood cells or platelets decreases to 50% of baseline or below.

For each case, at the start of each new cycle, re-treatment with azacitidine may not occur until the **Neutrophil and Platelet Recovery Parameters** described below are met:

Counts ≥(lowest count) + [0.5 × (baseline count – lowest count)]

PF-04449913

PF-04449913 treatment should be interrupted for toxicities described in Section 5.3.10.1. Re-commencement of treatment with PF-04449913 may not occur until the recovery parameters described below are met:

- Hematologic toxicities have returned to baseline or ≤ Grade 2 severity, provided that patietns recovered from myelosuppression (defined as ANC <500/μL or

platelets <10 x 10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia) within 42 days and re-treatment can occur safely as per the Investigator's judgment.

- Non-hematologic toxicities have returned to baseline or ≤ Grade 1 severity within ≤28 days of dose interruption or delay.

If these conditions are met, PF-04449913 may be resumed (see Section 5.3.10.3 for toxicities requiring dose reduction at the time of treatment resumption).

If myelosuppression (defined as ANC <500/μL or platelets <10 x 10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia) prolongs for >42 days or non-hematologic toxicities need >28 days of dose interruption or dalay, permanent discontinuation of treatment with PF-04449913 should be considered.

5.3.10.3. Dose Reductions for Azacitidine and PF-04449913 [Combination Cohort 3 (Azacitidine Combination)]

Following dosing interruption or cycle delay due to toxicity, the azacitidine and/or PF-04449913 dose may need to be reduced when treatment is resumed.

Dose reduction of azacitidine and/or PF-04449913 by 1 or if necessary, 2 dose levels will be allowed depending on the type and severity of toxicity encountered (Table 17). Patients requiring more than 2 dose reductions of azacitidine should permanently discontinue both azacitidine and PF-04449913. **NOTE**: In the specific situations where clinical benefit is observed, PF-04449913 can be reduced below 50 mg QD upon Sponsor approval. All dose modifications/adjustments must be clearly documented in the CRF.

Once the PF-04449913 dose has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Once the azacitidine dose has been reduced for a given patient, subsequent cycles should be administered at that dose level. If dose re-escalation could be acceptable (ex. a patient undergoes two cycles at a reduced dose without recurrent hematologic toxicity), dose re-escalation to the next higher dose level could be considered following discussion and agreement between the Investigator and Sponsor.

Table 17 Available Dose Levels (Combination Cohort 3)

Azacitidine (mg/m^2/day)	PF-04449913 (mg QD)
75 (100%)	100
50% of current dose	75
33% of current dose	50
	25 *

* NOTE: If clinical benefit is observed, PF-04449913 may be reduced below 50 mg QD following Sponsor approval.

Recommended dose modifications for treatment-related hematologic toxicities are outlined in Table 18.

Table 18 Recommended Dose Modifications for Hematologic Toxicities

<table>
<tr><th>Toxicity</th><th>Azacitidine dose at Start of Subsequent Cycle</th><th>PF-04449913[3] regardless of when it occurs in the cycle</th></tr>
<tr><td>Hematologic toxicity [1, 2]
Recovery[4] within 14 days from when the next cycle is due to start (corresponding to recovery before or on Day 42 of the current cycle)</td><td>No change</td><td>-</td></tr>
<tr><td>Hematologic toxicity [1, 2]
Recovery[4] after 14 days from when the next cycle is due to start (corresponding to recovery after Day 42 of the current cycle)</td><td>Without reduced baseline counts[1]
Decrease to 50% of the current dose

With reduced baseline counts[2]<table><tr><th>Bone marrow cellularity</th><th>Dose in the Subsequent Cycle</th></tr><tr><td>>50%</td><td>No change</td></tr><tr><td>15%-50%</td><td>Decrease to 50% of the current dose if recovery[4] after 21 days from when the next cycle is due to start</td></tr><tr><td><15%</td><td>Decrease to 33% of the current dose if recovery[4] after 21 days from when the next cycle is due to start</td></tr></table></td><td>-</td></tr>
<tr><td>Hematologic - ≤42 days prolongation of myelosuppression[5]</td><td>-</td><td>Withhold dose until toxicity is grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.</td></tr>
<tr><td>Hematologic - >42 days prolongation of myelosuppression[5]</td><td>Permanently discontinue</td><td>Permanently discontinue</td></tr>
</table>

1. For patients without reduced baseline counts (defined as ANC ≥1,500/μL, white blood cells ≥3,000/μL and platelets ≥75,000/μL prior to the first cycle): hematologic toxicity is defined as: ANC <1,000/μL or platelets <50,000/μL.

2. For patients with reduced baseline counts (defined as ANC <1,500/μL, white blood cells <3,000/μL or platelets <75,000/μL prior to the first cycle): hematologic toxicity is defined as: more than one parameter of ANC, white blood cells or platelets decreases to 50% of baseline or below.

3. PF-04449913 treatment should be interrupted for myelosuppression (defined as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia) regardless of when it occurs.

4. Counts ≥(lowest count) + [0.5 × (baseline count – lowest count)]

5. Myelosuppression is defined as ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia

Recommended dose modifications for treatment-related non-hematologic toxicities (excluding QTc prolongation) are outlined in Table 19.

Table 19 Recommended Dose Modifications for Non-Hematologic Toxicities

Toxicity (NCI CTCAE version 4.0)	**Azacitidine dose at Start of Subsequent Cycle Based on Worst Toxicity Observed in the Previous Cycle**	**PF-04449913 regardless of when it occurs in the cycle**
Renal Toxicity		
Serum creatinine or BUN ≥2x baseline value and >ULN	Azacitidine may be re-started at the next cycle when values have returned to baseline or normalized Reduce to 50% of the current dose	In case of Grade 2; Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. In case of Grade 3; 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. In case of Grade 4; 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. Permanently discontinue if the continuous treatment interruption or delay of >28 days.
Serum bicarbonate levels <20 mEq/L (venous)	Reduce to 50% of the current dose	No Change
Other Non-Hematologic Toxicities (Excluding QTc Prolongation, Muscle Spasms and Myalgia)		
Grade 1 toxicity	No change	Continue at the same dose level.

Toxicity (NCI CTCAE version 4.0)	Azacitidine dose at Start of Subsequent Cycle Based on Worst Toxicity Observed in the Previous Cycle	PF-04449913 regardless of when it occurs in the cycle
Grade 2 toxicity	No change	Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator. Permanently discontinue if the continuous treatment interruption or delay of >28 days.
≥ Grade 3 toxicity	Azacitidine should be interrupted regardless of when it occurs in the cycle. Azacitidine could be resumed when grade of the toxicity returns to baseline within 21 days from when the next cycle is due to start and ONLY if as per investigator judgment there will be a patient's clinical benefit to justify continuation of treatment	Nausea, vomiting, or diarrhea must persist at ≥ Grade 3 despite maximal appropriate medical therapy to require dose modification In case of Grade 3; 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. In case of Grade 4; 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. Permanently discontinue if the continuous treatment interruption or delay of >28 days

5.3.11. Recommended Dose Modifications for PF-04449913 QTcF Prolongation and Drug Class Related AEs [Monotherapy Cohort, Combination Cohort 1 (Unfit Patients), Combination Cohort 2 (Fit Patients), Combination Cohort 3 (Azacitidine Combination)]

QTcF Interval Monitoring and Management: Patients should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring. In case of QTc prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out or corrected. In case of clinically significant toxicities, PF-

04449913 administration should be interrupted and the dose reduced as indicated in Table 20 (PF-04449913 Dose Modifications for mean QTcF (mQTcF) Prolongation).

Concomitant administration of PF-04449913 with moderate/strong CYP3A4/5 inhibitors (Appendix 12) is not permitted. And concomitant administration of PF-04449913 with drugs with known risk of Torsade de Pointes (TdP) (Appendix 11) is not recommended due to the potential for drug-drug interaction to prolong the QTc interval. However, if it is medically necessary for patients to use these medications please refer to Section 7.1.5 for details on required assessments and monitoring procedures (excluding the Expansion Cohort of LDAC combination for efficacy).

All protocol specified QTcF prolongation-related exclusion criteria must be followed. Investigators must be aware of the QTcF-prolonging potential of all medications that patients on study at their site are taking, and should take appropriate action when clinically indicated. Given the potential for QTcF prolongation, the measurement and immediate correction of electrolyte abnormalities such as potassium and magnesium and of other reversible causes of QTcF prolongation such as hypoxia, are especially important during the study. In the event that the QTcF interval is prolonged beyond 480 ms (CTCAE v.4.03 ≥ Grade 2), the protocol Recommended PF-04449913 Dose Modifications for mean QTcF (mQTcF) Prolongation-Table 20 must be referenced and actioned. Throughout the study additional ECG and cardiac consultation should be obtained if clinically indicated.

