Protocol B1371005

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

Statistical Analysis Plan
(SAP)

Version: 4.0

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This Statistical Analysis Plan (SAP) v4 for study B1371005 is based on the protocol dated 21JAN2019 (protocol amendment 7) and the addition of the interim analysis. The analysis planned in SAP v4 will supersede the previous versions of the SAP and the statistical sections of the protocol.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	- Added the analysis plan of the 25 mg QD dose level in Monotherapy Cohort and amended the sample size of Monotherapy Cohort. - Added the analysis plan of the Combination Cohort 3. - Added the analysis plan of the Continuation Cohort. - Section 3 – Stated the timings of the primary and final analysis. - Section 6.1 – Added the definitions of the dates for the disease response. - Section 6.3.1 – Modified according to protocol amendment. - Section 7.4 – Conformed to Section 8.2.3.4 about analysis population. - Section 7.5 – Deleted the explanations of handlings of concentrations below/upper the limit of quantification. - Section 8.2.9.1.4 – Changed the definitions of the actual dose intensity and the relative dose intensities with reference to B1371003 - Section 8.2.9.1.4 – Added the listing of the actual dose intensity and the relative dose intensities with reference to B1371003 - Section 8.2.9.5 – Added the analysis plan of cytogenetics by European Leukemia Net.	- Protocol amendment 3. - Protocol amendment 4. - Protocol amendment 5. - To clarify the timing of each analysis. - To include the dates related the efficacy as endpoints. - Protocol amendment 4. - Refer to Section 8.2.3.4. - Further amendment of SAP will be planned after investigation of handling of PD endpoints. - To unify the definition of these endpoints in Glasdegib program. - To unify the definition of these endpoints in Glasdegib program. - This characteristic is the prognostic factor for AML and will also be corrected in Phase 3 study for AML patients

	- Section 8.2.9.11 – Added the analysis plan of cardiac function evaluation - Section of Investigators Comments – This section was deleted	B1371019. - The analysis plan of this item was simply omitted. - This item is not included in analysis dataset.
3	- Survival follow-up was added to Combination Cohort 1 (Unfit Patients) [Section 2.1]. - Expansion Cohort of LDAC combination for efficacy (Unfit Patients) was added to this study [Section 2.1, 2.2]. In this cohort, statistical test is planned [Section 4]. Other plans related to addition of this cohort were described [Section 5, 6, 7, 8]. - Timing of primary analysis was changed according to the statistical test [Section 3]. - Efficacy endpoints were added; DMR and transfusion independence [Section 6]. - Event definition of duration of response was changed [Section 6]. The definition was different with one described in Protocol. - Transfusion independence was added [Section 6.1]. - Handlings of missing values for OS and disease response were described [Section 7]. - Statistical methods for time-to-event endpoints and binary endpoints were added [Section 8.1]. - Analysis methods of DMR, disease response, duration of response, time to response, OS and transfusions were added [Section 8.2.2]. - Subset analysis by DMR was planned for OS and transfusions [Section 8.2.3]. - Worst on-study abnormality of	- Protocol Amendment 6. - Protocol Amendment 7. - Protocol Amendment 7. - Protocol Amendment 7. - To unify the definition described in Prorocol. - This endpoint was added as exploratory efficacy endpoint. - Protocol Amendment 7. - Protocol Amendment 7. - Protocol Amendment 7. - Protocol Amendment 7. - To conduct same analysis with

	laboratory test was added [Section 8.2.4.2]. - Details of ECG analyses were updated [Section 8.2.4.4]. - Analyses of risk category were added [Section 8.2.10.2]. - Physical examination were added [Section 8.2.10.10] - Description adjustment.	B1371003. - To conduct same analysis with B1371003. - To summarize and grasp the distributions of prognostic factors of AML and MDS.
4	- Possibility of interim analysis was added [Section 3].	- In Expansion Cohort of LDAC combination for efficacy (Unfit Patients), the study would be considered positive if at least 4 DMR responders in 15 patients are observed. This amendment describes the possibility to conduct interim analyses prior to the primary completion provided that this criterion is met. No analysis of the primary endpoint will be conducted at the interim analysis.

2. INTRODUCTION

This document describes the planned statistical analysis for Protocol B1371005. This statistical analysis plan (SAP) is meant to supplement the study protocol. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Any deviations from this SAP will be described in the Clinical Study Report (CSR).

Note: in this document any text taken directly from the protocol is *italicised*.

2.1. 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 Low-dose Ara-C (*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* acute myeloid leukemia (*AML*) *or high-risk* myelodysplastic syndrome (*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 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:

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.

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 Protocol *Table 1 (See* Protocol *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 Protocol *Inclusion Criteria) will receive PF-04449913 once daily continuously in combination with LDAC over 28 day cycles.*

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 Protocol *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 Protocol *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 and Disease Modifying Response (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.

Combination Cohort 2 (Fit Patients):

In this cohort, patients defined as "fit for intensive chemotherapy" based on pre-defined criteria (See Protocol *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.*

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 Protocol *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.

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). 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.

Continuation 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.

2.2. Study Objectives

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 (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 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.*

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.

Secodary 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:

- *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.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

The interim analyses could be performed after the enrollment of 15 patients is completed and 4 or more DMR responders are observed in the Expansion Cohort of LDAC combination for efficacy (Unfit Patients). In this interim analysis, the statistical test for the primary endpoint of this cohort will not be conducted and the achievement of at least 4 DMR responders in 15 patients of this cohort will be confirmed. The other analyses required at the interim analysis will be conducted according to this SAP.

The primary analysis will be performed after disease assessment on Cycle 9/Day 1 for the last (15th) patient treated in Expansion Cohort of LDAC combination for efficacy (Unfit Patients)*. 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* (Unfit Patients)*, assuming the enroll speed as 15 patients per year. The final analysis will be performed after all patients have died or 2 years after the first dose for the last patient treated, whichever occurs first. Further analyses could be performed, if necessary.*

Unblinding is not applicable, as this is an open-label study.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

For the Expansion Cohort of LDAC combination for efficacy (Unfit Patients), a total of 15 patients will provide 80.8% power to reject the null hypothesis DMR rate=6.8% when the true DMR rate=34.1% for the alternative hypothesis. The DMR rates for the hypotheses are based on the result of the analysis based on the derived response for B1371003 CSR (P2 Unfit, data cut off: 3 Jan 2017).

