**Protocol B1371012**

# AN OPEN-LABEL PHASE 1B STUDY OF PF-04449913 (GLASDEGIB) IN COMBINATION WITH AZACITIDINE IN PATIENTS WITH PREVIOUSLY UNTREATED HIGHER-RISK MYELODYSPLASTIC SYNDROME, ACUTE MYELOID LEUKEMIA, OR CHRONIC MYELOMONOCYTIC LEUKEMIA

**Statistical Analysis Plan**
**(SAP)**

**Version:** 4 (Corresponding to Protocol Amendment #6)

**Author:** PPD (Oncology Statistics – New York)

**Date:** 18 Dec -2017

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## APPENDICES

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

This amendment of the Statistical Analysis Plan was finalized following Protocol Amendment #5 dated August 22, 2017 and Amendment #6 dated Nov 27, 2017. The main changes relevant to this analysis plan are as follows:

Randomized Phase 2 component is removed from the protocol in amendment #5. Expansion component with two cohorts, MDS and AML, are added into the protocol. Bayesian decision rule is used in the expansion component of the study for potential early stopping.

In amendment 6, a set of safety stopping criteria are added. CRh as one of the secondary endpoints for AML patients, CCI as exploratory endpoints are added. PRO endpoint PGIS has been updated from a 7-point Likert scale to a 4-point Likert scale. All of these additions and changes were per FDA request.

## 2. INTRODUCTION

*PF-04449913 is a novel small molecule inhibitor of the Sonic Hedgehog (Hh) Pathway which is currently under development for the treatment of hematologic malignancies and solid tumors.*

*This multi-center open-label Phase 1b study is designed to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of PF-04449913 when combined with azacitidine in patients with previously untreated Higher-Risk Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), and Chronic Myelomonocytic Leukemia (CMML). This Phase 1b study includes two components: (a) a safety lead-in cohort (LIC) and (b) an expansion phase with two cohorts.*

### 2.1. Study Design

*This multi-center, open-label Phase 1b study is designed to evaluate the safety, efficacy, PK, and PD of PF-04449913 when combined with azacitidine in patients with previously untreated Higher-Risk MDS, AML, and CMML. The Phase 1b study includes two components: (a) a safety LIC, and (b) an expansion phase with two cohorts.*

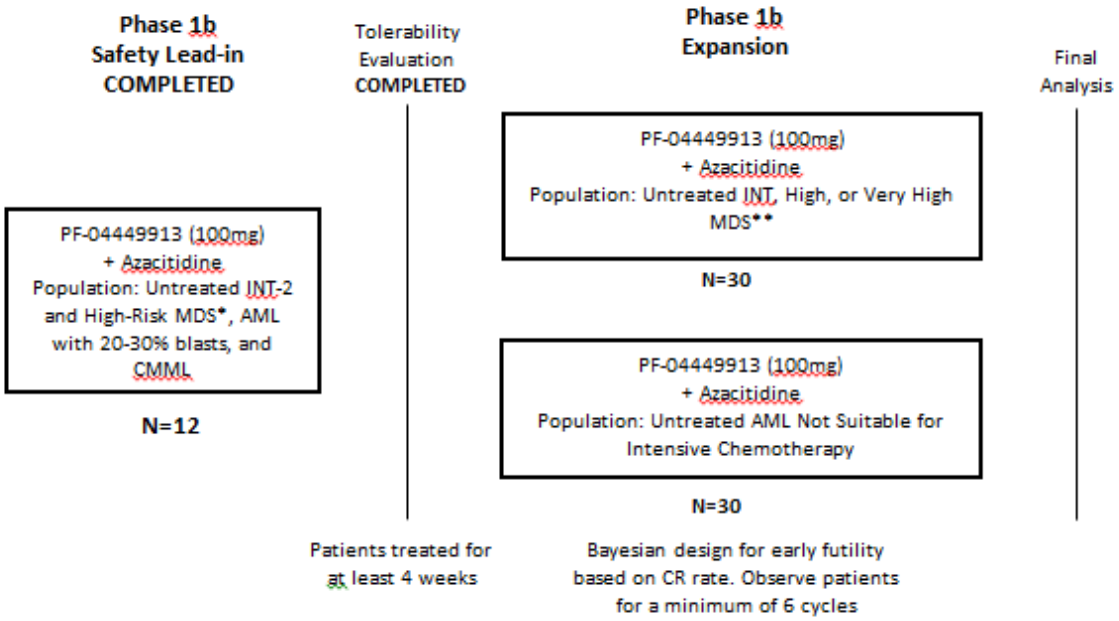
#### 2.1.1. *Safety Lead-In Cohort (LIC)*