Table 20. Recommended PF-04449913 Dose Modifications for mean QTcF (mQTcF) Prolongation

CTCAE v 4.03 Electrocardiogram QT corrected (QTc) interval prolonged *	Grade 1	Grade 2	Grade 3**	Grade 4
	450-480 msec	481-500 msec	⩾ 501 msec at least two separate ECGs	QTc >= 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be done by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart by using the Fridericia correction method (mQTcF).
** If mQTcF is ⩾ 501 msec continuous ECG monitoring and cardiology consultation are required.

		Grade			
Category	**Requirement**	**1**	**2**	**3**	**4**
ECG monitoring	Continuous ECG monitoring and cardiology consultation for mQTcF ⩾ 501 msec			x	x
Initial PF-04449913 action	Discontinue and do not re-challenge.				x
	Interrupt treatment		x	x	
	Continue at same level	x			
General management	Assess for and correct electrolyte abnormalities.	x	x	x	x
	Withhold any concomitant medications if possible that may cause QTc prolongation.		x	x	x
Resume PF-04449913 dosing	At prior dose if mQTcF returns to ⩽470 msec and to within 20 msec of baseline in 7 days and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ⩽470msec and to within 20 msec of baseline between 7-14 days. and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ⩽470 msec and to within 20 msec of baseline in 14 days if one prior dosing interruption related to mQTcF prolongation has occurred		x		
Management after dose resumed	An ECG should be repeated and mQTcF re-assessed approximately 7 days after PF-04449913 dosing resumption following interruption for a mQTcF prolongation		x	x	
Discontinue PF-04449913 permanently	The mQTcF prolongation does not return to⩽470 msec and to within 20 msec of baseline after 14 days		x	x	
	The Grade ⩾ 2 mQTcF prolongation recurs after one dose reduction related to mQTcF prolongation		x	x	
	The Grade ⩾3 mQTcF prolongation recurs after one prior dosing interruption related to mQTcF prolongation has occurred			x	
	If at any time during the 14 day window that PF-04449913 is stopped due to QTcF prolongation the patient has a confirmed mean QTcF interval >515 msec or becomes symptomatic		x	x	

Recommended dose modifications for PF-04449913 in case of drug class related AEs are outlined in Table 21.

Table 21 Recommended Dose Modifications for PF-04449913 in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	**Grade 1**	**Grade 2**	**Grade 3**
PF-04449913	Continue at same dose level. Administer oral rehydration solutions containing electrolytes. Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P). If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes. Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P). If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. If event persists, hold dose until resolution to Grade ≤1. Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	Hold dose. Administer oral re-hydration salts containing electrolytes. Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P). If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. Upon resolution to Grade ≤1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ≤1, at the discretion of the Investigator the dose may be restarted at the next lower dose level or the patient may be permanently discontinued from study treatment.

In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of PF-04449913 as preliminary analysis of available clinical data suggests that these events are not dose dependent.

5.3.12. Compliance

For PF-04449913, patients will maintain diaries to include missed or changed doses, or significantly delayed doses. Patients are required to return all bottles and unused study medications at each cycle and at end of treatment for compliance assessment and drug accountability. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded.

For medications administered in the study site (cytarabine, daunorubicin, and azacitidine in Combination Cohorts) the site will complete the required dosage Preparation Record. 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.

5.4. Drug Storage and Drug Accountability

Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. This includes thermometers for both room storage and refrigerator storage. Any temperature excursions should be reported immediately.

5.4.1. PF-04449913

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

The investigator, or an approved representative (eg, pharmacist), will ensure that all trial drug is stored in a secured area, under recommended storage conditions provided in the Study Manual and in accordance with applicable regulatory requirements. Under no circumstances should the investigator or other site personnel supply trial drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from Pfizer. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

Adequate records documenting receipt, use, return, loss or other disposition of PF-04449913 must be kept. PF-04449913 tablets must be used according to the protocol directions. The reason for missed dose should be entered on the CRF.

5.4.2. Cytarabine

Cytarabine will be stored in accordance with the drug label and institutional guidelines.

5.4.3. Daunorubicin

Daunorubicin will be stored in accordance with the drug label and institutional guidelines.

5.4.4. Azacitidine

Azacitidine will be stored in accordance with the drug label and institutional guidelines.

5.5. Concomitant Medication(s)

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

Every concomitant medication, blood products, and intervention (eg, paracentesis) required by the patient within 28 days prior to study drug treatment and during the trial (and up to 28 days following last treatment administration or until initiation of another oncologic treatment) and the reason for its administration, must be recorded on the CRF (After Protocol Amendment 8, these data are not required to be recorded on the CRF in the Expansion Cohort of LDAC combination for efficacy).

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

- **CYP3A4/5 Inhibitors:** In vitro studies with human liver microsomes and recombinant CYP enzymes indicated that PF-04449913 metabolism is primarily mediated by the drug-metabolizing enzyme CYP3A4/5. Clinically, there is likelihood that PF-04449913 plasma concentrations may be increased in the presence of co-administered inhibitors of the CYP3A4/5 enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of PF-04449913. Therefore a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and the use of strong/moderate CYP3A4/5 inhibitors are not permitted (unless approved by Sponsor) from 7 days prior to first dose of investigational product until study treatment discontinuation (eg, aprepitant, clarithromycin, cimetidine, ciprofloxacin, cyclosporine, diltiazem, erythromycin, tofisopam, verapamil, fluconazole, itraconazole, ketoconazole, and voriconazole). During this period, food, beverages, and herbal preparations which inhibit CYP3A4/5 are not permitted (eg, grapefruit juice). A comprehensive list of strong/moderate CYP3A4/5 inhibitors is provided in Appendix 12 of the protocol. These requirements/lists may be updated based on emerging data;

- **CYP3A4/5 Inducers:** PF-04449913 metabolism may be induced when taking CYP3A4/5 inducers, resulting in reduced plasma concentrations. The impact of CYP3A4/5 inducers on PF-04449913 pharmacokinetics has not been studied in the clinic. Therefore co-administration of PF-04449913 in combination with any of the following and other strong/moderate CYP3A4/5 inducers is not permitted (unless approved by Sponsor) from 7 days prior to first dose of investigational product until study treatment discontinuation (eg, avasimibe, mitotane, phenytoin, enzalutamide, semagacestat, bosentan, genistein, thioradazine, nafcillin, modafinil, carbamazepine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentine). During this period, food, beverages, and herbal preparations which induce CYP3A4 are not permitted (eg, St. John's Wort). A comprehensive list of strong/moderate CYP3A4/5 inducers is provided in Appendix 13 of the protocol. These requirements/lists may be updated based on emerging data;

- *In vitro* studies have indicated that PF-04449913 is a substrate for P-gp. Therefore, dosing of PF-04449913 in combination with P-gp inhibitors (eg, cyclosporine, erythromycin, itraconazole, ketoconazole, quinidine, tacrolimus and verapamil) and P-gp inducers (eg, St. John's Wort) is not permitted (unless approved by Sponsor) from 7 days prior to first dose of investigational product until the completion of all PK samples. These requirements/list may be updated based on emerging data;

- Immunosuppressants (including but not limited to cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) are not permitted from 14 days prior to first dose of investigational product until treatment discontinuation;

- **Drugs with known risk of Torsade de Pointes:** PF-04449913 has been shown to have the potential to prolong the QTc interval in pre-clinical studies and at doses >200 mg. While the PF-04449913 dose evaluated in this study is 100 mg, the concomitant administration of PF-04449913 and drugs with a known risk of Torsade de pointes should be avoided whenever possible. A list of such drugs is provided in Appendix 11 of the protocol. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to PF-04449913 the guidance provided in Section 7.1.5 requiring additional ECG monitoring before, during and after starting the medication (excluding the Expansion Cohort of LDAC combination for efficacy), electrolyte monitoring (including correction and re-checking values) and dose modifications for QT prolongation per Table 20 must be followed.

- QT prolonging medications (without a risk of TdP) should be avoided whenever possible.

- Concomitant administration of multiple moderate/strong CYP3A4/5 inhibitors,TdP drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended and must be discussed with the Sponsor Medical Monitor.