For other cohorts, there are no formal statistical hypotheses. The emphasis of the primary analysis will be on estimation of key summary statistics.

4.2. Statistical Decision Rules

For cohorts excluding the Expansion Cohort of LDAC combination for efficacy (Unfit Patients), *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.* For Expansion Cohort of LDAC combination for efficacy (Unfit Patients), the statistical decision rule is described as follows.

Monotherapy Cohort:

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 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.

Combination Cohorts:

Combination Cohort 1 (Unfit Patients):

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 more than 2 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.

Expansion Cohort of LDAC Combination for Efficacy (Unfit Patients):

The combination of PF-04449913 and LDAC will be considered superior to the historical data of LDAC as single-agent with respect to DMR if the DMR rate is statistically significant at the 1-sided 0.05 level using exact test for a single proportion. An observed DMR rate of 26.7% or above (eg, 4 or more responders out of 15 patients) will reject the null hypothesis.

Combination Cohort 2 (Fit Patients):

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 more than 2 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.

Combination Cohort 3 (Azacitidine Combination):

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 more than 2 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.

Continuation Cohort:

No decision rule for this cohort.

5. ANALYSIS SETS

Analysis sets are defined as below although the patients enrolled in the Expansion Cohort of LDAC combination for efficacy (Unfit Patients) *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.*

5.1. 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).

5.2. DLT-evaluable Analysis Set ('Per Protocol' 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.

5.3. Safety Analysis Set

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

5.4. Other Analysis Set

5.4.1. PK Analysis Set

The PK analysis set *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.*

5.4.2. PD Analysis Set

The PD analysis set is defined as all enrolled subjects who receive at least 1 dose of PF-04449913 and have at least 1 pharmacodynamic parameter in active treatment period.

5.4.3. QTc-evaluable Analysis Set

The QTc-evaluable analysis set *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.*

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

All deviations will be described in the CSR. *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.

6. ENDPOINTS AND COVARIATES

The assessments on the day of the lead-in dose of PF-04449913 for Monotherapy Cohort and Combination Cohort 2 (Fit Patients) are considered baseline whenever they are available. The assessments on Cycle 1 Day 1 for Combination Cohort 1 (Unfit Patients), Expansion Cohort of LDAC combination for efficacy (Unfit Patients), Combination Cohort 3 (Azacitidine Combination) and Continuation Cohort are considered baseline whenever they are available. If not available, the assessment closest and prior to the lead-in dose (for Monotherapy Cohort and Combination Cohort 2) or Cycle 1 Day 1 [for Combination Cohort 1, Expansion Cohort of LDAC combination for efficacy (Unfit Patients), Combination Cohort 3 and Continuation Cohort)] is considered baseline for patients in any arm, respectively.

6.1. Efficacy Endpoints (excluding the Continuation Cohort)

The efficacy endpoints of the disease response per investigator evaluation based on the Response Criteria CRF pages (see Protocol Appendix 5 through Appendix 9) is the primary method of documentation of disease. The response criteria differ for each hematologic malignancy (see Appendix 2 through Appendix 5 for details). Objective Response (OR) needs to be established before any subsequent documentation of progression.

The following dates are identified.

- The first objective response date: the assessment date of first documented objective response. However, these responses for MDS, CMML and CML need to be confirmed as described above.

- The first progression date: the assessment date of first documented (objective) disease progression.

- The first relapse date (except for CML): the assessment date of first documented relapse.

- The last disease assessment date: the date of last disease assessment date.

Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

The following efficacy endpoints are defined.

DMR and its rate includes complete remission (CR), CR with incomplete blood count recovery (CRi), morphologic leukemia-free state (MLFS), marrow CR (mCR) and partial remission (PR) (see Protocol Appendix 5 and Appendix 8).

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. The primary interest is the survival probability at 6 months and at 12 months.

Duration of response is only defined for patients who have ever achieved CR/CRi on study as the time from the date of first documentation of a CR/CRi (Protocol Appendix 5 and Appendix 8) to the date of loss of response after CR/CRi 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 (loss of response or death). Duration of DMR for patients who have ever achieved DMR on study is also defined.

Time to response is only defined for patients who have ever achieved CR/CRi on study as the time from the date of first dose of study drug to the date of first documentation of a CR/CRi. Time to DMR for patients who have ever achieved DMR on study is also defined.

Transfusion independence is defined as follows taking into consideration of the schedule of activity described in Protocol. Transfusion history includes the transfusions prior to first dose of study treatment including Cycle 1 Day 1. Transfusion status on study includes the transfusions after first dose of study treatment.

- Independence of transfusion history for AML patients in Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients) is defined as a lack of requirement for transfusion for at least 4 weeks;

- Independence of transfusion history for MDS patients is defined as a lack of requirement for transfusion for at least 8 weeks;

- Independence of transfusion status on study for AML and MDS patients is defined as a lack of requirement for transfusion for at least 8 weeks and ever met this definition after first dose of study treatment. Patients not followed by end of treatment for 8 weeks are not categorized as independent and dependent.

Combination Cohort 3 (Azacitidine Combination):

Same efficacy endpoints described in Combination Cohort 1 (Unfit Patients) will be defined. Note that only AML patients will be enrolled in this cohort.

The definition of transfusion independence of transfusion history is as follows:

- Independence of transfusion history in Combination Cohort 3 (Azacitidine Combination) is defined as a lack of requirement for transfusion for at least 8 weeks.

6.2. Safety Endpoints

6.2.1. Dose Limiting Toxicities [excluding the Expansion Cohort of LDAC Combination for Efficacy (Unfit Patient) and the Continuation Cohort]

The DLT evaluation of PF-04449913 is based on the definition in Protocol Section 3.2.

6.2.2. Adverse Events

Assessment of adverse events (AEs) *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.* AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be assigned to the appropriate cycle based on Day 1 of each cycle. Specifically, treatment emergent and treatment related AEs are defined as follows.

Treatment Emergent Adverse Events

- All deaths from start of treatment until 28 days after the final dose.
- All treatment related SAEs.
- All unrelated SAEs from treatment start until 28 days after final dose of treatment.
- All non-fatal AEs occurring after treatment start until 28 days after final dose of treatment.
- Disease progression is not considered a treatment emergent AE unless the subject dies of disease prior to 28 days after discontinuation of treatment.
- Events that are continuations of baseline abnormalities are considered treatment emergent AEs only if the grade increases from baseline.