*As of 23 September 2015, a safety LIC of 12 patients with previously untreated Intermediate-2 or High-Risk MDS per IPSS (n=7), AML with 20-30% blasts and multi-lineage dysplasia (n=3), erythroleukemia (n=1), and CMML (n=1) were enrolled and received open-label treatment with PF-04449913 at a starting dose of 100 mg given orally once/day in combination with azacitidine at the starting dose of 75 mg/m$^2$/day given SC for 7 consecutive days every 28 days. An evaluation of the DDI potential between PF-04449913 and azacitidine was performed. An internal safety review team reviewed the LIC data after each patient had received at least 4 weeks of treatment and determined that the safety profile of PF-04449913 in combination with azacitidine in the defined population was consistent with what is expected for PF-04449913 or azacitidine alone with no unexpected toxicities identified, therefore the combination was deemed acceptable to proceed to the next phase of development.*

### 2.1.2. *Expansion*

*Patients with previously untreated Intermediate, High, or Very High risk MDS per IPSS-R (n=30) or patients with AML who are not candidates for intensive chemotherapy (n=30) will receive PF-04449913 100 mg orally once/day in combination with azacitidine 75 mg/m$^2$/day given by SC or IV for 7 days (±3 days) every 28 days.*

**Figure 1. Schematic of Study Design**




*MDS patients enrolled in the Safety Lead-In component must have Intermediate-2 or High-Risk disease according to IPSS.
**MDS patients enrolled in the Expansion component must have Intermediate, High, or Very High risk disease according to IPSS-R.

## 2.2. Study Objectives

### 2.2.1. Objectives for the Safety LIC

**Primary Objective**

- *To assess the safety and tolerability of PF-04449913 when administered in combination with azacitidine in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20-30% blasts and multi-lineage dysplasia, and CMML.*

**Secondary Objectives**

- *To assess the Response Rate (RR);*
- *To assess other clinical efficacy measures;*
- *To characterize the PK of PF-04449913 and azacitidine alone and in combination;*

- *To characterize the effects of PF-04449913 in combination with azacitidine on QTc interval.*

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### 2.2.2. Objectives for the Expansion

Primary Objective

- *To determine the* complete remission *(CR) rate of PF-04449913 when administered in combination with azacitidine in patients with previously untreated Intermediate, High, or Very High risk MDS and AML not suitable for intensive chemotherapy.*

Secondary Objectives

- *To assess* overall survival *(OS);*
- *To assess other clinical efficacy measures;*
- *To assess duration of CR;*
- *To assess time to CR;*
- *To evaluate the overall safety profile of PF-04449913 + azacitidine;*
- *To evaluate the pharmacokinetic parameters of PF-04449913;*
- *To characterize any effects of PF-04449913 + azacitidine on QTc interval.*

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## 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

**Phase 1b Tolerability Evaluation**

Note that safety information from the Phase 1b safety LIC of the study will be reviewed by an internal safety review team to determine the safety and tolerability profile of the combination when all patients in the Phase 1b component have been followed for at least 4 weeks.

**Interim Futility Analysis**

A Bayesian decision rule will be used to continuously monitor CR rate without holding enrollment in the expansion component to allow early stopping of the study for futility. The decision rule is to stop enrollment for a specific expansion cohort if the posterior probability of the CR rate in study treatment is no more than 0.2 higher than historical azacitidine is greater than 95% in an expansion cohort, i.e., Pr(glasdegib+Aza response < historical Aza response + 0.2) > 0.95. The prior distribution assumptions for the Bayesian model are as follow: for MDS cohort, we assume a prior distribution of Beta(1,6) for the study treatment (based on data from MDS patients accumulated in the safety LIC [1 out of 7 MDS patients achieved CR]), and a prior distribution of Beta(15,75) by discounting historical CR rate by half (AZA 001 trial); for the AML cohort, a prior distribution of Beta(4,4) for the study treatment (based on pooled data on AML patients from the B1371003 study [1 out of 4 AML patients achieved CR] and the LIC [3 out of 4 AML patients achieved CR]), and a prior distribution of Beta(23.5,97) by discounting historical CR rate by half. The Multc Lean software (Version 2.1.0) developed by MD Anderson Cancer Center is used (https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=12), which properly models variability in historical control that is more often than not ignored. Stopping for toxicity is not modeled.

