1.0 Title Page

Statistical Analysis Plan

Study M19-072

A Phase 3b, Single-Arm, Multicenter Open-Label Study of Venetoclax in Combination with Azacitidine or Decitabine in an Outpatient Setting in AML Patients Ineligible for Intensive Chemotherapy

Date: 11 May 2022

Version 2.0

2.0 Table of Contents

List of Tables

3.0 Introduction

The statistical analysis plan describes the analyses of safety and efficacy data collected for Study M19-072. Analysis conventions to guide statistical programming conventions are provided.

Analyses will be performed using SAS Version 9.4 or higher.

4.0 Study Background

4.1 Objectives

Primary:

- To determine the composite complete remission rate (CR + CRi), during the initial 6 cycles of treatment, as determined by the modified International Working Group (IWG) criteria, of venetoclax in combination with azacitidine or decitabine given in an outpatient setting to treatment-naïve subjects with AML who are ineligible for intensive chemotherapy.

Secondary:

- To determine the incidence and severity of adverse events including, but not limited to, rates of TLS and neutropenia
- To assess the rate of transfusion independence upon treatment with venetoclax and azacitidine or decitabine.

4.2 Study Design

The study is a Phase 3b, open-label, single-arm, multicenter study evaluating the composite complete remission rate and safety of venetoclax in combination with azacitidine or decitabine in an outpatient setting for treatment-naïve subjects with AML who are ineligible for intensive chemotherapy.

Approximately 60 subjects will be enrolled in the trial. Treatment will be initiated with a venetoclax dose ramp-up over three days and adjusted as appropriate with concomitant use of CYP3A inhibitors. Ramp-up activities for subjects in this study will be done in an outpatient setting. The choice of azacitidine or decitabine will be made at the discretion of the investigator: the subject is to remain on their assigned therapy for the duration of the study.

All subjects will receive venetoclax daily. Subjects will receive either azacitidine for seven days or decitabine for five days of each 28 day cycle up to 6 cycles. After the sixth cycle, subjects may continue to receive AML-directed therapy, including commercially acquired venetoclax with azacitidine or decitabine, outside of this study protocol.

Subjects with progressive disease for whom the treating physician feels are still deriving clinical benefit can be continued on treatment until no longer achieving clinical benefit, unacceptable toxicity, withdrawal of consent, or other protocol criteria for discontinuation are met. All subjects will have a final visit performed when treatment is discontinued and a 30-day safety follow-up assessment.

4.3 Endpoints

4.3.1 Primary Efficacy Endpoint

The primary endpoint is the composite complete remission rate (CR + CRi): complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi) as described by the modified IWG criteria (Operations Manual, Section 3.15).

4.3.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- Response of CR or CRi: complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as described by the modified IWG criteria.

- Transfusion independence rate is defined as the proportion of subjects who achieved post-baseline transfusion independence, which is defined as a period of at least 56 days with no transfusion after the first dose of study drug and within 30 days of the last dose of study drug, death, initiation of post-treatment therapy, whichever is earliest. Transfusion independence rate will be calculated for both RBC transfusion and platelet transfusion separately and together.

4.3.3 Exploratory Efficacy Endpoints

The exploratory endpoints are:

- Time to the first improvement of absolute neutrophil count (ANC), platelets, and hemoglobin as well as duration of the first improvement of absolute neutrophil count, platelets and hemoglobin. See Section 9.4.1 for definitions of both endpoints.
- Rates of CR/CRi in molecular subtypes identified per institutional practices.

4.3.4 Safety Endpoint

Safety evaluations will include adverse event monitoring, clinical lab testing, vital signs measurements, and rate of hospitalization.

4.4 Sample Size Justification

A sample size of 60 subjects would ensure that the true CR + CRi rate will be within 13% of the observed rate with 95% confidence.

4.5 Interim Analysis

None are planned.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

Subjects who receive at least one dose of venetoclax, azacitidine, or decitabine will be included in all analyses unless specified otherwise.

5.2 Definition of Treatment Groups

Subjects will receive venetoclax in combination with one hypomethylating agent, either azacitidine or decitabine. Study results will be presented for 3 groups: Venetoclax in combination with either azacitidine or decitabine and for all treated subjects combined.

6.0 Analysis Conventions

6.1 Definition of Study Drug

Study drug in this document refers to venetoclax and hypomethylating agents azacitidine and decitabine.

6.2 Definition of Baseline

Baseline for a given variable will be the last value obtained on or prior to the first dose of any component of study drug.

6.3 Definition of Final Observation

The final observation is defined as the last non-missing observation collected after the first dose of any component of study drug to the last dose of any component of study drug + 30 days.

6.4 Definition of Rx Days

Study Day is defined as the number of days since or prior to the first dose of any component of study drugs. The day of the first dose of study drug is defined as study Day 1, while the day prior to the first dose of study drug is study Day –1.

7.0 Demographics, Baseline Characteristics, Medical History, Prior and Post-treatment Systemic Therapies, and Concomitant Medications

All analysis in this session will be summarized for the 3 treatment groups: venetoclax in combination with either azacitidine or decitabine, and all treated subjects combined. The number of subjects with missing information will also be summarized. There will be no statistical comparison for the variables summarized in this section.