Treatment Related Adverse Events

Treatment Related Adverse Events are AEs with cause categorized by the investigator as related to study treatment. Events that are continuations of baseline abnormalities (signs and symptoms) are not considered treatment emergent, and therefore not considered treatment related, unless there is an increase in grade over baseline.

6.2.3. Laboratory Safety Tests

Laboratory tests will be graded referring to CTCAE grade definitions. For laboratory tests without CTCAE grade definitions, results will be categorized as above, below, within or not done if the site has institutional ULN/LLN.

6.3. Other Endpoints

6.3.1. PK Endpoints (excluding the Continuation Cohort)

Monotherapy Cohort

Plasma PK parameters of PF-04449913.

The following single and multiple dose PK parameters will be calculated for PF-04449913 from the plasma concentration/time data obtained after PK Lead-In dose, on Day -5 (single dose) and Cycle 1 Day 21 (multiple dose), using non-compartmental method. Descriptive

statistics will be provided for these PK parameters in tabular form (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle and day.

- Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F, $t_{1/2}$, AUC_{inf} as data permit.
- Multiple Dose (assuming steady-state is achieved) - C_{max}, T_{max}, AUC_{τ}, C_{min}, C_{av}, C_{trough}, CL/F, R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}$ /$AUC_{sd,inf}$) as data permit.

Combination Cohort 1 (Unfit Patients), Expansion Cohort of LDAC Combination for Efficacy (Unfit Patients), Cohort 2 (Fit Patients) and Cohort 3 (Azacitidine Combination)

Plasma PK parameters of PF-04449913, cytarabine, daunorubicin, and azacitidine.

Standard plasma PK parameters include C_{max}, T_{max}, and AUC for each drug (and metabolite if relevant) will be estimated using non-compartmental method. If data permit or if considered appropriate, C_{min}, C_{ave}, C_{trough}, AUC_{inf}, and $t_{1/2}$ may 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 Expansion Cohort of LDAC combination for efficacy (Unfit Patients), descriptive summary of PF-04449913 concentration will be provided but PK parameters will not be calculated.

6.3.2. Drug-Drug Interaction Endpoints (Combination Cohorts Only)

6.3.2.1. 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.

6.3.2.2. 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 daunorubicin/cytarabine on the PK of PF-04449913.

6.3.2.3. Combination Cohort 3 (Azacitidine Combination): PF-04449913 and Azaciditine

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.

6.3.3. ECG

Triplicate, 12 lead ECGs for PF-04449913 is described in the relevant Schedule of Activities (see Protocol Table 1 through Table 6).

The baseline evaluations for ECGs are the average of the triplicate pre-dose values. The baseline ECG for Monotherapy Cohort and Combination Cohort 2 (Fit Patients) is defined as the last ECG(s) prior to the lead-in dose of PF-04449913. The baseline ECG for Combination Cohort 1 (Unfit Patients), Expansion Cohort of LDAC combination for efficacy (Unfit Patients), Combination Cohort 3 (Azacitidine Combination) is defined as the last ECG(s) prior to the dose of PF-04449913. If this was not collected, the baseline will be calculated from the ECG closest to the first dose of study drug during the screening period. If the last ECGs are triplicate ECGs (or only 2), they will be averaged. If the last ECG is a single, that will be used as baseline.

6.3.4. PD Biomarker Endpoints (excluding the Continuation Cohort)

PD Biomarker *assessments may include the following; (i) evaluation of Hh pathway genes and proteins, (ii) circulating cytokine 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.*

The baseline PD biomarker measurements are defined to follow Section 6.

6.3.5. Extramedullary Disease Endpoint (excluding the Continuation Cohort)

The baseline extramedullary disease assessments are defined to follow Section 6.

6.4. Covariates

Not applicable.

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used (unless for OS a later contact date in the month is established and then the day after will be used as the date of death for the patients with partial death date) to replace the missing date unless the calculation results in a negative time duration (eg, date of onset cannot be prior to day one date). In this case, the date resulting in duration of 1 day will be used. Pfizer standards are also used if both month and day are missing (Jan 1 unless negative time duration or for OS the day after the latest contact date in that year will be used as the date of death for the patients with partial death date).

7.2. Efficacy Analysis

For efficacy analyses, no values will be imputed for missing data. Censoring for time-to-event endpoints is defined in Section 6.1.

In the assessment of CR/CRi or DMR rate, patients who are not known to have achieved the endpoint of interest (CR/CRi or DMR) will be counted as non-responders.

7.3. PK

Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated with concentrations set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

PK Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

For evaluation of changes in pharmacokinetics of a compound when administered alone vs. in combination, only subjects with matching pair of pharmacokinetic assessments under both conditions will be included in the pharmacokinetic summary (ie, alone and in combination).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

7.4. QTc

For analyses using the QTc-evaluable analysis set and safety analysis set, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG parameter are missing, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and this subject will be excluded from the analyses related to this time point. Unplanned ECGs will be in triplicate and averaged.

7.5. PD Parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Hypothesis testing will be performed as discussed in Section 4.

8.1.1. Analyses of Time-to-Event Endpoints

Unless otherwise stated, time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically (with number of patients still at risk noted on the horizontal axis) when appropriate.

Median event times and two-sided 90% and 95% confidence intervals (CIs) for each time-to-event endpoint will be provided. Point estimate of selected survival probabilities and two-sided 90% and 95% CIs will also be provided, where the log-log transformation and back-transformation will be used in the calculation.

8.1.2. Analyses of Binary Endpoints

The rates of binary endpoints will be provided along with the corresponding two-sided 90% and 95% CIs using exact method.

8.1.3. Analyses of Continuous Data

The descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints.

8.2. Statistical Analyses

For the Continuation Cohort, only the listings will be produced and the tables and figures will not be produced.

8.2.1. Analysis of Primary Endpoints

Monotherapy Cohort:

Analysis set: DLT-evaluable Analysis Set.

Table produced by: dose level.

Analysis:

> The safety and tolerability is determined by quantification of patients experiencing DLTs at each dose level during the PK lead-in period and the first cycle of treatment.

Table: Number of patients who experienced DLT will be tabulated by dose level.

Listing: All records on DLT CRF page will be listed.

Combination Cohorts Other Than Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Analysis set: DLT-evaluable Analysis Set.

Table produced by: cohort (Combination Cohort 1, 2 and 3).

Analysis:

> The safety and tolerability is determined by quantification of patients experiencing DLTs at each dose level during the PK lead-in period and the first cycle of treatment.