- Prior or concurrent treatment with a Hh inhibitor or concurrent treatment with other investigational agents not specified in the protocol is not permitted;

- Use of Oral anticoagulant (ie, warfarin) is strongly discouraged if alternate medication (eg, low molecular weight heparin) can be substituted. Warfarin is a CYP3A4 substrate and drug interactions causing variability in INR are possible. If oral anticoagulants are needed, frequent monitoring of the INR is recommended and the dosage of oral anticoagulant should be adjusted as needed.

5.5.1. Other Prohibited or Restricted Concomitant Medications

5.5.1.1. Combination Cohort 3 (Azacitidine Combination)

The following medications are not allowed during the active study treatment period:

- Hydroxyurea (except for the use before and for up to 1 week after first dose of PF-04449913 for control of rapidly progressing leukemia) or other anti-cancer agents (eg, tacrolimus, hormones, cytokines, etc.);

- Immunosuppressant agents (eg, cyclosporine);

The following medications have use restrictions during the active study treatment period:

- Aspirin in doses exceeding 300 mg per day is not permitted.

5.5.1.2. Continuation Cohort (Monotherapy Cohort)

The following medications have restrictions on use or dose during the study treatment period:

- Aspirin in doses exceeding 150 mg per day is not permitted.
- Topical androgen therapies for condition unrelated to MF are permitted; other androgens are not permitted.

The following medications and surgical/medical procedures are prohibited during study treatment:

- Hematopoietic growth factor receptor agonists [eg, erythropoietin (Epo), granulocyte colony stimulating factor (GCSF), romiplostim, and eltrombopag].
- Moderate or high-dose steroids (eg, >10 mg QD prednisone);
- Androgens (eg, fluoxymesterone);
- Focal irradiation;
- Allogeneic peripheral stem cell or bone marrow transplantation;
- Splenectomy;
- Investigational agents;
- Other treatments routinely used to treat MF.

5.5.2. Other Anti-Cancer or Experimental Drugs

No additional anticancer therapy (including herbal supplements) will be permitted while patients are receiving study therapy. All anti-cancer treatments (unless specified) should be discontinued ≥2 weeks from first dose of investigational product, for example, targeted chemotherapy, radiotherapy, investigational agents, hormones, anagrelide, or cytokines.

- Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving IT therapy at first dose of investigational product are considered eligible, and will continue to receive IT therapy.

5.5.3. Prophylactic Medications

Patients with high circulating blasts counts may receive hydroxyurea or leukopheresis to reduce their blast count for up to 1 week in Cycle 1 after the first dose of PF-04449913 of the study. Continuation of hydroxyurea or leukopheresis after that time period must be approved by the Sponsor.

Renal function abnormalities should be treated aggressively and corrected. Patients should be adequately hydrated and receive anti-nephrotoxic medications and antimicrobial prophylaxis according to institutional practice.

5.5.3.1. Tumor Lysis Syndrome (TLS) Prophylaxis

Optimal management of the TLS should involve preservation of renal function as well as prevention of dysrhythmias and neuromuscular irritability. Patients should be managed according to institutional practice and guidelines. In addition, the following practice is recommended:

- Ensure adequate IV hydration.
- Reduce uric acid levels with allopurinol or rasburicase.
- Correct hyperkalemia, hypocalcemia, and hyperphosphatemia.

5.5.3.2. Infection Prophylaxis

Patients should be managed according to institutional practice and guidelines. In addition, the following practice is recommended:

- Extremely careful hand washing by all members of health care team is encouraged.
- Diet should exclude raw fruits, vegetables, and unprocessed foods per institutional guidelines.
- Prophylaxis with antimicrobial agents is strongly recommended for all patients as indicated in the following table when absolute neutrophil count (ANC) <500/μL. Specific anti-microbial agents are prohibited per protocol because of their ability to inhibit CYP3A, resulting in a high-risk for a drug-drug interaction with PF-04449913. These include ketoconazole, itraconazole, voriconazole, clarithromycin, erythromycin, fluconazole and ciprofloxacin. Nephrotoxic agents (eg, gentamicin) should be avoided if possible.
    - For Unfit Patients (Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy): Antimicrobial prophylaxis is indicated during all cycles when ANC is <500/μL and stopped when the ANC ≥500/μL and the patient is afebrile.

- For Fit Patients (Combination Cohort 2): Antimicrobial prophylaxis should start at the initiation of induction chemotherapy. Treatment with all agents may be stopped when ANC is ≥500/μL for 3 consecutive days and the patient is afebrile. During consolidation and maintenance, antimicrobial prophylaxis is indicated when ANC is <500/μL during all cycles and stopped when the ANC ≥500/μL and the patient is afebrile.

- Antimicrobial agents may be chosen at the discretion of local institutional guidelines; however, in the table below the following agents are suggested to decrease the potential for a drug-drug interaction with PF-04449913. These agents are not mandatory and the following table should only be used as a guideline, other agents may be used as long as not prohibited as described in Section 5.5.

Table 22 Suggested Antimicrobial Agents and Doses

AGENT	DOSE	ROUTE
Capsofungin Or Micafungin Or Amphotericin B (Fungizone/ AmBisome)	70 mg loading dose on Day 1 followed by 50 mg q 24h 150 mg per day (treatment of esophageal candidiasis) Or 50 mg per day (prophylaxis of Candida infections in HSCT recipients) Please refer to dosing instructions on drug label	IV IV IV
Acyclovir Or Valacyclovir	800 mg q 12h Or 250 mg/m^2 q 12h 500 mg q 24h	PO Or IV PO

Management of neutropenic infections should follow institutional guidelines.

5.5.3.3. Blood Product, Mucosal, Ocular and Nutritional Support

Administration of blood products, mucosal, ocular and nutritional support should be consistent with institutional guidelines. The following are suggested:

- Red blood cell and platelet transfusions may be utilized throughout the study as clinically indicated.

- The hemoglobin should be maintained at a safe level (eg, hemoglobin >8-10 grams/dL), especially in severely thrombocytopenic patients or those with co-morbid diseases.

- Efforts should be made to maintain the platelet counts above 10 $x10^9$/L in asymptomatic patients. In the presence of fever or hypertension, platelet transfusion to 20 $x10^9$/L is recommended. In the presence of active hemorrhage or suspected gastrointestinal bleeding, platelet transfusion to a minimum count of 50 $x10^9$/L is recommended.

- For patients receiving cytarabine consolidation therapy, ocular prophylaxis consisting of combined dexamethasone and diclofenac eye drops should be instituted to prevent ocular toxicity.

5.5.4. Supportive care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and institutional guidelines.

In the Continuation Cohort, the use of red blood cell and platelet transfusions, low-dose aspirin and/or non-therapeutic doses of steroids will be permitted at any time.

5.5.5. Hematopoietic Growth Factors (excluding the Continuation Cohort)

Primary prophylactic use of granulocyte-colony stimulating factors/granulocyte-macrophage colony stimulating factors is not permitted during Cycle 1 in the Monotherapy Cohort, Cycle 1 for the Unfit populations, during Induction cycle(s) for the Fit populations, and Cycle 1 in the Combination Cohort 3 (Azacitidine Combination), but they may be used to treat treatment-emergent complicated neutropenia as indicated by institutional guidelines. [57]

Erythropoietin may be used at the investigator's discretion for the supportive treatment of emergent anemia (Erythropoietin is not allowed in the Combination Cohort 3 [Azacitidine Combination]) but prophylactic use is discouraged.

5.5.6. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted at the investigator's discretion. The choice of the prophylactic drug is at investigator discretion assuming the drug is not contraindicated as described in Section 5.5.

5.5.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-04449913 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-04449913 is recommended at least 1 week prior to elective surgery. Postoperatively, the decision to reinitiate PF-04449913 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

Study entry is defined as the first day of the lead-in PK period (Cycle 1/Day -5) in the Monotherapy Cohort, Cycle 1/Day 1 in the Combination Cohort 1 and the Expansion Cohort

(unfit patients) and Combination Cohort 3 (Azacitidine Combination), Cycle 1/Day -3 in the Combination Cohort 2 (fit patients) and Cycle 1/Day 1 in the Continuation Cohort.

6.1. Screening

For screening procedures, refer to the Schedule of Activities and Assessments section.

6.2. Study Period

For treatment period procedures, refer to the Schedule of Activities and Assessments section.

6.3. Follow-up Visit

For follow-up procedures, refer to the Schedule of Activities and Assessments section.