The Bayesian decision rule applies once the minimum number of patients (i.e., 10) in each expansion cohort has achieved the required follow-up duration (i.e., 28 weeks for the expansion MDS cohort and 24 weeks for the expansion AML cohort). The enrollment to the respective expansion cohort will be stopped if the minimum number of responders in that expansion cohort is not achieved (for expansion MDS cohort, and for expansion AML cohort in Protocol Section 3.3). For instance, if there are no more than 4 responders in the first 17 patients who have achieved 28 weeks follow-up, the enrollment into the expansion MDS cohort should be stopped for futility.

**Safety Stopping Analyses**

Analysis of specific safety criteria will be performed to evaluate stopping enrollment for a specific cohort when there is at least 70% probability that the toxicity rate of any of the predefined safety events of interest (Protocol Section 3.3) in that cohort is above 25%.
The safety stopping criteria will be applied separately within each cohort (AML or MDS) starting when at least 10 patients have completed the required follow-up period (28/24 weeks

for MDS/AML respectively) and applied continuously afterwards. Enrollment will continue unless the stopping boundary is crossed (Table 10 in Section 3.3 of the Protocol). Patients who have completed the required follow-up period or patients who have experienced any pre-defined safety events of interest within the required follow-up period will be included in the safety decision making. The same stopping criteria will be used for the AML and MDS cohorts; however, the two cohorts will be analyzed independently.

**Final Analysis**

The timing of the final analysis is determined by the expansion component of the study. The final analyses for MDS cohorts will be performed after all patients in the expansion MDS cohort have been followed for at least 28 weeks (to allow for confirmation of response per IWG 2006). The final analyses for the AML cohort will be performed after all patients in this cohort have been followed for at least 24 weeks.

**Unblinding**

The safety LIC and expansion component of the study are open-label and unblinding does not apply.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

There are no formal statistical hypotheses for the Phase 1b safety LIC and expansion component of the study.

### 4.2. Statistical Decision Rules

The decision rule at the interim analysis is described in Section 3.

## 5. ANALYSIS SETS

### 5.1. Full Analysis Set (FAS)

The full analysis set will include all enrolled patients in the respective cohort (LIC, expansion MDS, and expansion AML cohort separately), who received at least one dose of any study treatment (PF-04449913 or azacitidine). This will be the primary analysis population for evaluating efficacy endpoints and patient characteristics.

### 5.2. Safety Analysis Set

The safety analysis set will include all patients in the respective cohort (LIC, expansion MDS, and expansion AML cohort separately) who receive at least one dose of any study treatment (PF-04449913, or azacitidine). It will be the primary analysis population for evaluating treatment administration/compliance and safety endpoints.

### 5.3. PK Analysis Set

The PK concentration analysis set is defined as all patients who are treated and who have at least 1 value of analyte concentration of PF-04449913 or azacitidine available. The PK

parameter analysis set is defined as all patients who are treated and who have at least 1 of the PK parameters of interest.

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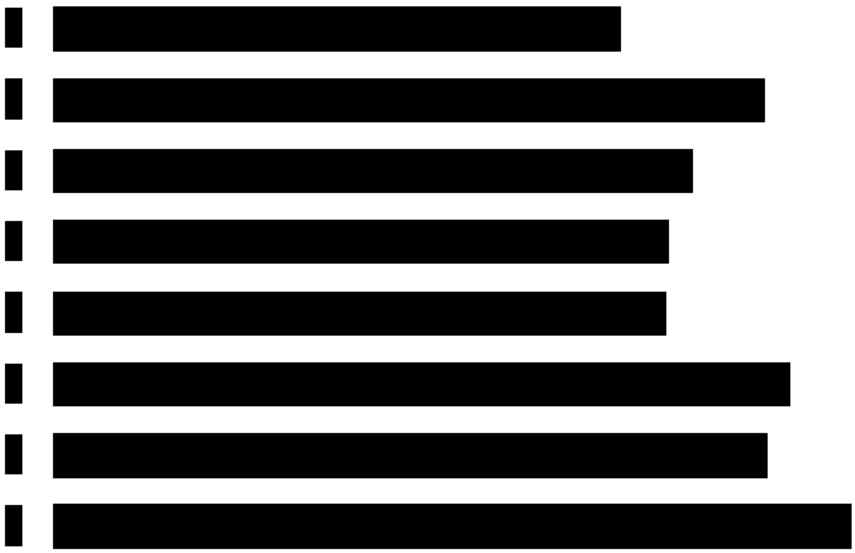

## 5.5. QTc Analysis Set

The QTc analysis set will be defined as all subjects enrolled in the study having at least one ECG assessment after receiving at least one dose of PF-04449913 or azacitidine. This will be the primary set for the ECG analysis. All ECGs obtained during the study will be evaluated for safety. ECG collected prior to the first day of dosing will be considered the baseline ECG.