Table: Number of patients who experienced DLT will be tabulated by cohort.

Listing: All records on DLT CRF page will be listed.

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

Analysis set: Full Analysis Set.

Table produced by: Not applicable.

Analysis:

> The DMR is defined in Section 6.1. The number and percentage of patients who have ever achieved DMR will be summarized for irrespective of AML and MDS patients. An exact test for a single proportion (1-sided significance level: 0.05) will be used. The null hypothesis is that DMR rate=6.8%, and the alternative hypothesis is that DMR rate=34.1%. The two-sided 90% and 95% CIs will be also presented.

Table: Table will include the number and percentage of DMR responders, p-value and CI.

Listing: Not applicable. The listing of DMR will be included in the listing of disease response (see Section 8.2.2.1).

8.2.2. Analysis of Efficacy Endpoints

All efficacy analyses are secondary excluding the primary endpoint for Expansion Cohort of LDAC combination for efficacy (Unfit Patients) in the section above.

For Combination Cohort 1 (Unfit Patients), Expansion Cohort of LDAC combination for efficacy (Unfit Patients), and Combination Cohort 3 (Azacitidine Combination), the statistical analysis methods are described in the following sections.

For other cohorts, listings of subject's disease status on study will be provided by dose level, cohort and malignancy using the Full Analysis Set.

8.2.2.1. Disease Response

Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Analysis set: Full Analysis Set.

Table produced by: Table will be produced by cohort. See the following.

Analysis:

For AML patients, the best overall response will be summarized in frequency tables. The further endpoints of interest including CR/CRi and DMR will also be summarized with 90% and 95% exact CIs.

For MDS patients, the best overall response will be summarized in frequency tables. The further endpoints of interest including CR and DMR will also be summarized with 90% and 95% exact CIs.

For irrespective of AML and MDS patients, CR/CRi rate and DMR rate will be summarized in frequency tables with 90% and 95% exact CIs.

Table:

- Best overall response, CR/CRi and DMR for AML patients;
- Best overall response, CR and DMR for MDS patients;
- CR/CRi rate and DMR rate for irrespective of AML and MDS patients.

Listing: The disease responses will be listed by malignancy.

Combination Cohort 3 (Azacitidine Combination):

Same analyses described in Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients) will be conducted. Note that only AML patients will be enrolled in this cohort.

8.2.2.2. Duration of Response

Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Analysis set: Full Analysis Set.

Table produced by: AML, MDS and irrespective of AML and MDS.

Analysis:

Kaplan-Meier estimates (productlimit estimates) will be presented together with a summary of associated statistics including the median duration of CR/CRi or DMR with two-sided 90% and 95% CIs.

Table:

- Summary of duration of response.

Figure:

- Kaplan-Meier curve of duration of response.

Listing:

- Listings include, but are not limited to, event/censor date, event/censor day from first dose, event type, reason for censoring, European Leukemia Net (ELN) cytogenetic risk and age (≤60 vs >60 years).

Combination Cohort 3 (Azacitidine Combination):

Same analyses described in Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients) will be conducted. Note that only AML patients will be enrolled in this cohort.

8.2.2.3. Time to Response

Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Analysis set: Full Analysis Set.

Table produced by: AML, MDS and irrespective of AML and MDS.

Analysis:

Kaplan-Meier estimates (productlimit estimates) will be presented together with a summary of associated statistics including the time to CR/CRi or DMR with two-sided 90% and 95% CIs.

Table:

- Summary of time to response.

Figure:

- Kaplan-Meier curve of time to response.

Listing:

- Listings include, but are not limited to, event/censor date, event/censor day from first dose, event type, reason for censoring, ELN cytogenetic risk and age (≤60 vs >60 years).

Combination Cohort 3 (Azacitidine Combination):

Same analyses described in Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients) will be conducted. Note that only AML patients will be enrolled in this cohort.

8.2.2.4. Overall Survival

Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients):

Analysis set: Full Analysis Set.

Table produced by: AML, MDS and irrespective of AML and MDS.

Analysis:

OS time will be summarized using the Kaplan-Meier method (product-limit estimates) and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. In addition, the median OS and its two-sided 90% and 95% CIs using the Brookmeyer and Crowley method[1] will be provided.

The OS rate at 6, 12, and 18 months will be estimated with corresponding two-sided 90% and 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the timepoints defined above will be derived using the log(-log) method according to Kalbfleisch and Prentice[2] (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented.

Table:

- Summary of OS.

Figure:

- Kaplan-Meier curve of OS.

Listing:

- Listings include, but are not limited to, event/censor date, event/censor day from first dose, event type, reason for censoring, ELN cytogenetic risk and age (≤60 vs >60 years).

Combination Cohort 3 (Azacitidine Combination):

Same analyses described in Combination Cohort 1 (Unfit Patients) and Expansion Cohort of LDAC combination for efficacy (Unfit Patients) will be conducted. Note that only AML patients will be enrolled in this cohort.

8.2.2.5. Transfusions

Analysis set: Full Analysis Set.

Table produced by: AML, MDS, irrespective of AML and MDS for Combination Cohort 1 (Unfit Patients), Expansion Cohort of LDAC combination for efficacy (Unfit Patients), and Combination Cohort 3 (Azacitidine Combination), respectively.

Tables:

For the transfusion independence, the transfusion history and transfusion status on study will be summarized in frequency tables as following.

Mock Table:

Number (%) of Subjects			n++
Transfusion Status on Study			
Independent			n+1 (n+1/n++)
Dependent			n+2 (n+2/n++)
Not Followed for 8 Weeks			n+3 (n+3/n++)
Transfusion History			
Independent			n1+ (n1+/n++)
	Transfusion Status on Study		
		Independent	n11 (n11/n1+)
		Dependent	n12 (n12/n1+)
		Not Followed for 8 Weeks	n13 (n13/n1+)
Dependent			n2+ (n2+/n++)
	Transfusion Status on Study		
		Independent	n21 (n21/n2+)
		Dependent	n22 (n22/n2+)
		Not Followed for 8 Weeks	n23 (n23/n2+)

Notation:

Transfusion History	Transfusion Status on Study			
	Independent	Dependent	Not Followed for 8 Weeks	Total
Independent	n11	n12	n13	n1+
Dependent	n21	n22	n23	n2+
Total	n+1	n+2	n+3	n++ (Full Analysis Set)

Listings:

- Transfusion records including transfusion type, date of transfusion and number of units (Listing by dose level, cohort);

- Transfusion independence: transfusion history and transfusion status on study.

