Protocol B1371019

A MULTI-CENTER CONTINUATION STUDY EVALUATING AZACITIDINE WITH OR WITHOUT GLASDEGIB (PF-04449913) IN PATIENTS WITH PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA, MYELODYSPLASTIC SYNDROME OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Statistical Analysis Plan
(SAP)

Version: 6.0

Date: 19-May-2021

TABLE OF CONTENTS

LIST OF TABLES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1371019 is based on Protocol Amendment #6 dated 02 Feb2021.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	The PRO sections were revised following comments from FDA. Minor clarifications were made in other sections.	Following Protocol Amendment #2
3	The Pharmacogenomics Analysis Set was removed. Clarification regarding select endpoints were made (CRi or better, and CRh or better). Add analysis method for China subset patients.	Following Protocol Amendment #3 and satisfying CFDA requirement
4	Region (rest of world versus China) added as a stratification factor to the applicable efficacy analyses for the intensive study. Updated the definition of "on-treatment" for assessments and treatment-emergent adverse events.	Following Protocol Amendment #5
5	Add OS subgroup analysis. Add sensitivity analyses for handling potential missing or unclean data due to COVID-19.	Following FDA feedback
6	SAP is updated throughout.	Following Protocol Amendment #6

	The efficacy analysis is no longer applicable. The safety analysis will be conducted for B1371019 and B1371012 separately and independently.	

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the safety data collected in study B1371019 Protocol Amendment 6. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

The purpose of Protocol Amendment 6 is to provide continued access to study intervention (azacitidine with or without glasdegib), and collection of safety data for eligible participants who continue to derive a clinical benefit from study treatment in studies B1371019 and B1371012. The safety analyses of participants from Study B1371019 and participants originating from Parent Study B1371012 will be conducted separately and independently. The safety analysis set will include all participants who receive at least one dose of study treatment after consenting to Protocol Amendment 6.

2.1. Study Objective

Type	Objectives	Endpoints	Additional Definitions	Analyses and Summaries
Safety	To monitor the safety and tolerability of the investigational drugs in participants continuing study intervention from this study and participants originating from Parent Study B1371012.	All AEs and SAEs	Section 3.3	Section 6.3.1

2.2. Study Design

Study design is as described in the B1371019 Protocol (Amendment 5, 12 April 2019) and Study B1371012 Protocol (Amendment 7, 14 June 2018). This is an open-label, continuation protocol for eligible NINT cohort participants enrolled in Study B1371019 or Study B1371012 eligible participants.

A maximum of 34 participants from Study B1371019 and 3 participants from Study B1371012 may continue to access to study intervention.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Efficacy Endpoint

Not Applicable.

3.2. Baseline Variables

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of any study drug. The date of last dose of study treatment is the latest date of non-zero dosing of any study drug.

No windowing will be applied when defining baseline. Any deviations from the protocol specified window will be documented as protocol deviations.

3.2.1. Stratification

Not applicable.

3.3. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment is defined as the time from the first non-zero dose of study treatment to the last non-zero dose + 28 days.

3.3.1. Adverse Events

An adverse event is considered treatment emergent (TEAE) relative to a given treatment if the event occurs during the on-treatment period (regardless if it was seen prior to the start of treatment). An adverse event is considered treatment-related as assigned by the investigator.

Adverse events (AEs) will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study treatment will be considered as baseline assessments.

Safety data collected outside the on-treatment period as described above will be listed but not summarized.

3.3.2. Laboratory Data

Not applicable.

4. ANALYSIS SETS

The B1371019 and B1371012 participants will be analyzed separately and independently. Analysis sets and the applicable analysis using the analysis set is summarized in the table below.

Analysis Set	Population	Applicable Analysis (for additional information see Section 6)
Safety Analysis (SA) Set	All participants who received at least one dose of study after consenting to participate in Protocol Amendment 6	Safety analysis for B1371019 Safety analysis for B1371012

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not applicable.

5.2. General Methods

For study B1371019, demographic data will be summarized by treatment arm and for both treatment arms combined. Disposition, exposure, and safety data will be summarized by treatment arm only. For study B1371012, summary will be provided for all participants continuing to Protocol Amendment 6.