The evaluable set for the purpose of QTc vs. concentration analysis will be defined as all subjects enrolled in the study as described above and also having at least one matched PK assessment (not different between the ECG and PK assessment by greater than 10% of the half-life). This will be the primary set for evaluating all of the planned ECG and PK assessments.

### 5.6. Treatment Misallocations

Patients' treatment arm assignment is allocated with an Interactive Response Technology (IRT) system for both the safety LIC and the expansion component of the study. Patients will be analyzed in the arm they are treated.

### 5.7. Protocol Deviations

A major deviation in the safety LIC and expansion component of the study includes, but is not limited to, treatment misallocation.

## 6. ENDPOINTS AND COVARIATES

### 6.1. Efficacy Endpoint(s)

For this study there are two different types of efficacy endpoints:

- Response-related endpoints
- Time to event endpoints

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#### 6.1.1. Response endpoint

- **CR rate**

  Primary endpoint for the expansion component of the study is proportion of patients achieving CR. Of note a confirmation of response (Peripheral Blood only) is required 4 weeks after the first assessment per IWG 2006 for MDS patients.

- **Response Rate**

  Response rate (percentage of patients achieving CR + PR) is defined by modified IWG criteria (2006) (Appendix 2).

  Of note a confirmation of response (Peripheral Blood only) is required 4 weeks after the first assessment per IWG 2006 for MDS patients.

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#### 6.1.2. Response-related endpoints disease-specific

##### 6.1.2.1.1. AML Cohort

Hematologic Responses

- CR, for AML also named as Complete Response
- Complete Remission with partial hematologic recovery (CRh)
- CR with incomplete Blood Recovery (CRi)
- Morphologic Leukemia-Free State (MLFS)
- Partial Remission (PR)
- Stable Disease (SD)

Cytogenetics Responses

- Cytogenetic Complete Response (CRc)
- Molecular Complete Response (CRm)

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**6.1.2.1.2. MDS Cohort**

Hematologic Responses

- CR
- PR,
- marrow CR (mCR)
- SD
- Complete or Partial Cytogenetic Response

Hematologic Improvement (HI):

HI (defined only for MDS patients) is derived based on hematology lab and RBC transfusion data according to criteria detailed in Appendix 2.

Of note that HI for neutrophils improvement obtained within 3 weeks of the last administration of growth factors (GCSF/GM-CSF) is considered not evaluable. Additionally, HI for erythroid improvement obtained within one week of the last administration of transfusion of red blood cell is considered not evaluable, and HI for platelets improvement obtained within 3 days of the last administration of transfusion of platelets is considered not evaluable.

### 6.1.3. Time to event endpoints

- **OS**

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

  OS (months) = [date of death or censoring–date of the first dose +1]/30.4375.

- **Duration of complete response (DoCR)**

  DoCR is only defined in MDS patients or AML patients achieving a CR in the expansion component. DoCR is defined as the duration from date of first achieving CR to the date of disease progression (relapse) after CR, or death due to any cause. Patients last known to be alive who are free from disease progression or relapse after CR are censored at the date of the last assessment that verifies their disease status. The minimum DoCR is 4 weeks by definition (CR must last at least 4 weeks to qualify as such per IWG 2006) for MDS patients.

- **Duration of response (CR+PR)**

  Duration of Response (DoR) (including CR+PR) is defined for patients in Safety LIC and the expansion cohort who have ever achieved CR or PR on study as the time from date of first achieving CR or PR to the date of disease progression, or relapse after CR/PR, or death due to any cause. Patients last known to be alive who are free from disease progression or relapse after CR/PR are censored at the date of last disease assessment that verifies their status. Note that minimum DoR is 4 weeks by definition (CR/PR must last at least 4 weeks to qualify as such per IWG 2006) for MDS patients.

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- **Time to Response (CR)**
  Time to response (TTR) is only defined for patients in the expansion component of the study who have ever achieved CR on study as the time from date of the first dose of study drug to date of the first documentation of response (CR). Note that response needs to be confirmed by definition (CR must last at least 4 weeks to qualify as such per IWG 2006) for MDS patients.