8.2.3. Subset Analysis

Subset analyses will be performed for OS (Section 8.2.2.4) and transfusion independence (Section 8.2.2.5) based on the FAS for the subgroups defined below.

The following subgroups will be defined and used for analyses:

- DMR
  - DMR responder vs non-responder

Subset analyses for OS will use the primary censoring rules described in Section 6.1. All the subgroup analyses are exploratory.

8.2.4. Analysis of Safety Data

Patients in Monotherapy Cohort will be analyzed by dose level and regardless of them. Patients in Combination Cohort will be analyzed separately as Combination Cohort 1 (Unfit Patients), Combination Cohort 2 (Fit Patients) and Combination Cohort 3 (Azacitidine Combination).

8.2.4.1. Adverse Events

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Analysis:

> *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.* See Section 6.2.2 for the definition of treatment emergent adverse event. *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).* For the summaries of AEs occurring at Cycles beyond 1, only the patients who start the study treatment of Cycle 2 will be analyzed.

Table:

> Every table as described below will be created for any AE and treatment related AE.

- Discontinuations due to AEs;
- Temporary discontinuations or dose reductions due to AEs;
- Overall summary of AEs;

- Number of patients observed with AEs and corresponding percentages by MedDRA system organ class and preferred term;
- Number of patients observed with AEs and corresponding percentages by MedDRA preferred term sorted by frequency;
- Summary of death (Frequency of subject who died on-treatment, subject who died during follow-up, and cause of death).

Listings:

- AEs (all grade, and grade 3 and greater);
- Death;
- SAE.

8.2.4.2. Laboratory Tests

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Analysis:

> *The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay.* The summary and shift summary of baseline grade by maximum post-baseline CTCAE grade will be presented. *For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.*

Tables:

- Summary results by maximum CTCAE grade;
- Shift summary results of baseline grade by maximum post-baseline CTCAE grade;
- Worst on-study abnormality.

Figure:

Individual values will be plotted over time for each continuous laboratory parameters by dose level and cohort as data allow.

Listings:

- Measured data;
- NCI-CTCAE grades;

- Measured data with NCI-CTCAE grades 3 and 4;
- Abnormality records (by subject, by test).

8.2.4.3. Hy's Law

Analysis set: Safety Analysis Set.

Table produced by: Not applicable.

Analysis: The subjects will be identified as potential Hy's Law cases based on Protocol Section 8.6.2.

Tables: Not applicable.

Figure: Not applicable.

Listings: Listing includes baseline values, actual value, ULN, and ratio of actual value to ULN with flag indicates the result meets the Hy's law criteria for each laboratory test (bilirubin, AST, ALT, and alkaline phosphatase) by study day measured laboratory test. Listing will be produced by dose level, cohort and malignancy.

8.2.4.4. Analysis of ECG

Analysis set:

(1) QTc-evaluable Analysis Set; (2) Safety Analysis Set

Table produced by: dose level, cohort. For the Continuation Cohort, only the listings will be produced.

Analysis:

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. The average of triplicate or duplicate measurements will be rounded off and handle as integer in the analyses of ECG.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc, QT, HR, PR, QRS *values and changes from baseline in QTc*, QT, HR, PR, QRS *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.* Categorical summarization *of the QTc (using the most appropriate correction method)*, QT, HR, PR, QRS *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* baseline *absolute values over >200 msec*, or PR changes from baseline ≥50% and baseline absolute values over ≤200 msec;
- PR ≥300 msec;
- *QRS changes from baseline ≥25% and* baseline *absolute values over >110 msec*, or QRS changes from baseline ≥50% and baseline absolute values over ≤110 msec;
- QRS ≥200 msec.

Shift tables will be provided for baseline vs. worst on study QTc (one or more correction methods may be used) using the categories described above.

Tables:

- Descriptive statistics of absolute values by time point [analysis set (1) and (2)];
- Descriptive statistics of change from baseline values by time point [analysis set (1)];
- Descriptive statistics of maximum post-baseline values [analysis set (1)];
- Descriptive statistics of maximum increase from baseline values [analysis set (1)];
- Categorical summary of post-baseline maximum absolute values [analysis set (1) and (2)];
- Categorical summary of maximum increase from baseline values [analysis set (1)];
- Shift summary of QTcF results [analysis set (1)].

Listings:

- Measured data (QT, HR, PR, QRS and QTcF);
- Change from baseline (QT, HR, PR, QRS and QTcF);
- Qualitative results;
- Maximum values (QT, HR, PR, QRS and QTcF);
- Maximum change from baseline (QT, HR, PR, QRS and QTcF).

8.2.5. Analyses of Vital Signs

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Table: Not applicable.

Figure:

For actual measures and changes from baseline, individual plot will be created for each vital sign as data allow. Actual time from Cycle 1 Day 1 will be used as X-axis in unit of day.

Listing:

Listing will be prepared for each vital sign, and will include actual measures, change from baseline and both met the specific categories (see Appendix 1).

8.2.6. Analysis of PK Data (excluding the Continuation Cohort)

8.2.6.1. Pharmacokinetic Parameters [excluding the Expansion Cohort of LDAC combination for efficacy (Unfit Patients)]

Analysis set: PK Parameter Analysis set

Each PK parameter will be summarized wherever applicable. The set of summary statistics as specified in the table below will be included:

Parameter	Summary statistics
AUC, C_{max}, C_{min}, C_{avg}, C_{trough}*, CL (CL/F), Vz (Vz/F)	N, geometric c mean, median, geometric CV%, standard deviation, minimum, maximum, arithmetic mean
T_{max}, $R_{ac,}$ Rss	N, median, minimum, maximum
$t_{½}$	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum.

* C_{trough} is defined as the observed concentration prior to dose administration.

These summary tables will be generated by analyte for the PK analysis set. The PK parameters generated will be summarized by cohort, analyte, dose, cycle and day.

C_{trough} will be summarized separately for each cohort. Additionally, summaries will be generated for ONLY patients that received PF-04449913 daily without interruptions or dose reductions 6 days prior to the day of sample collection.

- Box and whisker plots for individual subject parameters by analyte (AUC, C_{max} and $C_{trough,}$ CL/F, Vz/F) and overlaid with geometric means will be presented for the PK analysis set and for ONLY patients that received PF-04449913 daily without interruptions or dose reductions 6 days prior the day of sample collection.