The safety analyses of participants from Study B1371019 and participants originating from Parent Study B1371012 will be conducted separately and independently of each other.

5.2.1. Pooling of Data by Center

Not applicable.

5.2.2. Definition of Study Day

Start day of study treatment is the day of the first non-zero dose of any study treatment.

The study day for assessments occurring on or after the start day of study treatment (eg, adverse event onset, laboratory date) will be calculated as:

Study day = Date of the assessment/event - start date of study treatment + 1.

The study day for assessments occurring prior to the start day of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event –start date of study treatment.

The study day will be displayed in all relevant data listings.

5.2.3. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per patient and not per study treatment.

- For Cycle X, the actual cycle start date for each subject is the earliest start date of dosing (dose>0 at that visit) in Cycle X visit CRF exposure page.
- For all but the last cycle.
    - Actual cycle end date is calculated as the start date of the next cycle minus one day.
    - Actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows:

        Actual Cycle Duration = cycle end date – cycle start date + 1.
- For the last cycle, actual cycle duration is calculated as follows:
    - Actual Cycle Duration = last date of non-zero study treatment– cycle start date + 1.

The cycle day will be calculated as:

Cycle day = Date of the assessment/event – cycle start date + 1.

5.2.4. Date of Last Contact

Not applicable.

5.2.5. Disease Assessment Date

Not applicable.

5.2.6. Unscheduled Assessments

Not Applicable.

5.2.7. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Percentages will be reported to one decimal place. The rounding will be performed to closest integer/first decimal using the common mid-point between the two consecutive values, eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.8. Analyses for Continuous Data

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

In case the analysis refers only to certain visits, estimates will be based on the number of patients with an assessment at that visit, unless otherwise specified.

5.2.9. Analyses for Categorical Data

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients with an assessment at that visit, unless otherwise specified.

5.2.10. Analyses for Time to Event Data

Not applicable.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all patient data listings imputed values will be presented and flagged as imputed.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' for not done, 'NR' for not reached or 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'.

CDISC Safety Rulebook will be followed when handling the missing/partial dates, treatment emergent AE algorithm, missing AE grades, etc.

5.3.1. Missing Dates

For purposes of data listings, dates will reflect only the information provided by the investigator on the CRF.

If start dates for adverse events are completely missing a worst case approach will be taken whereby the events will be considered treatment emergent. If only partial information are available (eg, only a month and year or only a year) and the partial information provide sufficient information to indicate the dates are prior to the start of study treatment (eg, month/year less than month/year of first dose) then these will be considered to have started prior to treatment; otherwise a similar worst case approach will apply and these will be considered to have started after treatment.

Date of Last Dose of Study Treatment

No imputation will be done for first dose date. Date of last dose of study treatment, if unknown or partially unknown, will be imputed as follows:

- If the last date of study treatment is completely missing and there is no Disposition CRF page for the treatment phase and no death date, the patient should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or

- If the last date of study treatment is completely or partially missing and there is EITHER a Disposition CRF page for the treatment phase OR a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (Date of Completion/Discontinuation from the Disposition CRF page for the treatment phase, death date),

  = Last day of the month, if both Year and Month are available and Year = Year of min (Date of Completion/Discontinuation from the Disposition CRF page for the treatment phase, death date) and Month < the month of min (Date of Completion/Discontinuation from the Disposition CRF page for the treatment phase, death date), or

  = min (Date of Completion/Discontinuation from the Disposition CRF page for the treatment phase, death date), for all other cases.

Missing or Partial Death Dates

Not Applicable.

Date of Start of New Anti-cancer Therapy

Not applicable.

AE Onset Date:

The following imputation rules apply if the event is unique for a patient or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

- If the AE Collection Date is not missing, is less than the Date of First Exposure to Treatment, and is less than the AE Stop Date, then AE Onset Date is set to the Date of AE Collection.

- If the Previous Visit Date is greater than the Date of First Exposure to Treatment and less than the AE Stop Date, the AE Start Date is set to the previous visit date.