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## 6.2. Safety Endpoints

**Adverse Events:**

Adverse Events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). For other AEs without specific CTC definitions, results are identified according to CTCAE "other" categories. Adverse events 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 even if occurring after 28 days after the final dose or after EOT.
- All treatment unrelated SAEs from treatment start until 28 days after final dose of treatment.
- All treatment Non-fatal AEs occurring after treatment start up until 28 days after final dose of treatment.
- Disease progression is not considered a treatment emergent adverse event 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 adverse events only if there is an increase in grade over baseline.

**Treatment Related Adverse Events**

Treatment Related Adverse Events are treatment emergent adverse events 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.

**Laboratory Test Abnormalities:**

Laboratory tests with CTCAE grade definitions will be graded. For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal or not done.The assessments on Cycle 1 Day 1 are considered baseline whenever they are available. If not available, the assessment closest and prior to the first dose of study drug is considered baseline for all patients.

### 6.3. Other Endpoints

**PK Endpoints**

- PK parameters of PF-04449913 and azacitidine, including but not limited to $C_{max}$, $T_{max}$ and AUC (safety LIC );
- $C_{trough}$ for PF-04449913 (expansion cohorts only);

QTc interval

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## 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 (e.g., 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 primary and secondary efficacy analyses, no values will be imputed for missing data. Censoring for time-to-event endpoints are defined in Section 6.1. In the assessment of response (at interim or final analysis), patients who are not known to have achieved response will be counted as non-responders.

## 7.3. Pharmacokinetics

**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 (i.e., not done) or NS (i.e., 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.

**Pharmacokinetic 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 (i.e., 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 (i.e., 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 (i.e., 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 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 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 no analyses related to this time point will be performed. Unplanned ECGs will be in triplicate and averaged.

### 7.5. Pharmacodynamic Parameters

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

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## 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 8.1. Statistical Methods

*Efficacy analyses will use the FAS. They will be reported for the safety LIC, the expansion MDS cohort, and expansion AML cohort separately. Safety analyses will be reported separately for the safety LIC and each cohort in the expansion, as well as all three cohorts pooled.*

#### 8.1.1. Analyses for Binary Endpoints

The rates of binary endpoints will be provided along with the corresponding two-sided 95% confidence intervals using exact method unless otherwise stated.

#### 8.1.2. Analyses for Time-to-Event Data

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

### 8.1.3. Analyses for Continuous Data

Descriptive statistics, such as the mean, standard deviation, coefficient of variation, median, minimum, and maximum values, will be provided for continuous endpoints. Biomarker and PK summaries will also include coefficient of variation percent (%CV).

## 8.2. Statistical Analyses

### 8.2.1. Analysis of Primary Endpoints

**Analysis of Primary Endpoint of Safety LIC**

The primary endpoint of safety LIC of the study is safety and is detailed in Section 8.2.3.1.

**Analysis of Primary Endpoint of the Expansion Component**

The proportion of patients achieving CR is the primary endpoint for the expansion cohorts.

A confirmation of response (peripheral blood only) is required 4 weeks after the first assessment per IWG 2006 for MDS patients. The final analyses for MDS cohorts will be performed after all patients in the expansion MDS cohort have been followed for at least 28 weeks (to allow for confirmation of response per IWG 2006). No confirmation is needed for the expansion AML cohort. The final analyses for the AML cohort will be performed after all patients in this cohort have been followed for at least 24 weeks.

The proportion and two-sided 95% CI (using exact method) of patients achieving CR will be provided at the time of the final analysis based on the FAS for MDS cohort and AML cohort separately.

### 8.2.2. Analysis of Secondary Endpoints

#### 8.2.2.1. Analysis of Secondary Endpoints of Safety LIC

##### 8.2.2.1.1. Response Rate (RR)

Response rate (CR+PR) is a secondary endpoint for the safety LIC. A confirmation of response (Peripheral Blood only) is required 4 weeks after the first assessment per IWG 2006. The final analyses will be conducted after all patients in the safety LIC have been followed for 28 weeks (to allow for confirmation of response per IWG 2006).

The proportion and two-sided 95% CI (using exact method) of patients achieving response will be provided for the safety LIC.

#### 8.2.2.1.2. Other Efficacy Measures

The proportion of patients ever achieving HI (MDS only), mCR, Cytogenetic Response (complete and partial), and SD will be estimated with two-sided 95% CI (using exact method) respectively for the safety LIC.