- A listing of PK parameters by cohort, analyte, dose cycle, and day.

8.2.6.2. Pharmacokinetic Concentrations

Analysis set: PK Concentration Analysis set

- A listing of daily dosing including dose modification status and day as appropriate for each cohort by analyte.

- A listing of all plasma concentrations sorted by cohort, analyte, dose, cycle, day and nominal time post dose. The listing of plasma concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of plasma concentrations by cohort, analyte, dose, cycle, day and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (% CV), minimum, maximum and the number of concentrations above the lower limit of quantification for the PK analysis set. Plasma concentrations by cohort, analyte, dose, cycle, day and nominal time post-dose, will be reported also for ONLY patients that are considered dose compliant (steady state with respect to that analyte).

- Median plasma concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by analyte and dose for the PK analysis set and for ONLY patients that are considered dose compliant (steady state with respect to that analyte).

- Individual plasma concentration time plots by analyte and dose (on both linear and semi-log scales) against actual time post-dose.

- Individual C_{trough} plasma concentration time plots for PF-04449913 (on linear scales) against Cycle/Day.

8.2.7. Analysis of Drug-Drug Interaction (Combination Cohorts 1, 2, 3 Only)

8.2.7.1. Unfit Cohort: PF-04449913 and LDAC

The primary pharmacokinetic parameters, AUC and C_{max}, will be utilized to estimate the effect of co-administration of PF-04449913 and LDAC on the pharmacokinetics 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 LDAC. 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.

8.2.7.2. Fit Cohort: PF-04449913 and Daunorubicin/Cytarabine

The primary pharmacokinetic parameters, AUC and C_{max}, will be utilized to estimate the effect of co-administration of PF-04449913 and daunorubicin/cytarabine on the pharmacokinetics 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 daunorubicin/cytarabine 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 daunorubicin/cytarabine. The effect of PF-04449913 on daunorubicin/cytarabine will not be conducted within the study due to the inability to dose daunorubicin/cytarabine alone.

8.2.7.3. Azacitidine Combination Cohort: 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 its 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 azacitidine + PF-04449913 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.

8.2.8. Analysis of PD Biomarker Data (excluding the Continuation Cohort)

PD biomarkers will be assessed separately for blood, serum, normal skin biopsies, bone marrow aspirate and bone marrow biopsies. 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.

If data permit, *data from biomarker assays will be analyzed using graphical methods and descriptive statistics such as linear regression, Wilcoxon and ranked sum*. Moreover, *the statistical approach may examine correlations of biomarker results with pharmacokinetic parameters and measures of anti tumor efficacy*.

Analysis set: PD Analysis Set.

Table produced by: dose level, cohort and biomarker type (plasma and cells).

Analysis:

Summaries of baseline and change from baseline (screening) to post-treatment as measured using ratio to baseline will be provided by time point. Graphical displays will be provided, as appropriate. All data will be listed.

For Combination Cohort 2 (Fit patients), summaries will be done separately for the induction, consolidation and maintenance periods, as well as together across periods. When summaries will be done separately for perieds, the baseline in each period will be defined as the pharmacodynamic biomarker assessments on the first dosing day of study treatment in each period.

Tables:

- Summaries of actual value from baseline to post-treatment;
- Summaries of change from baseline (screening) to post-treatment by ratio to baseline.

Figure:

Individual plot will be plotted over time for each biomarker by dose level and cohort as data allow.

Listings: Each PD biomarker data will be listed.

8.2.9. Population PK Analysis or PK/PD Modeling (excluding the Continuation Cohort)

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.

8.2.10. Other Analyses

8.2.10.1. Standard Analyses

8.2.10.1.1. Study Conduct and Subject Disposition

An accounting of the study subjects will be tabulated. Subjects not completing the treatment/study (completing the treatment means the subject completes treatment for 12 cycles; completing the study means the subject completes the post-treatment follow-up period) will be listed along with the reason for discontinuation.

Analysis set: Screened patients.

Table produced by: dose level and cohort.

Table:

Subject disposition and evaluability will be summarized. Summary table will include following number of subjects:

- Assigned to study treatment (treated, completed, discontinued);
- Analyzed for DLT;
- Analyzed for safety (AEs, laboratory data);
- Analyzed for PK (PK parameter, PK concentration);
- Analyzed for PD;
- Analyzed for QTc.

Listings: Subject disposition and evaluability will be listed.

8.2.10.1.2. Subject Discontinuation

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Table: Subject discontinuation will be summarized.

Listing: Information of subject discontinuation will be listed.

8.2.10.1.3. Baseline Characteristics

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Tables:

- Demography (sex, age, race, weight, height);
- Subject accrural (site No.);
- Primary diagnosis (diagnosis, duration);
- Medical history (past, present);
- ECOG performance status at Screening.

The duration of primary diagnosis is obtained by the time from the date of histopathological diagnosis to one of enrollment.

Listings:

All the above characteristics will be listed. In addition, following information will be also provided.

- Prognostic scores (Sokal Score for CML, IPSS for MDS, Dupriez Score for MF);
- Childbearing potential (childbearing potential, contraceptive method);
- Primary diagnosis as AML (AML-Fab subtype, AML disease history).

8.2.10.1.4. Treatment Administration

Analysis set: Safety Analysis Set.

Table produced by: dose level, cohort and regimen. (Regimen is for Combination Cohort 2, fit patients; induction, consolidation and maintenance) For the Continuation Cohort, only the listings will be produced.

Analysis: Initial planned dose is defined as prescribed dose at the start day defined below. The units of the prescribed daily dose of cytarabine and daunorubicin (Combination Cohort 2, fit patients), and azacitidine (Combination Cohort 3) are transformed mg/m^2 to mg based on body surface area (BSA) on Cycle 1 Day 1.

Definition of the start day for initial planned dose

- PF-04449913 in Combination Cohort 1: Cycle 1 Day 3;
- PF-04449913 on induction cycle in Combination Cohort 2: Cycle 1 Day -3;
- PF-04449913 in Combination Cohort 3: Cycle 1 Day 2;
- PF-04449913 for others, LDAC, daunorubicin, cytarabine and azacitidine: Cycle 1 Day 1.