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:

- Need for treatment delay or continuous interruption for >28 days due to ongoing study treatment-related non-hematologic toxicity (or >42 days for prolonged study treatment related myelosuppression) unless the patient is demonstrating clinical benefit as agreed by the investigator and sponsor;
- Need for more dose reductions than allowed in Sections 0 and 5.3.10.3;
- Objective disease progression or relapse according to the response criteria for each hematologic diseases (Appendix 5 through Appendix 9);
- 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;
- Refusal for further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, 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 which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, triplicate ECG (12-lead), laboratory assessments (including bone marrow assessments, cytogenetics and immunophenotyping) and verification of concurrent medications and interventions. In the Expansion Cohort of LDAC combination for efficacy, safety assessments will include assessment of AEs and SAEs, and all other safety assessments will be performed per local clinical practice after Protocol Amendment 8. In the Continuation Cohort, safety assessments will include collection of AEs, SAEs, weight, triplicate ECG (12-lead), Complete Blood Count with differential, verification of concurrent medications and interventions and other safety assessments that might be performed according to local clinical practice.

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, will be performed on two occasions (one occasion for the Continuation Cohort) prior to starting study therapy - once at the start of screening (excluding the Continuation Cohort) and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception defined in Section 4.3 must be commenced and a further negative pregnancy result will then be required at the baseline visit 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 study therapy and additionally whenever one 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 study medication but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by IRB/IECs 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 4.0) 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

Haematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories.

After Protocol Amendment 8, the timings and items of these assessments will be determined according to local clinical practice in the Expansion Cohort of LDAC combination for efficacy.

Hematology	**Chemistry (excluding the Continuation Cohort)**	**Urinalysis (excluding the Continuation Cohort)**	**Coagulation tests (excluding the Continuation Cohort)**
Hemoglobin	ALT	Microscopic urinalysis: pH, specific gravity, protein, glucose, ketones, red and white blood cells, leukocyte esterase, casts, crystals and nitrite.	PTT (or aPTT)
Platelets	AST		INR
WBC	Alk Phos		PT (Monotherapy Cohort, Combination Cohort 1, Expansion

Hematology	Chemistry (excluding the Continuation Cohort)	Urinalysis (excluding the Continuation Cohort)	Coagulation tests (excluding the Continuation Cohort)
			Cohort and Combination Cohort 2 only)
Neutrophils	Sodium		
Lymphocytes	Potassium		
Monocytes	Magnesium		
Eosinophils	Chloride		
Basophils	Calcium		
Blast Count	Total Bilirubin		
	BUN or Urea		
	Creatinine		
	Uric Acid		
	Glucose		
	Albumin		
	Total Protein		
	Phosphorus		
	LDH		
	Creatine kinase		
	CO_2 (Combination Cohort 3 only) if possible		

7.1.4. Vital Signs and Physical Examination

Vital signs will include blood pressure (sitting or supine but same position should be used for each assessment when possible) and heart rate. Patients will have a physical exam (PE) including an examination of major body systems, measurement of spleen and liver size to assess extramedullary disease (EMD), weight, assessment of ECOG status. If PE obtained within 48 hours of previous assessments, the evaluation need not be repeated. Height will be measured at baseline only. Weight must be recorded at Screening and Day 1 of each cycle (in the Continuation Cohort, at Screening and thereafter Day 1 of every 3 cycles, and at the End of Treatment). In the Continuation Cohort, only height and weight should be assessed and recorded.

After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE) in the Expansion Cohort of LDAC combination for efficacy.

7.1.5. Triplicate (12-Lead) ECG

Triplicate 12-lead (with a 10-second rhythm strip) tracing in the supine position will be performed for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. The acceptable mean on treatment upper limit of QTc interval will be using the Fridericia (QTcF) correction methods. At each time point three

consecutive ECGs will be performed approximately 2 minutes (but no longer than 5 minutes) apart, to determine the mean QTcF intervals.

After Protocol Amendment 8, these assessments will be conducted according to local clinical practice and the additional ECG monitoring will be required when abnormal findings are observed as described below. The ECG data is not required to be reported in CRF (AE must be reported in CRF if any observation is considered as AE).

If Grade 3 mean QTcF (mQTcF) prolongation (mQTcF≥501 msec) occurs, continuous ECG monitoring and cardiology specialist evaluation and guidance are required (excluding the Expansion Cohort of LDAC combination for efficacy).

The acceptable mean on treatment upper limit of QTcF interval is 480 msec. If any patient has a mean pre- or post-dose QTcF value >480 msec, please refer to Table 20 of the protocol for detailed instructions on management of QTcF prolongation and handling dose delays and dose modifications for PF-04449913.

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

- Prior to the start of a moderate/strong CYP3A4/5 inhibitor or TdP drug:
  - ECGs pre-PF-04449913 dose, 1 and 4 hours post- PF-04449913 dose
  - Follow dose modifications for QT prolongation (Table 20)
- After starting a moderate/strong CYP3A4/5 inhibitor or TdP drug: ECGs on Day 2 or 3 and on Day 5, 6, or 7:
  - ECGs pre- PF-04449913 dose, 1 and 4 hours post- PF-04449913 dose
  - Follow dose modifications for QT prolongation (Table 20)
- Perform additional ECG testing as appropriate
- Perform routine electrolyte monitoring (Ca, K, Cl, Mg), implement timely electrolyte correction, followed by appropriate re-checking of values

When there is an urgent need to start a moderate/strong CYP3A4/5 inhibitor or TdP drug, administration of these medications should not be delayed, the Investigator should consider temporarily interrupting PF-04449913 dosing and should implement these additional monitoring procedures as soon as it is reasonably possible.

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

7.1.6. Cardiac Testing (MUGA/ECHO)

For all fit patients in Combination Cohort 2, an ECHO or MUGA scan is required at screening. If the left ventricular ejection fraction (LVEF) is ≥45%, the patient may proceed to their first induction therapy. If LVEF <45%, the patient will be considered unfit according to the definition provided in Section 4.1.2 and may be eligible for treatment with LDAC. If a second cycle of induction chemotherapy is indicated, a second MUGA or ECHO is required prior to initiating the second cycle if clinically indicated (eg, patient exhibiting signs of cardiac failure). If the second MUGA or ECHO demonstrates a LVEF of <45%, the patient is not eligible to receive additional induction chemotherapy and study treatment will be discontinued.

7.2. PK Assessments (excluding the Continuation Cohort)

As noted in the Schedule of Activities, blood samples for PF-04449913 concentrations will be collected at approximately the same time as the PD samples and ECGs whenever possible (even accounting for scheduling changes).

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, ± 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. The pre-dose PK sample should be collected within 15 minutes prior to administration of the drug (unless the drug is being administered for the very first time). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and sponsor.

PK samples will be assayed for PF-04449913, cytarabine/Ara-U, daunorubicin/ daunorubicinol and azacitidine using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.

PK blood draws should be collected from a location other than any study drug infusion site.

7.3. Blood samples for PK analysis (excluding the Continuation Cohort)

7.3.1. Monotherapy cohort

PF-04449913:

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of PF-04449913 for all cohorts as outlined in the Schedule of Activities (Table 1): during the lead-in period on Day -5, in Cycle 1 on Day 1, Day 8, Day 15 and Day 21. PK samples will also be collected on Day 1 in Cycle 2, 3, and 4. The PK assessments during Cycle 1 may be repeated if the PK sampling is missed for any reason or if the PK data collected are deemed inevaluable by the Sponsor.

7.3.2. Combination Cohort 1 and Expansion Cohort of LDAC combination for efficacy (Unfit Patients, PF-04449913 + LDAC)

PF-04449913:

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of PF-04449913 as outlined in the Schedule of Activities (Table 2 for Combination Cohort 1 and Table 3 for Expansion Cohort of LDAC combination for efficacy).

Cytarabine (Combination Cohort 1 only):

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of LDAC/Ara-U as outlined in the Schedule of Activities (Table 2).

7.3.3. Combination Cohort 2 (Fit Patients, PF-04449913 + Cytarabine/Daunorubicin)

PF-04449913:

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of PF-04449913 as outlined in the Schedule of Activities (Table 4).

Daunorubicin/Daunorubicinol:

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of daunorubicin/daunorubicinol as outlined in the Schedule of Activities (Table 4).

Cytarabine:

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of cytarabine/Ara-U as outlined in the Schedule of Activities (Table 4).

7.3.4. Combination Cohort 3 (PF-04449913 + Azacitidine)

PF-04449913:

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of PF-04449913 as outlined in the Schedule of Activities (Table 11).