7.1 Demographic and Baseline Characteristics

All baseline characteristic summary statistics and analyses are based on characteristics prior to the first dose of study drug.

Summaries of continuous characteristics will consist of the number of non-missing observations, mean, standard deviation, and range. Categorical characteristics will be summarized by the frequencies and percentages of subjects within each category.

The following demographic, baseline, and disease-related characteristics will be summarized:

Demographics:

Age (years) and age categories (12 – < 18, 18 – < 65, 65 – < 75 years, ≥ 75 years)

Gender (male, female)

Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander)

Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)

Height (cm)

Weight (kg)

Baseline and Disease-Related Characteristics:

ECOG performance status (Grade 0, 1, 2, 3)

Cytogenetic risk (favorable, intermediate, poor)

Bone marrow blast count (< 30%, ≥ 30% – < 50%, ≥ 50%)

Bone marrow blast count (%)

White blood cell count ($\times 10^9$/L)

CTC grade of neutropenia

Neutrophil value ($\times 10^9$/L)

CTC grade of anemia

Hemoglobin value (G/L)

CTC grade of thrombocytopenia

Platelet count ($\times 10^9$/L)

Type of AML (de novo, secondary, therapy-related AML)

Reasons for being ineligible for standard induction therapy

Antecedent hematologic history of MDS or MPN (Yes, No)

Baseline packed RBC transfusion dependence (Yes, No)

Baseline platelet transfusion dependence (Yes, No)

Molecular marker (FLT3-ITD, FLT3-TKD, IDH1, IDH2, IDH1/2, TP53, NPM1, CEBPA, TET2, ASXL1, DNMT3A, Other)

Hepatic impairment (Yes [Mild Impairment, Moderate Impairment, Severe Impairment], No)

Renal impairment (Yes [Mild Impairment, Moderate Impairment, Severe Impairment], No)

7.2 Medical History

Medical history will be summarized according to the MedDRA dictionary, with presentation organized by system organ class (SOC) and preferred term (PT). The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each body system. The number and percentage of subject with a particular PT will be summarized. Subjects reporting more than one PT within a SOC will be counted only once for that SOC.

7.3 Prior and Post-treatment Systemic Therapies and Concomitant Medications

A prior medication is defined as any medication taken prior to the first dose of study drug. A concomitant medication is defined as any medication that started prior to the first dose of study drug and continued to be taken after the first dose of study drug, or any medication that started after the first dose of study drug, but not after the last dose of study drug.

The number and percentage of subjects who took at least one dose of concomitant medication other than study drug will be summarized by the generic medication name coded by WHO dictionary. A subject who reports the use of two or more medications with same start date will be counted only once in the summary of "Any Concomitant Medication." A subject who reports two or more uses of the same medication will be counted only once in the total for the associated WHO generic drug name.

The number and percentage of subjects who have prior or post-treatment systemic therapies will be summarized by generic medication name coded by WHO dictionary.

The number and percentage of subjects who have taken TLS prophylaxis agents including intravenous hydration on or prior to the first dose of study drug and concomitant to the study treatment will be summarized separately.

The number and percentage of subjects who have received transfusions on or prior to first dose of study drug will be summarized by transfusion type.

8.0 Patient Disposition and Study Drug Exposure

All analysis in this session will be summarized for the 3 treatment groups: venetoclax in combination with either azacitidine or decitabine, and all treated subjects combined. The number of subjects with missing information will also be summarized. There will be no statistical comparison for the variables summarized in this session.

8.1 Patient Disposition

The number of screen failures and screen failure reasons will be tabulated. The numbers and percentages of subjects will be summarized by treatment groups for each of the following categories for all enrolled subjects:

- Subjects enrolled into the study
- Subjects who received at least one dose of study drug
- Subjects who were enrolled but not treated with any component of study drug
- Subjects who discontinued venetoclax due to all reasons and primary reason
- Subjects who discontinued azacitidine due to all reasons and primary reason
- Subjects who discontinued decitabine due to all reasons and primary reason

8.2 Study Drug Exposure

Exposure to each of the three study drugs will be summarized in days using sample size (N), mean, standard deviation, median, and range for each of the following variable:

- The duration of exposure which is defined for each subject as (last dose date − first dose date) + 1;

- The number of cycles that subjects were exposed to study drug.
- Average dosed days per cycle which is defined for each subject as (total number of days subject received study drug)/(the number of cycles subject was exposed to study drug).
- Dose intensity accounting for dose reduction.
- Dose intensity accounting for dose reduction and interruption.

The number and percentage of subjects with dose reduction or dose interruption will be summarized by the number of occurrences of dose reduction or interruption as no, 1 time, 2 times, or > 2 times.