Tables:

Dose administration will be summarized as follows:

- Treatment duration (day) by regimen. (Number (%) of subjects with duration category, median, range) [Duration category (day): ≤1, 2-7, 8-14, 15-28, 29-56, 57-84, 85-112, ≥113];
- Total number of cycle started (median, range);
- Number (%) of subjects started each cycle;

- Number (%) of subjects with at least one cycle delay, where cycle delay is defined as any delay of the cycle start date, based on the previous cycle's start date;

- Number (%) of subjects with at least one dose reduction, where dose reduction is defined as a day when the actual dose taken is less than the initial planned dose for any reason with the exception that a day with total dose administered of 0 mg is not considered a dose reduction [by study treatment]. In the event that the prescribed dose varies across cycles as a result of body weight change of >10% per protocol, the adjusted prescribed dose is considered the initial planned dose for the relevant cycles;

- Number (%) of subjects with at least one dose interruption/missed dose, where dose interruptions/missed dose is defined as a planned dosing day with 0 mg total dose administered only PF-04449913.

Relative dose intensity will be summarized using mean, standard deviation, median, and range as follows:

- Actual dose intensity [mg/week] = total dose received / (cycle length / 7), where

    - Total dose received [mg/cycle] is an actual total dose in the cycle,

    - Cycle length [day/cycle] = date of end of treatment in the cycle − date of start of treatment in the cycle + 1, that is the cycle length includes the delay until the next cycle.

- Relative dose intensity by cycle = {total dose received / (dose duration / 7)} / planned dose intensity, where

    - Dose duration [day/cycle] = sum of dose duration from each dosing record,

    - Planned dose intensity [mg/week] = (prescribed dose at start of cycle * planned dose duration per protocol) / (planned dose duration per protocol / 7).

- Overall relative dose intensity = {sum of "total dose received" / (sum of "dose duration" / 7)} / {sum of "prescribed dose at start of cycle * planned dose duration per protocol" / (sum of "planned dose duration per protocol" / 7)}.

Listings:

- Listings by subject: study drug, start date and stop date of each dosing period within each cycle (including records with 0 mg), prescribed dose and actual received dose for each period, any missed doses with unknown dates (Y/N), number of missed doses with unknown dates, reason for any dosing changes.

- Listings by study treatment, subject and each cycle: cycle start/stop date and study day, planned total dose (based on prescribed dose at Day 1 of each cycle), prescribed total dose, total dose received, percentage of starting dose (compared to Day 1 prescribed dose for that cycle), percent of prescribed dose (ie, compliance derived by

the following equation, total dose received/planned total dose), dose delay (yes/no), dose reduction (yes/no), dose interruption (yes/no).

- Listings of dose intensity by study treatment, prescribed dose at start of cycle, planned dose duration per protocol, total dose received, cycle length, dose duration, planned dose intensity, actual dose intensity, relative dose intensity by cycle.

8.2.10.1.5. Prior, concomitant, post-treatment drug and non-drug treatments

Analysis set: Safety Analysis Set.

Table produced by: dose level and cohort. For the Continuation Cohort, only the listings will be produced.

Tables:

- Prior treatments (prior surgery, Y/N; prior radiation, Y/N; previous drug therapy for primary diagnosis, number of regimen [0/1/2/3/4+]);
- Previous drug therapy for primary diagnosis [Frequency of drug;
- Prior nondrug treatments/procedures (radiation therapies, surgeries, non-drug treatment/procedures);
- Concomitant drug treatments;
- Concomitant nondrug treatments/procedures (radiation therapies, surgeries, non-drug treatment/procedures).

Listings:

All the above information will be listed. In addition, following information will be also provided.

- Previous drug therapies for primary diagnosis (excluding the Continuation Cohort);
- Previous drug therapies;
- Prior radiation therapies (excluding the Continuation Cohort);
- Prior surgeries for primary diagnosis (excluding the Continuation Cohort);
- Concomitant drug therapies;
- Concomitant radiation therapies;
- Concomitant surgeries for primary diagnosis;
- Non-drug treatment/procedure.

8.2.10.2. Risk Category (excluding Combination Cohort 3 and the Continuation Cohort)

Analysis set: Not applicable.

Table produced by: Table will be produced by cohort.

Tables:

- AML risk category;
- MDS risk category.

Listings: The listing will be presented based on AML Risk Category and MDS Risk Category CRF pages.

8.2.10.3. Prior Therapy Response (excluding the Continuation Cohort)

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings:

Listing will be produced by dose level, cohort and malignancy.

- Prior therapy response (MDS);
- Prior therapy response (CMML);
- Prior therapy response (MF);
- Prior therapy response (AML);
- Prior therapy response (CML-AP/BP);
- Prior therapy response (CML-CP).

8.2.10.4. Bone Marrow Biopsy or Aspirate (excluding the Continuation Cohort)

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings: Listing will be prepared for each sample site by dose and cohort.

8.2.10.5. Cytogenetics and Immunophenotyping (excluding the Continuation Cohort)

Cytogenetics data will be referred to the Cytogenetic Blood CRF page and the Cytogenetic Bone Marrow CRF page.

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings:

Listing will be produced by dose level, cohort and malignancy.

- Cytogenetics (blood, bone marrow);
- Immunophenotyping.

8.2.10.6. Cytogenetics (excluding the Continuation Cohort)

Cytogenetics data will be referred to the Genetic Record CRF page.

Analysis set: Safety Analysis Set.

Table produced by: Table will be produced by cohort.

Tables:

Cytogenetics data will be summarized. Summary table will include following number of subjects:

- Adequate sample (Yes);
- Done cytogenetics (Yes).

Denominator for the followings is a numbers of patients done cytogenetics;

- Karyotype (normal, abnormal);
- Abnormality (favorable, intermediate, adverse) [AML Patients in Expansion Cohort of LDAC combination for efficacy (Unfit patient) and Combination Cohort 3 only];
- Abnormality detail: the number of patients and its percentage with each cytogenetics will be summarized.

Listings: The listing will be presented based on Genetic Record CRF pages.

8.2.10.7. Extramedullary Disease (excluding the Continuation Cohort)

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings:

A listing of extramedullary disease will be produced (ie, involvement of liver (Y/N), spleen (Y/N), and other organs (Y/N, if other organs are involved, also provide the organ names)) by dose level, cohort and malignancy. Spleen and liver size (in cm) will be listed for all subjects at each assessment (including baseline, which is defined below). The absolute change from baseline, as well as change from the most extreme value (maximum or minimum), in liver and spleen size will be also listed. Note that an extramedullary disease of "not palpable" is considered 0 cm, and "Indeterminate" is considered null and the absolute change from baseline will not be calculated in the reporting.