Azacitidine:

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of azacitidine (and possibly metabolites) as outlined in the Schedule of Activities (Table 11).

7.4. PD Assessments (excluding the Continuation Cohort)

Biomarker assessments will be used to help understand the *in vivo* mechanism of action of PF-04449913, as well as potential mechanisms of resistance. Such results may help in the future development of this drug as a single-agent and/or in combination with the agents under investigation in this protocol. PD biomarker assessments will be performed on all patients enrolled in this study. These assessments may include the following; (i) evaluation of Hh pathway genes and proteins, (ii) circulating protein levels, and (iii) molecular analysis of somatic mutations and translocations with a known frequency of occurrence in the AML and MDS populations. Additional PD biomarkers may also be included, based on emerging data on Hh pathway biology. A brief description of the types and frequencies of sample collection is provided below and summarized in Table 23. For collection timepoints, refer to the Schedule of Activities and Assessments section.

7.4.1. PD Sample Collections

7.4.1.1. Blood Sample Collections

Approximately 6 mL of blood will be collected from all patients for circulating protein and gene expression analysis at the time points indicated in the Schedule of Activities. When possible, PD blood collections will be matched with PK sample collections for PK/PD evaluations. Full details regarding collection, processing, storage and shipping of all PD biomarker samples will be provided in the lab manual.

7.4.1.2. Normal Skin Biopsies [Monotherapy Cohort, Combination Cohort 1 (Unfit Patients) and Combination Cohort 2 (Fit Patients)]

Normal skin punch biopsies will be obtained from all patients in Monotherapy Cohort, Combination Cohort 1 and Combination Cohort 2 at screening and Cycle 1/Day 21 (±7 day of nominal time on Day 21). Skin samples should be taken from the same area of the body. Skin samples will be analyzed for treatment-related changes in the RNA transcript levels of Hh pathway-regulated genes (eg, Gli1, Gli2) and potentially other signaling pathways. When possible, PD skin sample collections will be matched with PK sample collections for PK/PD evaluations. Samples will be processed and shipped as described in the Lab Manual.

7.4.1.3. Bone Marrow Sample Collections

Bone marrow aspirates (approximately 2 mL) will be analyzed for genetic abnormalities frequently associated with AML. These genetic abnormalities include known mutations in the genes such as NPM1, CEBPA, FLT3, RUNX1, IDH1, IDH2, KIT, K-Ras, N-Ras and WT1. Additional genes with mutations known to be associated with AML and MDS may also be evaluated if feasible. Treatment-related changes in the RNA transcript levels of Hh pathway-regulated genes (eg, Gli1, Gli2) and potentially other signaling pathways may be analyzed in the Expansion Cohort of LDAC combination for efficacy (unfit patients). Methylation profiling and leukemia stem cell gene expression signature(s) may also be performed to identify candidate epigenetic markers in the Combination Cohort 3.

All bone marrow samples will be prepared according to the study Lab Manual. All bone marrow samples (aspirates) will be collected as outlined in the Schedule of Activities. When possible, PD sample collection timing will be matched with PK sample collection.

After Protocol Amendment 8, PD sample collection are not required in the Expansion Cohort of LDAC combination for efficacy.

Table 23. Summary of Biomarker Assessments

Assay	Source
Mutational Analysis Epigenetic Analysis (Combination Cohort 3 only) Leukemia stem cell gene expression Analysis (Combination Cohort 3 only)	Bone marrow aspirate
Circulating Protein Analysis	Peripheral blood and serum
Expression of Hh family genes	Peripheral blood, serum and skin biopsy Bone marrow aspirate (Expansion Cohort of LDAC combination for efficacy only)

7.5. Disease Response Assessment (excluding the Continuation Cohort)

7.5.1. Response Criteria

Monotherapy Cohort:

Assessment of response will be made using response criteria for selected hematologic diseases, each having specific clinical response criteria (Appendix 4 through Appendix 8). The response criteria for CML are derived from Faderl et al 1999[58] and Cohen et al 2005[59]. Response criteria for CMML/MDS, MF and AML are derived and defined by the disease specific International Working Groups and World Health Organizations (WHO) Guidelines.

Combination Cohorts:

Assessment of response will be made using response criteria for MDS and AML derived and defined by the disease specific International Working Groups and World Health Organizations (WHO) Guidelines (Appendix 5 and Appendix 8).

7.5.2. Bone Marrow

Bone marrow aspirate and/or biopsy will be collected for clinical staging and for PD biomarker assessments as outlined in the Schedule of Activities. If a bone marrow aspirate and/or biopsy has been collected within 28 days (excluding the screening sample), it does not need to be repeated. With the Sponsor's approval, a bone marrow does not need to be performed based on the patient characteristics, or a bone marrow performed prior to screening may be used for study inclusion.

After Protocol Amendment 8, bone marrow samples are not required to be submitted for PD assessments in the Expansion Cohort of LDAC combination for efficacy.

7.5.3. Immunophenotyping, Cytogenetics and Mutation Analysis

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

After Protocol Amendment 8, these assessments are not required in the Expansion Cohort of LDAC combination for efficacy.

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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 adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as a 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 study drug 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 one dose of study treatment through the patient's last visit (for Combination Cohort 3 and Expansion Cohort of LDAC combination for efficacy, 28 days after the last administration of the investigational product). In the Continuation Cohort, ongoing adverse events which had occurred in the previous study should also be recorded on the CRF;

- 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. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (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 (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE grade 5 (refer to 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 (refer to the Section 8.14.1 SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

Concurrent with

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

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, 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, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical 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 work-up 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;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as 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

If required on the AE CRFs, the investigator will use the following definitions of severity in accordance with CTCAE Version 4.0 (Publish Date: May 28, 2009, http://ctep.cancer.gov/reporting/ctc.html) to describe the maximum intensity of the AE. If the event is serious, the CTCAE grade reported in the AE CRF must be consistent with the description of CTCAE grade included in the narrative section of the SAE report.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 CTCAE document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for 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 serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not 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 (refer to 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:

- 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 women (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- 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 a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the

anticipated date of delivery (see the 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

8.11. Occupational Exposure

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

An occupational exposure is reported to the drug safety unit within 24 hours of 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 (Refer to the Section 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 a 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 timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, 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/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for 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

Adverse event 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 trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. The SAP 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. Unless otherwise stated, the monotherapy cohort and the combination cohorts will be analyzed separately. The data from the Continuation Cohort will not be analyzed and will be presented in the form of patient data listings separately from the other cohorts.

The primary analysis will be performed after disease assessment on Cycle 9/Day 1 for the last (15^{th}) patient treated in Expansion Cohort of LDAC combination for efficacy. The timing of the primary analysis is estimated to be after approximately 19 months after the first dose for the first patient in Expansion Cohort of LDAC combination for efficacy, assuming the enroll speed as 15 patients per year.

The final analysis will be performed after all patients have died or after the last patient last visit, whichever occurs first. Further analyses could be performed, if necessary.

9.1. Analysis Sets

In this study, analysis sets are defined as below although the patients enrolled in the Expansion Cohort of LDAC combination for efficacy are excluded from DLT-evaluable analysis set and the patient enrolled in the Continuation Cohort is excluded from all of these analysis sets except the safety analysis set. The patient enrolled in the Continuation Cohort is included in the safety analysis set if the patient receives at least one dose of study medication.

1. Safety analysis set:

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

2. Full analysis set:

   The full analysis set includes all enrolled patients who receive at least one dose of study medication on or after Cycle 1/Day 1 (Induction Cycle/Day 1 for fit patients in the Combination Cohort 2).

3. DLT-evaluable analysis set:

The per protocol analysis set includes all enrolled patients who receive at least one dose of study medication and who do not have major treatment deviations during first cycle (DLT observation period). Patients with major treatment deviations during the DLT observation period are not evaluable for the DLT assessment and will be replaced as needed. Major deviations include, but are not limited to, administration of less than 80% of the planned dose during the DLT observation period of PF-04449913 or any component of the combination therapy [LDAC for Combination Cohort 1 (Unfit Patients), cytarabine/daunorubicin for Combination Cohort 2 (Fit Patients), and azacitidine for Combination Cohort 3 (Azacitidine Combination)] for reasons other than drug related toxicity.

4. PK analysis sets:

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

5. QTc-evaluable analysis set:

   The QTc-evaluable dataset is defined as all patients who have baseline and at least one triplicate ECG assessment after having at least one PF-04449913 dose on study.