### 8.2.2.2. Analysis of Secondary Endpoints of Expansion Component

#### 8.2.2.2.1. Overall Survival (OS)

OS will be analyzed and displayed graphically using the Kaplan-Meier method for each expansion cohort separately. The median event time and corresponding two-sided 95% CI will be provided for expansion MDS and AML cohorts separately.

The Kaplan-Meier estimate of survival probabilities at 12, 18, and 24 months and their two-sided 95% CI (using log-log transformation and back-transformation) will be provided for each cohort separately.

The FAS will be used.

#### 8.2.2.2.2. Other Efficacy Measures

Specifically, for AML cohort, the following binary efficacy endpoints (with 95% exact CI) will be summarized in frequency tables, proportion of patients achieving CR, CRh, CRi, CR/CRi, MLFS, PR, SD, CRc, , CRm, and CR+PR.

For MDS cohort, the following binary efficacy endpoints (with 95% exact CI) will be summarized in frequency tables, proportion of patients achieving CR, marrow CR, PR, SD, CR+PR, and Partial or Complete Cytogenetic Response, as well as the proportion of patients ever achieving HI.

The FAS will be used.

#### 8.2.2.2.3. DoCR

DoCR will be analyzed and displayed graphically for each expansion cohort separately using the Kaplan-Meier method. The median DoCR for each cohort and corresponding two-sided 95% CI will be provided.

The subset of patients in the FAS who have ever achieved CR on study will be used.

#### 8.2.2.2.4. Time to Response (CR)

For patients in the expansion cohorts with an objective CR, TTR will be analyzed and displayed graphically for each cohort separately using the Kaplan-Meier method. The median TTR for each cohort and corresponding two-sided 95% CI will be provided.

The subset of patients in the FAS who have ever achieved CR on study will be used.

### 8.2.3. Analysis of Safety Data

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

Unless otherwise specified, the same definition applies to the endpoints in the safety LIC and the expansion component.

**Adverse Events:**

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 lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and all Cycles beyond 1). A 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.

### 8.2.3.1. Analysis of Primary Endpoint of Safety LIC

All patients who receive any study treatment will be included in the summaries and listings of safety data. Overall safety profile and tolerability will be characterized by type, frequency, severity, timing, and relationship to study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

Safety analysis set for safety LIC will be used.

### 8.2.3.2. Analysis of Secondary Endpoint of Expansion Component

All patients who receive any study drug will be included in the summaries and listings of safety data. Overall safety profile and tolerability of PF-04449913 + azacitidine will be characterized by type, frequency, severity, timing, and relationship to study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

The safety analysis set will be used for expansion MDS cohort and AML cohort, separately. The pooled analysis of safety data will utilize the combined LIC and expansion cohorts.

### 8.2.4. Pharmacokinetic Analyses

Analysis Set: PK Analysis set

**PK Parameters:**

For the safety LIC, 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, plasma trough concentration ($C_{trough}$), average plasma concentration ($C_{ave}$) will be estimated.

For the expansion cohorts, the plasma trough concentration ($C_{trough}$) will be reported.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations for PF-04449913 and azacitidine will be presented in tabular form by treatment cohort, dose level, cycle, day and nominal time.
- In the Phase 1b safety Lead-in, linear and semi-log plots of mean and median plasma concentrations by nominal time for PF-04449913 and azacitidine will be presented for PK sampling days by cycle, study day, and by treatment. Similar plots will be presented for each individual patient concentrations.
- Pharmacokinetic parameters (as treated and dose compliant groups) PF-04449913 and azacitidine will be listed and summarized by treatment cohort/dose level and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, and geometric mean and its associated %CV). PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. If an intra patient dose escalation or reduction occurs, data for that patient will only be included in descriptive statistics and summary plots up to the time of the dose change.
- Matchstick plots for $C_{max}$ and AUC for PF-04449913 and azacitidine for the drug-drug interaction analysis dataset.

#### 8.2.4.1. Evaluation of Drug-Drug Interaction Potential (Safety LIC)

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 study is not powered to detect differences in PF-04449913 and azacitidine pharmacokinetics. CCI [redacted]

If data permit and considered appropriate, the geometric mean ratios and its 95% confidence intervals for the PK parameters may be used for assessment of the extent of interaction for

PF-04449913+ azacitidine vs. PF-04449913 alone. A similar assessment may be conducted for azacitidine + PF-04449913 vs. azacitidine.

PF-04449913 AUC and $C_{max}$ when administered alone (Cycle 1/Day 15) 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.