- Extramedullary disease (liver);
- Extramedullary disease (spleen);
- Extramedullary disease (other extramedullary disease).

8.2.10.8. Molecular Studies for CML

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings:

The listing will include the molecular biology records based on the Molecular Biology of Disease CRF page, and also include the change from baseline of the number of abnormal transcripts (Listing by dose level, cohort and malignancy).

8.2.10.9. Molecular Studies for CMML, AML, MDS and MF (excluding the Continuation Cohort)

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings: The listing will include sample source and mutation for each assessment (Listing by dose level, cohort and malignancy).

8.2.10.10. Physical Examination

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings: The listing will be presented based on “Physical Examination – Screening” and “Physical Examinstion - Brief” CRF pages, respectively.

8.2.10.11. Medication Error

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings: The listing will be presented based on Medication Error CRF pages.

8.2.10.12. Cardiac Function Evaluation [Combination Cohorts 2 (Fit Patients) Only]

Analysis set: Not applicable.

Table produced by: Not applicable.

Tables: Not applicable.

Listings: The listing will be presented based on Cardiac Function Evaluation CRF pages.

9. REFERENCES

1. Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982.

2. Kalbfleisch JD, Prentice, RL. Statistical Analysis of Failure Time Data, 2nd Edition.Hoboken, Wiley Interscience.

10. APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs

Categories for QTcF

QTcF (ms)	max. < 450	450 ≤ max. ≤ 480	481 ≤ max. ≤ 500	501 ≤ max.
QTcF (ms) increase from baseline	max. < 30	30 ≤ max. <60	60 ≤ max.	

Categories for PR and QRS

PR (ms)	max ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max ≥200	
QRS (ms) increase from baseline	Baseline >110 and max. ≥25% increase	Baseline ≤110 and max. ≥50% increase

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Heart rate (bpm)	min. <40	max. >120

Appendix 2. Response Criteria for Myelodysplasia and CMML

Objective response and Disease Progression

The objective status at each evaluation is determined per investigator evaluation (Protocol Appendix 5). However, the status will be verified per clinical judgment by the Sponsor. More specifically, the following categories on the CRF page will be considered objective response and disease progression for the purpose of this study.

Objective Response (OR)

Disease status assessments (if available)

- Complete remission (CR);
- Partial remission (PR);
- Marrow complete remission (mCR).

Cytogenetic response (if available)

- Complete cytogenetic response;
- Partial cytogenetic response.

Hematologic improvement (if available)

- Erythroid response;
- Platelet response;
- Neutrophil response.

Objective Disease Progression

Disease status assessments (if available)

- Disease progression;
- Failure;
- Relapse after CR or PR.

Cytogenetic response (if available)

- Loss of cytogenetic response.

Hematologic improvement (if available)

- Progression or relapse after HI.

Relapse

Disease status assessments (if available)

- Relapse after CR or PR.

Cytogenetic response (if available)

- Loss of cytogenetic response.

Hematologic improvement (if available)

- Progression or relapse after HI.

Appendix 3. Response Criteria for Myelofibrosis

Objective response and Disease Progression

The objective status at each visit is determined per investigator evaluation (Protocol Appendix 7). However, the status will be verified per clinical judgment by the Sponsor. More specifically, the following categories on the CRF page will be considered objective response and disease progression for the purpose of this study.

Objective Response

Disease status assessments (if available)

- Complete remission (CR);
- Partial remission (PR);
- Clinical improvement (CI).

Cytogenetic response (if available)

- Major cytogenetic response;
- Minor cytogenetic response.

Objective Disease Progression

Disease status assessments (if available)

- Progressive disease (PD);
- Relapse.

Cytogenetic response (if available)

- Loss of cytogenetic response.

Relapse

Disease status assessments (if available)

- Relapse.

Cytogenetic response (if available)

- Loss of cytogenetic response.

Appendix 4. Response Criteria for Acute Myeloid Leukemia

Objective response and Disease Progression

The objective status at each visit is determined per investigator evaluation (Protocol Appendix 8). However, the status will be verified per clinical judgment by the Sponsor. More specifically, the following categories on the CRF page will be considered objective response and disease progression for the purpose of this study.

Objective Response

Disease assessments

- Morphologic complete remission (CR);
  - Cytogenetic CR (CRC);
  - Molecular CR (CRM);
- Morphologic complete remission with incomplete blood count recovery (CRi);
- Morphologic leukemia-free state (MLFS);
- Partial remission (PR);
- Partial remission with incomplete blood count recovery (PRi);
- Minor response (MR).

Disease Progression

Disease assessments

- Treatment failure
  - Resistant disease;
  - Aplasia;
  - Indeterminate cause.
- Relapse
  - Morphologic relapse;
  - Molecular relapse;
  - Cytogenetic relapse.

Relapse

Disease assessments

- Relapse
  - Morphologic relapse;
  - Molecular relapse;
  - Cytogenetic relapse.

Appendix 5. Response Criteria for Chronic Myeloid Leukemia

Objective response and Disease Progression

The objective status at each visit is determined per investigator evaluation (see Protocol Appendix 9). However, the status will be verified per clinical judgment by the Sponsor. Reporting will be done for subjects in chronic phase and accelerated phase/blast crisis at baseline separately. The following categories on the CRF page will be considered objective response and disease progression respectively for the purpose of this study. A response needs to be confirmed by a subsequent investigator assessment a minimum of 4 weeks later. Subjects whose response is not confirmed will be deemed as un-confirmed responders.

Accelerated Phase/Blast Crisis (AP/BC)

Objective Response (hematologic)

Disease assessments

- Complete hematologic response (CHR);
- No evidence of leukemia (NEL);
- Return to chronic phase;
- Minor response.

Disease Progression

- Progressor to Accelerated Phase or Blast Crisis from Chronic Phase or Return to Chronic Phase;
- Progressor from Accelerated Phase to Blast Crisis;
- Loss of confirmed CHR;
- Loss of major cytogenetic response.

Chronic Phase

Objective Response

Disease status assessments

- Complete hematologic response (CHR);
- No Evidence of Leukemia (NEL).

Disease Progression

- Early progressor from Chronic Phase;
- Progressor to Accelerated Phase or Blast Crisis from Chronic Phase or Return to Chronic Phase;
- Loss of confirmed CHR;
- Loss of major cytogenetic response.