9.2. Sample Size Determination

Cohorts excluding the Expansion Cohort of LDAC combination for efficacy

No statistical sample size determination was performed. The number of patients to be enrolled in the study depends on the observed safety profile within the cohorts. The total expected number of patients is estimated to be 34 patients.

The Expansion Cohort of LDAC combination for efficacy

The total expected number of patients is estimated to be 15 patients.

A one stage design with 15 patients provides 80.8% power with a one-sided type I error rate of 0.05 to test the null hypothesis that the true investigator-reported DMR rate is 6.8% vs the alternative hypothesis that the investigator-reported DMR rate is 34.1%. The study would be considered positive if 4 responses are observed. The null DMR rate and the alternative DMR rate are based on the result of the analysis based on the derived response for B1371003 CSR (P2 Unfit, data cut off: 3 Jan 2017).

9.3. Efficacy Analysis (excluding the Continuation Cohort)

Disease response will be presented in the form of patient data listings that include, but are not limited to, malignancy type, tumor response at each visit, and best overall response. In addition, disease progression date, date of first disease response, and last disease assessment date will be listed.

In Combination Cohort 1 (unfit patients), survival follow-up data will be presented in the form of patient data listings and summary table as needed. The listings include, but are not limited to, malignancy type, event date, event day from first dose, type, reason for censoring and age (≤60 vs >60 years).

In Expansion Cohort of LDAC combination for efficacy (unfit patients), the DMR rate will be estimated for patients in the full analysis set. DMR includes CR, CRi, morphologic leukemia-free status (MLFS), marrow CR (mCR) and PR (Appendix 5 and Appendix 8). CR rate and median OS will also be estimated. The time-to-event endpoints including OS, duration of response and time to response, will be presented in the form of patient data listings, respectively. The listings include, but are not limited to, event date, event day from first dose, type, reason for censoring, AML/MDS risk, European Leukemia Net (ELN) cytogenetic risk and age (≤60 vs >60 years).

In Combination Cohort 3 (Azacitidine Combination), the time-to-event endpoints including OS, duration of response and time to response, will be presented in the form of patient data listings, respectively. The listings include, but are not limited to, event date, event day from first dose, type, reason for censoring, ELN cytogenetic risk and age (≤60 vs >60 years).

OS is defined as the time from the date of first dose of study drug to the date of death due to any cause. Patients last known to be alive will be censored at the date of last contact.

Duration of response is the time from the date of first documentation of a CR/CRi and DMR to the date of first documentation of relapse after CR/CRi and DMR or death due to any cause. Duration of response data will be censored on the date of the last adequate response assessment for patients who do not have an event (relapse or death).

Time to response is the time from the date of first dose of study drug to the date of first documentation of a CR or CRi and DMR.

9.4. Analysis of Other Endpoints (excluding the Continuation Cohort)

9.4.1. Analysis of PK

9.4.1.1. PK Analysis of PF-04449913, Cytarabine/Ara-C, Daunorubicin, and Azacitidine

Standard plasma PK parameters including the observed maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC) for each drug (and metabolite if relevant), will be estimated using non-compartmental analysis. If data permit or if considered appropriate, minimum plasma concentration (Cmin), average plasma concentration (C_{ave}), area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F, CL), apparent volume of distribution (V_d/F, V_d), accumulation ratio (R_{ac}) will be estimated. Descriptive statistics will be provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by analyte, dose, administration route, cycle and day.

For drug concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by dose, cycle, day of assessment, and nominal time in tabular form. Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

9.4.1.2. Evaluation of Drug-Drug Interaction Potential

9.4.1.2.1. Combination Cohort 1 (Unfit Patients): PF-04449913 and LDAC

The primary PK parameters, AUC and C_{max}, will be utilized to estimate the effect of coadministration of PF-04449913 and LDAC on the PK of either PF-04449913 or LDAC. The geometric mean ratios and its 90% confidence intervals (if data permit) for the PK parameters will be used for assessment of the extent of interaction for PF-04449913 in presence of LDAC and PF-04449913 alone.

PF-04449913 AUC and C_{max} when administered alone (Cycle 1/Day 21) will be compared to Cycle 1 Day 10 AUC and C_{max}, when administered in combination with LDAC. A similar assessment will be performed to determine the effect of PF-04449913 on Ara-C. The AUC and C_{max} on Cycle 1/Day 2 when LDAC is administered alone will be compared to Cycle 1 Day 10 AUC and C_{max} when administered in combination with PF-04449913.

9.4.1.2.2. Combination Cohort 2 (Fit Patients): PF-04449913 and Cytarabine/Daunorubicin

The primary PK parameters, AUC and C_{max}, will be utilized to estimate the effect of coadministration of PF-04449913 and cytarabine/daunorubicin on the PK of PF-04449913. The geometric mean ratios and its 90% confidence intervals (if data permit) for the PK parameters will be used for assessment of the extent of interaction for PF-04449913 in presence of cytarabine/daunorubicin and PF-04449913 alone.

PF-04449913 AUC and C_{max} when administered alone (Induction Cycle Day 10) will be compared to Induction Cycle Day 3 AUC and C_{max}, when administered in combination with cytarabine/daunorubicin. The effect of PF-04449913 on cytarabine/daunorubicin will not be conducted within the study due to the inability to dose cytarabine/daunorubicin alone.

9.4.1.3. Combination Cohort 3: PF-04449913 and Azacitidine

The primary PK parameters, AUC and C_{max}, will be utilized to estimate the effect of co-administration of PF-04449913 and azacitidine on the PK of either PF-04449913 or azacitidine. The geometric mean ratios and their 90% confidence intervals (if data permit) for the PK parameters will be used for assessment of the extent of interaction for PF-04449913+ azacitidine vs. PF-04449913 alone. A similar assessment will be conducted for PF-04449913 + azacitidine vs. azacitidine alone.

PF-04449913 AUC and C_{max} when administered alone (Cycle 1/Day 21) will be compared to Cycle 1/Day 7 AUC and C_{max}, when administered in combination with azacitidine. A similar assessment will be performed to determine the effect of PF-04449913 on azacitidine. The AUC and C_{max} on Cycle 1/Day 1 when azacitidine is administered alone will be compared to

Cycle 1/Day 7 AUC and C_{max} when azacitidine is administered in combination with PF-04449913.

9.4.1.4. Population PK Analysis or PK/PD Modeling

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

9.4.1.5. Statistical Analysis of Biomarker Endpoints

PD biomarkers will be assessed separately for blood, serum, normal skin biopsies and the bone marrow samples. In each case, summaries of baseline levels, changes from baseline (where appropriate), and mutation status will be reported. Summary statistics may include the mean and standard deviation, median, %CV and minimum/maximum levels of biomarker measures or frequency statistics, as appropriate. Data from biomarker assays will be analyzed using graphical methods and descriptive statistics such as linear regression, Wilcoxon and ranked sum. The statistical approach may examine correlations of biomarker results with pharmacokinetic parameters and measures of anti tumor efficacy.

Due to the exploratory nature of the proposed biomarkers, the data analysis will be conducted with the goal of identifying biomarkers with the strongest concordance to clinical outcome, encompassing both safety and efficacy. Candidate biomarkers will be validated in subsequent trials.

9.5. Safety Analysis

Summaries and analyses of safety parameters will include all patients in the safety analysis sets. However, safety data from the patient enrolled in the Continuation Cohort will be separately presented in the form of patient data listings.

For Combination Cohort 1 and Expansion Cohort, the pooled analysis will be considered in addition to separated analysis for each cohort.

9.5.1. Analysis of Adverse Events

Dose Limiting Toxicity (DLT) is the primary endpoint of the study. For each cohort, DLTs will be summarized by MedDRA preferred term.

Adverse Events

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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 medication. The number and percentage of patients who experienced any AE, serious 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).

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

9.5.2. Analysis of ECG

The analysis of ECG results will be based on patients in the safety analysis set with both baseline and on-treatment ECG data. All ECGs obtained during the study will be evaluated for safety.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis (duplicate ECGs will also be averaged and single ECGs used if necessary). 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 as individual values obtained at unscheduled time points.

Data will be summarized and listed for QT, HR, RR, PR, QRS and QTcF by treatment arm and cohort. Individual QTc intervals will be listed by treatment arm, cohort and time point.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc by treatment arm, cohort and time point. For each patient and by treatment, the maximum increase from baseline as well as the maximum post-baseline value will be calculated across time points using the correction method(s) deemed appropriate. Outlier analysis of the QTc (using the most appropriate correction method) data will be conducted and summarized as follows:

- The number of patients with maximum increase from baseline in QTc (<30, 30-60, and ≥60 msec);
- The number of patients with maximum post-dose (post-baseline) QTc (<450, ≥450-≤480, ≥481-≤500, and ≥501 msec);
- PR changes from baseline ≥25% and absolute values over >200 msec;
- QRS changes from baseline ≥25% and absolute values over >110 msec;
- Number and percentage of individuals with abnormal ECG findings.