PK data from the lead-in portion of the PK analysis set will be used.

#### 8.2.4.2. Population Pharmacokinetic Analysis or PK/PD Modeling

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies 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.

### 8.2.5. Electrocardiogram Analysis

The QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. QTcF (per Fridericia's correction) is planned to be the primary analysis method for the QTc endpoint. In addition a study-specific correction method (QTcS) and QTcB (per Bazett's correction) may also be evaluated for the QTc evaluable patients. The most appropriate correction method that eliminates any QT vs. RR relationship may be chosen after review of the data. Study conclusions will be based on the most appropriate correction method for the analysis.

#### 8.2.5.1. Summary and Categorical Analysis of Electrocardiogram Findings

The analysis of ECG results will be based on patients with both baseline and on-treatment ECG data. All ECGs obtained during the study will be evaluated for safety. ECG collected prior to the first day of dosing (typically the pre-dose ECG prior to first dose of PF-04449913) will be considered the baseline ECG.

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

Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB by treatment phase (safety LIC or expansion cohorts). Individual QTc (all evaluated corrections) intervals will be listed by time. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment, and by treatment and time point. For each patient by treatment the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTc data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, ≥ 30-<60, and ≥60 msec);
- The number of patients with maximum post-dose (post-baseline) QTc (≤450, >450-≤480, >480- ≤500, and >500 msec);
- PR changes from baseline ≥25% and absolute values >200 msec;
- QRS changes from baseline ≥25% and absolute values >110 msec;
- Number and percentage of individuals with abnormal ECG findings.

Shift tables will be provided for baseline versus worst on study QTc (one or more correction methods will be used) using Maximum CTCAE Grade. Tables of ECG abnormality at baseline (yes, no, not done: (n, %)) will also be provided. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The QTc analysis set will be used.

### 8.2.5.2. Exposure-QTc Analysis

Linear mixed effect modeling to quantify the relationship between plasma concentrations of PF-04449913 and QTc interval will be performed. Additionally, the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship will be explored including diagnostic evaluation. CCI [redacted]

The exposure-QTc analyses will be reported in a separate document. Data may be pooled with data from other studies and/or explored further with a PK/PD model.

The QTc-concentration analysis set will be used.

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## 9. REFERENCES

1. 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.

2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4): 424-47.

3. Greenberg PL, Tuechler H, Schanz J et al. Revised International prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454-65.

# 10. APPENDICES

## Appendix 1. Categorical Classes for ECG and Vital Signs

### Categories for QTcB and QTcF

| | | | | |
|---|---|---|---|---|
| QTcB/QTcF (ms) | max. < 450 | 450≤ max. <480 | 480≤ max.<500 | max. ≥500 |
| QTcB/QTcF (ms) increase from baseline | max. < 30 | 30≤ max. <60 | max. ≥60 | |

### 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 >100 and max. ≥25% increase | Baseline ≤100 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 |
| Supine pulse rate (bpm) | min. <40 | max. >120 |

- Measurements that fulfill these criteria are to be listed in Appendix A of the study report.

## Appendix 2. IWG Criteria: Response Criteria and Progression Definitions for Myelodysplasia***

| Response Criteria (responses CR, PR, mCR must last at least 4 weeks) | **Peripheral Blood** | | | | **Bone Marrow Blasts (BMB) (%)** | **Other** |
|---|---|---|---|---|---|---|
| | Hgb(g/dL) | Neutrophils (L) | Platelets (L) | Blasts (%) | | |
| **Complete Remission (CR)**** | ≥11 | ≥1 x $10^9$ | ≥100 x $10^9$ | 0 | ≤5 | Normal maturation of all cell lines, note if has persistent dysplasia |
| **Partial Remission (PR)**** | | | | | Decreased by ≥50% but still >5% | All CR criteria if abnormal before treatment except BMB |
| **Marrow CR (mCR)** | 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 (m)CR or PR** | | | | | ICH | At least one of the following:<br><br>Return to pre-treatment BMB %<br><br>Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets<br><br>Reduction in Hgb ≥1.5g/dL or transfusion dependence |