- If the Date of First Exposure to Treatment is greater than the previous visit date and less than the AE Stop Date, the AE Onset Date is set to the Date of First Exposure to Treatment.

- Otherwise AE Onset Date is set to the AE Stop Date.

AE Stop Date:

Ongoing events will have the AE Stop Date set to one of the following values:

- Date of Death, if the patient died and a date of death exists.

- Maximum of (Withdraw date, AE Onset Date, AE Collection Date) if the patient withdrew from the study and a date of withdraw exists.

- Maximum of (AE Onset Date, Subject Summary Collection Date, AE Collection Date) if the Disposition CRF page for the long-term follow-up phase exists but a date of completion/discontinuation does not exist.

- Maximum of (Last Treatment Date, AE Onset Date) if no Disposition CRF page for the long-term follow-up phase exists.

Imputation will only occur if event is unique for the patient, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. Adverse Events are deemed similar if they have the same verbatim term.

Resolved events will have the AE Stop Date set to the maximum of the AE collection date and the AE Onset date.

Other Missing or Partial Dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date.

- If both the day and month are missing for a start date, the first day of the year is used.

- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

- If the date is completely missing, no imputation will be performed.

5.3.2. Missing Toxicity Grade of Adverse Events

During Study Treatment: If no toxicity grade is available or the grade is reported as unknown for an adverse event during the study treatment, then the event will be considered treatment emergent.

In summaries which present maximum toxicity grade, the maximum of non-missing grades will be displayed. Missing grade will only be displayed for cases where a patient reported only one event and the grade is missing.

5.3.3. Missing Pharmacokinetic (PK) Data

Not applicable.

5.3.4. Missing ECG Data

Not applicable.

5.3.5. Missing Biomarker Data

Not applicable.

6. ANALYSES AND SUMMARIES

Analyses for B1371019 and B1371012 will be conducted separately and independently.

All participants who receive any study treatment (safety analysis set) will be included in the summaries and listings of safety data. Overall safety profile and tolerability of azacitidine or glasdegib + azacitidine will be characterized by type, frequency, severity, seriousness, timing, and relationship to study therapy of AEs.

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

In all summaries, emphasis will be placed on TEAEs (events occurring from Amendment 6 consent up to last dose + 28 days). AEs will be summarized by the frequency of participants experiencing TEAEs corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) grade.

6.1. Efficacy Endpoint

Not applicable.

6.2. Baseline and Other Summaries and Analyses

6.2.1. Baseline Summaries

Not applicable.

6.2.2. Study Conduct and Patient Disposition

The following analyses will be based on the SA set by treatment arm for study B1371019 and by pooling across cohorts for study B1371012.

6.2.2.1. Patient Disposition

A summary of the number of patients enrolled overall will be provided.

Discontinuation of treatment overall and for each study drug, and discontinuation of study will be summarized separately and by reason for discontinuation. Discontinuations from study treatment will be summarized using the safety analysis set. Once a patient discontinues all study drugs they will be considered discontinued overall from study treatment. The reason and date corresponding to the last drug discontinued should be used for the overall summary. If multiple drugs were discontinued on the same date with different reasons then the reason for discontinuing blinded therapy will be used.

Discontinuations from study treatment due to adverse events will be identified as either related or not related to study treatment. If causality is missing the event will be considered related to treatment.

An additional summary to meet European Union Disclosure requirements will categorize discontinuations due to adverse events based on the following categories:

- Adverse Event, not serious.
- Adverse event, serious non-fatal.
- Adverse event, serious fatal.

6.2.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and important protocol deviations will be summarized by category (n(%)) for the SA set by treatment arm. Categories will be assigned by the study Clinician.

6.2.3. Study Treatment Exposure

The following analyses will be based on the SA set.

6.2.3.1. Exposure to Glasdegib

The summary of treatment exposure for glasdegib will include the following information:

- Treatment duration (weeks).

The duration of glasdegib (in weeks) is defined as:

$$\text{Treatment duration (weeks)} = (\text{last dose date} - \text{first dose date} + 1)/7.$$

6.2.3.2. Exposure to Cytarabine (Induction, Intensive Study Only)

Not applicable.