Shift tables will be provided for baseline vs. worst on study QTc (one or more correction methods may be used) using maximum CTCAE Grade, as well as tables of ECG abnormality

at baseline (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The ECG analyses described above for the safety population may be repeated separately for the QTc-evaluable population.

9.6. 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 cohort in an on-going 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

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to

third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

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

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

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

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

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

13. DEFINITION OF END OF TRIAL

End of Trial is defined as date upon which enrollment is completed according to protocol planned sample size and the assessments and requirements are completed according to protocol (including the follow-up period).

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

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 has no objection to publication by an Investigator of any information collected or generated by the Investigator, whether or not the results are favorable to the Investigational Drug. 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 before it is submitted or otherwise disclosed.

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

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

If the study is part of a multi-centre study, the Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. ECOG Performance Status

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

Appendix 2. Table of French-American-British (FAB) classification of Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) Diagnosis	FAB Classification
Myeloblastic leukemia minimally differentiated	M0
Myeloblastic leukemia without maturation	M1
Myeloblastic leukemia with maturation	M2
Hypergranular promyelocytic leukemia Variant, microgranular promyelocytic leukemia	M3 M3V
Microgranular variant Myelomonocytic leukemia With bone marrow eosinophilia	M4 M4Eo
Monocytic Leukemia Poorly differentiated Differentiated	M5 M5a M5b
Erythroleukemia	M6
Megakaryoblastic Leukemia	M7

Appendix 3. WHO Classification of Myelodysplastic Syndromes (MDS)

Disease	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia *only* < 5% blasts < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia *only* ≥ 15% ringed sideroblasts < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines < 5% blasts in marrow No Auer rods < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods < 1 x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in 2 or more myeloid cell lines ≥ 15% ringed sideroblasts < 5% blasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias < 5% blasts No Auer rods < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods ± < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes < 5% blasts No Auer rods
MDS associated with isolated del(5q)	Anemia < 5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts No Auer rods Isolated del(5q)

Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;(100):2292-2302.[60]

Appendix 4. Diagnostic Criteria for Chronic Myelomonocytic Leukemia (CMML)*

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

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

Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;(100);2292. [60]

Appendix 5. Response Criteria and Progression Definitions for Myelodysplasia and CMML

Response Criteria	Peripheral Blood				Bone Marrow Blasts (BMB) (%)	Other
	Hgb (g/dL)	Neutrophils (L)	Platelets (L)	Blasts (%)		
Complete Remission	≥11	≥1 x 10^9	≥100 x 10^9	0	≤5	Normal maturation of all cell lines, note if has persistent dysplasia
Partial Remission					Decreased by ≥50% but still >5%	All CR criteria if abnormal before treatment except BMB
Marrow CR	If hematologic improvement (HI) response, note in addition to Marrow CR				≤5% & decreased by ≥50%	
Stable Disease						Failure to achieve PR & no evidence of progression*
Failure						Death, or disease progression: worsening cytopenia, increase in % BM blasts, progression to a more advanced MDS FAB subtype
Relapse after CR or PR						At least one of the following: Return to pre-treatment BMB % Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hb ≥1.5g/dL or transfusion dependence

Cheson BD, Greenberg PL, Bennett JM et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood 2006; 108(2) 419-25.[61]

*SD must last > 8 weeks but response is documented regardless of duration.

Additional Response Criteria for Myelodysplasia and CMML

Cytogenetic Response Complete Partial	 Disappearance of chromosomal abnormality with no appearance of new ones ≥50% reduction of chromosomal abnormality
Disease Progression **For patients with % blasts at screening:** <5% bone marrow blasts 5-10% bone marrow blasts 10-20% bone marrow blasts 20-30% bone marrow blasts For all categories, any of:	 ≥50% increase to >5% bone marrow blasts ≥50% increase to >10% bone marrow blasts ≥50% increase to >20% bone marrow blasts ≥50% increase to >30% bone marrow blasts At least 50% decrease from maximum remission/response in granulocytes or platelets Reduction in Hgb by ⩾2 g/dL Transfusion dependence

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

Erythroid response (pre-treatment <11g/dl)*	Hb increase by ≥1.5 g/dl Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks as compared to the pretreatment transfusion number in the previous 8 weeks (only RBC transfusions given for Hb≤9/dL pretreatment will count in the RBC transfusion evaluation).
Platelet Response (pretreatment <100 $x10^9$)*	Absolute increase of ≥30 $x10^9$ /L if starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 $x10^9$/L and by at least 100%
Neutrophil Response (pretreatment <1$x10^9$/L)*	At least a 100% increase and an absolute increase >0.5 $x10^9$/L
Progression or relapse after HI in the absence of another explanation	At least one of the following: At least 50% decrease from maximum response levels in granulocytes or platelets; Reduction in Hgb by ≥1.5g/dL; Transfusion dependence

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart.

** Hematologic Improvement must last ≥ 8 weeks and is derived based on lab data entered in the database.

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Appendix 6. 2008 WHO Diagnostic Criteria for Primary Myleofibrosis*

Major Criteria	1. Megakaryocyte proliferation and atypia† accompanied by either reticulin and/or collagen fibrosis, *or* In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e., pre-fibrotic PMF). 2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm. 3. Demonstration of $JAK2^{V617F}$ or other clonal marker, *or* no evidence of reactive marrow fibrosis.
Minor Criteria	1. Leukoerythroblastosis 2. Increased serum LDH 3. Anemia 4. Palpable splenomegaly

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

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

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

Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 2008; (22) 14.[67]

Appendix 7. Response Criteria and Progession Definitions for Myleofibrosis

Response Criteria	Peripheral Blood				BM Blasts (%)	Other
	Hgb (g/L)	Neutrophils (L)	Platelets (L)	Other		
Complete Remission (CR)	≥110	≥1 x 10^9	≥100 x 10^9	All ≤ULN	≤5%	Complete resolution of disease-related symptoms & signs including hepatosplenomegaly. Normal leukocyte differential. Bone marrow histologic remission including osteomyelofibrosis Grade ≤1
Major Cytogenetic Response						This is a failure to detect a cytogenetic abnormality if pre-existing
Minor Cytogenetic Response						≥ 50% reduction in abnormal metaphases
Partial Remission (PR)	≥110	≥1 x 10^9	≥100 x 10^9	All ≤ULN		All CR criteria except for bone marrow histologic remission. A repeat bone marrow biopsy is required.
Clinical Improvement (CI)						In the absence of both PD & CR/PR requires one of the following for ≥8 weeks (over any 8-week period): -≥20g/L increase in Hgb, or becoming transfusion independent (baseline <100 g/L). - either ≥50% reduction in splenomegaly of >10 cm or palpable at >5 cm at baseline and becomes not palpable. -Minimum 100% increase in ANC and ANC ≥ 0.5 x 10^9/L if baseline neutrophil <1x 10^9/L -Minimum 100% increase platelet count and absolute platelet count of 50,000x10^9/L if baseline <50x10^9/L
Progressive Disease (PD)						One of the following: - progressive splenomegaly* - leukemic transformation confirmed by bone marrow blasts >20% - >20% increase peripheral blood blast lasting >8 wks
Stable Disease (SD)						None of the above
Relapse						Loss of CR, PR or CI

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

Tefferi A, Barosi G, Mesa RA et al. International working group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for myelofibrosis research and treatment (IWG-MRT). Blood 2006; 108(5):1497-1503. [68]

Appendix 8. Response Criteria and Progression Definitions for Acute Myeloid Leukemia

Hematologic Responses to Treatment

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

There is no minimum requirement for bone marrow cellularity or hemoglobin concentration for response criteria

Cytogenetic Responses to Treatment

Response Criteria	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Cytogenetic CR (CRc)	>1,000	>100,000	<5	Cytogenetics - normal, no EMD
Molecular CR (CRm)	>1,000	>100,000	<5	Molecular-negative, no EMD