## Additional Response Criteria for Myelodysplasia

| | |
|---|---|
| **Cytogenetic Response**<br><br>Complete<br><br>Partial | <br><br>Disappearance of chromosomal abnormality with no appearance of new ones<br><br>≥50% reduction of chromosomal abnormality |
| **Disease Progression**<br>**For patients with % blasts at screening:**<br><5% bone marrow blasts<br>5-10% bone marrow blasts<br>11-20% bone marrow blasts<br>21-30% bone marrow blasts<br><br>For all categories, any of: | <br><br>≥50% increase to >5% bone marrow blasts<br>≥50% increase to >10% bone marrow blasts<br>≥50% increase to >20% bone marrow blasts<br>≥50% increase to >30% bone marrow blasts<br><br>At least 50% decrease from maximum remission/response in granulocytes or platelets<br>Reduction in Hgb by ≥2 g/dL<br>Transfusion dependence |

## Proposed modified IWG Myelodysplasia Response Criteria for Hematologic Improvement (HI)**

| | |
|---|---|
| Erythroid response (pre-treatment <11g/dL)* | Hgb increase by ≥1.5 g/dL<br>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 g/dL pretreatment will count in the RBC transfusion evaluation). |
| Platelet Response (pretreatment <100 $x10^9$/L)* | Absolute increase of ≥30 $x10^9$/L if starting with >20 x $10^9$/L platelets<br>Increase from <20 x $10^9$/L to >20 $x10^9$/L and by at least 100% |
| Neutrophil Response (pretreatment <1 x $10^9$/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:<br>• At least 50% decrease from maximum response levels in granulocytes or platelets;<br>• Reduction in Hgb by ≥1.5g/dL;<br>• 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.

***This criteria will be applied also to patients with oligoblastic AML and CMML without proliferative disorder.

## Appendix 3. IPSS-R Classification System for Myelodysplastic Syndromes*

| Prognostic variable | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| Cytogenetics | Very Good | | Good | | Intermediate | Poor | Very Poor |
| Bone Marrow Blast % | ≤2 | | >2 to <5 | | 5-10 | >10 | |
| Hemoglobin | ≥10 | | 8 to <10 | <8 | | | |
| Platelets | ≥100 | 50-<100 | <50 | | | | |
| ANC | ≥0.8 | <0.8 | | | | | |

| **Risk Category** | **Risk Score** |
|---|---|
| Very Low | ≤1.5 |
| Low | >1.5-3 |
| Intermediate | >3-4.5 |
| High | >4.5-6 |
| Very High | >6 |

Adapted from 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.

*Only applies to MDS patients enrolled in the Expansion component of the study.

## Appendix 4. 2017 ELN Response Criteria for Acute Myeloid Leukemia

| *Response Criteria* | *Neutrophils (μL)* | *Platelets (μL)* | *Bone Marrow Blasts (%)* | *Other* |
|---|---|---|---|---|
| **Complete Remission without Minimal Residual Disease ($CR_{MRD-}$)** | | | | Assessed in CR and CRi patients only by central multiparameter flow cytometry |
| **Morphologic Complete Response (CR)** | ≥1,000 | ≥100,000 | <5 with spicules; no peripheral blasts, no blasts with Auer rods | Transfusion independent, no EMD |
| **Complete Remission with partial hematologic recovery (CRh)**[1] | >500 | >50,000 | <5; no peripheral blasts; no blasts with Auer rods | No EMD; Not qualifying for CR |
| **Morphologic CR with incomplete blood count recovery (CRi)** | <1,000 -or- | <100,000 | <5 | Either neutrophils **or** platelets not recovered, no EMD |
| **Morphologic leukemia-free state (MLFS)** | <1,000 -and- | <100,000 | <5 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 blasts and ≥50% decrease from pretreatment | Blasts ≤5% if Auer rod positive |
| **Stable Disease (SD)** | | | | Absence of $CR_{MRD-}$, CR, CRi, PR, MLFS and criteria for PD not met. Should last at least 3 months. |

| | | | | |
|---|---|---|---|---|
| **Progressive Disease (PD)** | | | >50% increase in blasts from pretreatment (if baseline is <30% blasts, must have at least 15% increase; or >70% blasts for ≥3 months; no improvement in ANC (>0.5 x $10^9$/L [500 μL], and/or platelet count to >50 x $10^9$/L [50 000 μL nontransfused]; or > 50% increase in peripheral blasts (WBC count x % blasts) to >25 x $10^9$/L (25000 μL); or new EMD | |

ANC=Absolute neutrophil count; WBC=white blood cell; EMD=extramedullary disease.

There is no minimum requirement for bone marrow cellularity or hemoglobin concentration for response criteria.

Composite 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 and Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4): 424-47.[2]

[1]CRh is not part of the 2017 ELN recommendations, but is a required assessment for this study.