6.2.3.3. Exposure to Cytarabine (Consolidation, Intensive Study Only)

Not applicable.

6.2.3.4. Exposure to Daunorubicin (Induction Only, Intensive Study Only)

Not applicable.

6.2.3.5. Exposure to Azacitidine (Non-intensive Study Only)

The summary of treatment exposure for azacitidine will include the following information:

- Treatment duration (weeks).

Azacitidine is administered by subcutaneous injection (SC) or intravenous (IV) infusion 75 mg/m^2 daily for 7 days, in 28 day cycles.

The dose level for azacitidine captured in the CRF is calculated as actual dose administered/body surface area (BSA) (mg/m^2). The last available weight of the patient on or prior to the day of dosing will be used.

The duration of azacitidine (in weeks) during the study for a patient is defined as:

Treatment duration (weeks) = (last dose date – first dose date + 1)/7.

6.2.3.6. Dose Reductions and Interruptions due to Adverse Events

A dose reduction due to an AE is defined as a non-zero dose where reason for adjustment on the dosing CRF is AE.

The number and percentage of patients with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / ≥3) and/or the dosage administered will be summarized by treatment and by treatment arm.

An interruption due to an AE is defined as a 0 mg dose administered where reason for adjustment on the dosing CRF is AE. The number and percentage of patients with dose interruptions will be summarized by treatment and by treatment arm. Percentages will be calculated based on the total number of patients in the safety analysis set.

6.2.4. Concomitant Medications and Non-Drug Treatments

Not applicable.

6.2.5. Prior and Subsequent Anti-Cancer Therapies/Procedures

Not applicable.

6.3. Safety Summaries and Analyses

Unless otherwise specified, summaries of AEs and other safety parameters will be based on the safety analysis population by treatment arm.

6.3.1. Adverse Events

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.3.1.

Seriousness, toxicity grade, study drug action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries by treatment arm, SOC and PT in decreasing frequency based on the frequencies observed in the glasdegib arm will be provided for:

- Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
- Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related);Serious Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
- Serious Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related).

An event will be considered treatment related if the investigator considered the event related to the study drug or this information is unknown.

- Treatment Emergent Adverse Events Leading to Dose Interruptions by Maximum Toxicity Grade (All Causality) separately for each study drug, for chemotherapy, and for any study treatment;
- Treatment Emergent Adverse Events Leading to Dose Reductions by Maximum Toxicity Grade (All Causality) separately for each study drug, for chemotherapy, and for any study treatment;
- Treatment Emergent Adverse Events Leading to Permanent Withdrawal by Maximum Toxicity Grade (All Causality) separately for each study drug, for chemotherapy, and for any study treatment;
- Serious Treatment Emergent Events (All Causality).

Each patient will be counted only once within each PT.

As described in Section 5.3.2, in case a patient has events with missing and non-missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a patient and the grade is missing.

6.3.1.1. Basic Results

For basic results disclosures in the US and EU the following additional summaries will be provided:

- Treatment Emergent Non Serious Adverse Events by SOC and PT in >5% of patients in either treatment arm;
- Treatment Emergent Serious Adverse Events by SOC and PT; and
- Fatal Adverse Events by SOC and PT.

Each of the above summaries will include a count of the number of patients with all causality events and the number of patients with treatment related events.

6.3.1.2. 3-Tiered Adverse Events Analysis

Not Applicable.

6.3.1.3. Adverse Events of Special Interest

Not applicable.

6.3.2. Deaths

Not applicable.

6.3.3. Laboratory Data

Not applicable.

6.3.4. Electrocardiogram

Not applicable.

6.3.5. Physical Examination

Not applicable.

6.3.6. Left Ventricular Ejection Fraction (LVEF)

Not applicable.

6.3.7. Performance Status

Not applicable.

6.3.8. Hospitalization

Not applicable.

7. INTERIM ANALYSES

The interim analyses were performed prior to Amendment 6.

8. REFERENCES

None.