Criteria for Treatment Failure

Definition	Criteria
TF due to resistant disease	Pt survives ≥7 days post chemo; persistent AML >25% blasts in blood or BM
TF due to aplasia	Pt survives ≥7 days post chemo; death while cytopenic with aplastic bone marrow
TF indeterminate cause	Pt dies <7 days post therapy; Pt dies >7 days post therapy with no PB blasts, but no bone marrow exam; Pt does not complete 1st course of therapy
TF due to morphologic relapse	Reappearance of blasts post CR in PB or ≥5% blasts in bone marrow not attributed to another cause
TF due to molecular or cytogenetic relapse	Reappearance of molecular or cytogenetic abnormality

Modified from Cheson BD, Bennett JM, Kopecky KJ et al. Revised recommendations of the International Working group for diagnosis, standardization of response criteria, treatment on outcomes and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003; 21(24) 4642-4649.[62]

Appendix 9. Response Criteria and Progression Definitions for Chronic Myeloid Leukemia

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

Subjects with Accelerated or Blast Phase CML	
Hematologic Responses	Definition
Return to Chronic Phase	Disappearance of features defining accelerated & blast phases, but still in chronic phase (May have platelets <100 x10^9/L, if related to therapy) Persistence of clonal evolution, if present at the time of therapy, is acceptable for return to chronic phase
Minor Response	<15% blasts in marrow and blood < 30% blasts + promyelocytes in marrow and same in blood < 20% basophils in peripheral blood No extramedullary disease other than spleen and liver
No Evidence of Leukemia (NEL)	Blast ≤ 5% in bone marrow 0.5 x10^9 ≤ ANC <1.0 x10^9/L 20x10^9 ≤ Platelets < 100 x10^9/L No blood blasts or promyelocytes <20% basophils in blood Myelocytes + metamyelocytes <5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Complete Hematologic Response	Blast ≤5% in bone marrow No peripheral blasts or promyelocytes Myelocytes + metamyelocytes <5% in blood ANC ≥ 1.0 x10^9/L WBC ≤ institutional ULN Platelets ≥ 100 but <450 x10^9/L, unless related to therapy <20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Subjects with Chronic Phase CML	
No Evidence of Leukemia (NEL)	0.5 x10^9 ≤ ANC <1.0 x10^9/L 20x10^9 ≤ Platelets <100 x10^9/L No blood blasts or promyelocytes <20% basophils in blood Myelocytes + metamyelocytes <5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Complete Hematologic Response	No Peripheral blasts or promyelocytes Myelocytes + metamyelocytes <5% in blood ANC ≥ 1.0 x10^9/L WBC ≤ institutional ULN Platelets ≥ 100 but <450 x10^9/L, unless related to therapy <20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)

Cytogenetic Responses to Treatment (Any Phase of CML)

Cytogenetic Responses*	% Philadelphia chromosome positive cells
None	> 95%
Minimal	66-95%
Minor	36-65%
Partial	1-35%
Complete	0%
Major	Complete + Partial Rates

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

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

Molecular Responses	PCR for BCR-ABL
None	No Change
Partial	< 3 log reduction from standardized baseline
Major	≥ 3 log reduction from standardized baseline
Complete	Undetectable BCR-Abl

Definitions of Treatment Failure and Disease Progression

DEFINITIONS OF TREATMENT FAILURE

- **OCCURRENCE OF AT LEAST ONE OF THE CRITERIA FOR DISEASE PROGRESSION SHOWN BELOW**
- **DEATH (ANY CAUSE)**
- **WITHDRAWAL FROM TREATMENT OWING TO AN ADVERSE EVENT, SUBJECT REFUSAL, OR LOSS TO FOLLOW-UP**

DEFINITIONS OF PROGRESSION

Definition	Criteria
Early Progressor from CP	For Chronic Phase: If subject enters study in chronic phase clearly progresses to advanced phase during the first 4 weeks of therapy (to be considered a progressor to accelerated phase, a subject must have an absolute increase of at least 10% in their count(s) qualifyinf the subject for accelerated phase)
Progressor to Accelerated Phase or Blast Crisis from Chronic Phase or Return to Chronic Phase	Subject evolving from chronic phase or return to chronic phase to accelerated phase or blast crisis (on two consecutive assessments at least a week apart).

Progressor to Accelerated Phase to Blast Crisis	A subject evolving from accelerated phase to blast crisis (on two consecutive assessments at least a week apart).
Loss of Confirmed CHR	Loss of confirmed CHR that is confirmed by a subsequent hematologic assessment ≥ at least 2 weeks after the initial finding of loss
Loss of MCyR	Loss of MCyR-Ph+ rate increased by 30%

Appendix 10. Doxorubicin Equivalent

	Doxorubicin equivalent
Doxorubicin	×1
Daunorubicin	×3/4
Epirubicin	×1/2
Pirarubicin	×1/2
Mitoxantron	×3

Appendix 11. List of drugs with known risk of Torsade de Pointes

The following drugs are known to have the risk of Torsade de Pointes due to QTc prolongation and their current use in combination with PF-04449913 is not recommended. If any of these drugs are considered to be medically necessary, then they should be used with caution in combination with PF-04449913.

Generic Name	Drug Class	Therapeutic Use	Route
Aclarubicin	Anti-cancer	Cancer	injection
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	oral,injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Anti-cancer	Leukemia	injection
Astemizole	Antihistamine	Allergic rhinitis	oral
Azithromycin	Antibiotic	Bacterial infection	oral,injection
Bepridil	Anti-anginal	Heart pain	oral
Cesium Chloride	Toxin	Alternative therapy cancer	oral,injection
Chloroquine	Anti-malarial	Malaria infection	oral
Chlorpromazine	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea	oral,injection,suppository
Chlorprothixene	Anti-psychotic	Schizophrenia	oral,injection
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Antibiotic	Bacterial Infection	oral, injection
Cisapride	GI stimulant	Heartburn	oral
Citalopram	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Antibiotic	Bacterial infection	oral
Cocaine	Local anesthetic	Topical anesthesia	oral, topical
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	oral
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	oral
Domperidone	Anti-nausea	Nausea	oral,injection,suppository
Donepezil	Cholinesterase inhibitor	Dementia	oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	oral,injection
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Anti-fungal	Fungal infection	oral, injection
Gatifloxacin (Off market worldwide)	Antibiotic	Bacterial infection	oral, injection
Grepafloxacin (Off market worldwide)	Antibiotic	Bacterial infection	oral
Halofantrine	Anti-malarial	Malaria infection	oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	oral,injection

Generic Name	Drug Class	Therapeutic Use	Route
Hydroquinidine	Anti-arrhythmic	Arrhythmia	oral
Hydroxychloroquine	Anti-malarial, anti-inflammatory	Malaria infection, systemic lupus erythematosus, rheumatoid arthritis	oral
Ibogaine	Psychedelic	Narcotic addiction, unproven	oral
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection
Levomepromazine	Anti-psychotic	Schizophrenia	oral, injection
Levomethadyl	Opiate	Pain control, narcotic dependence	oral
Levosulpiride	Anti-psychotic	Schizophrenia	oral, injection
Meglumine antimoniate	Antiparasitic	Leishmaniasis	injection
Mesoridazine	Anti-psychotic	Schizophrenia	oral
Methadone	Opiate	Pain control, narcotic dependence	oral,injection
Moxifloxacin	Antibiotic	Bacterial infection	oral,injection
Nifekalant	Anti-arrhythmic	Arrhythmia	injection
Ondansetron	Anti-emetic	Nausea, vomiting	oral,injection
Oxaliplatin	Anti-neoplastic	Cancer	injection
Papaverine HCl	Vasodilator, Coronary	Diagnostic adjunct	injection
Pentamidine	Antibiotic	Pneumocystis pneumonia	injection,inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Probucol	Antilipemic	Hypercholesterolemia	oral
Procainamide	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Propofol	Anesthetic	Anesthesia	injection
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral,injection
Roxithromycin	Antibiotic	Bacterial infection	oral
Sertindole	Anti-psychotic, atypical	Schizophrenia, anxiety	oral
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin	Antibiotic	Bacterial infection	oral
Sulpiride	Anti-psychotic, atypical	Schizophrenia	oral
Sultopride	Anti-psychotic, atypical	Schizophrenia	oral, injection
Terfenadine	Antihistamine	Allergic rhinitis	oral
Terlipressin	Vasoconstrictor	Septic shock	injection
Terodiline	Muscle relaxant	Bladder spasm	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

Source: Credible Meds.org (http://crediblemeds.org/healthcare-providers/drug-list/?rf=All). TdP risk category filtered on “Drugs with known TdP risk”. Revision date: December 17, 2020.


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