In addition, the number and percentage of subjects exposed to each of the three study drugs will be summarized for the following categories of exposure duration:

- 0 to 4 weeks (0 to 28 days),
- 4 weeks to 8 weeks (28 to 56 days),
- 8 weeks to 12 weeks (57 to 84 days),
- 12 weeks to 16 weeks (85 to 112 days),
- 16 weeks to 20 weeks (113 to 140 days),
- 20 weeks to 24 weeks (141 to 168 days).

The number and percentage of subjects who received CYP3A inhibitors and/or P-gp inhibitors during the period from first exposure to study drug to last exposure of study drug will be summarized by the type: moderate/strong CYP3A inhibitor, moderate P-gp inhibitors.

9.0 Efficacy Analysis

9.1 General Considerations

All analyses in this session will be presented for the 3 treatment groups: venetoclax in combination with either azacitidine or decitabine, and all treated subjects combined.

9.1.1 Analysis of Efficacy Endpoints by Variable Type

The primary endpoint is composite complete remission (CR + CRi), a complete remission (CR) with or without complete hematologic recovery (CRi). The secondary endpoints are rates of complete remission (CR), complete remission with incomplete hematologic recovery (CRi), and transfusion-independence rates for red blood cells and platelets separately and combined. The observed rates for each endpoint will be presented with a 95% confidence interval. Rates of composite complete remission (CR + CRi) in molecular subtypes will be similarly presented.

Time to the first absolute neutrophil count improvement and hemoglobin improvement as well as duration of the first absolute neutrophil count improvement and hemoglobin improvement will also be analyzed using Kaplan-Meier curve, where median time to improvement and duration of improvement with their corresponding 95% CI will be provided.

9.1.2 Missing Data Imputation for Efficacy Endpoints

Subjects who do not have any post-baseline IWG assessments will be considered as non-responders in the remission rate analyses.

9.2 Primary Efficacy Analysis

The primary endpoint is the composite complete remission rate (CR + CRi) as identified by the investigators during the study. An exact 95% confidence interval based on the binomial distribution will be provided along with the rate.

9.3 Secondary Efficacy Analyses

9.3.1 Remissions

Rates of complete remission and complete remission with incomplete hematologic recovery (as the best response) as identified by the investigator will be tabulated separately. Exact 95% confidence intervals will also be provided.

9.3.2 Transfusion Independence

Post baseline transfusion independence rate will be calculated as the proportion of subjects who achieved transfusion independence post baseline regardless of their baseline transfusion status. Transfusion independence is defined as a period of at least 56 days (≥ 56 days) with no transfusion after the first dose of study drug and on or before the last dose of study drug + 30 days, relapse, death, or before the initiation of post-treatment therapy, whichever is earliest. The transfusion independence rate will be evaluated for 1) red blood cells (RBC), 2) platelets, and 3) RBC and platelets. Exact 95% confidence intervals will also be provided.

9.4 Exploratory Efficacy Analysis

Time to blood counts improvement as well as duration of the improvement will be summarized by descriptive statistics (mean, median, and range) and analyzed by Kaplan-Meier (KM) methodology. KM plots will be presented. Median improvement time and median duration of improvement and their corresponding 95% confidence intervals will be provided.

Blood count improvement is defined separately for ANC, platelet count and hemoglobin.

- Improvement of Grade 4 Neutropenia defined as ANC lab values < 0.5 × 10^9/L lasting for at least 7 days: when ANC lab values improve to ≥0.5× 10^9/L sustaining for a minimum of 5 days.
- Improvement of Grade 4 Thrombocytopenia defined as platelet count lab values <25 × 10^9/L lasting for at least 7 days: when platelet count lab values improve to ≥25 × 10^9/L sustaining for a minimum of 5 days.
- Improvement of Grade 3 Anemia defined as hemoglobin lab values <80 G/L lasting for at least 7 days: when hemoglobin lab values improve to ≥80 G/L sustaining for a minimum of 5 days.

9.4.1 Time to Blood Count Improvement

Time to blood count improvement will be analyzed for subjects who achieved bone marrow blast clearance (CR/CRi/MLFS).

9.4.1.1 Time to Improvement of Grade 4 Neutropenia

9.4.1.1.1 Time to Improvement of Grade 4 Neutropenia Present at the Time of Blast Clearance

For subjects whose ANC lab value is <0.5× 10^9/L at the time of blast clearance, their time to improvement of Grade 4 neutropenia present at the time of blast clearance is defined as number of days from the blast clearance to the first date of ANC lab value recovered to ≥0.5 × 10^9/L.

9.4.1.1.2 Time to Improvement of First Grade 4 Neutropenia Onset Post Blast Clearance

For 1) subjects whose ANC lab value is ≥0.5× 10^9/L at the time of blast clearance and for 2) subjects whose ANC lab value is <0.5× 10^9/L at the time of blast clearance and is recovered to ≥0.5× 10^9/L post blast clearance, their time to improvement of first Grade 4 neutropenia onset post blast clearance is defined as number of days from the first date when ANC lab value drop to <0.5× 10^9/L post blast clearance to the first date when ANC lab recovered to ≥0.5 × 10^9/L.

9.4.1.2 Time to Improvement of Grade 4 Thrombocytopenia

Analyses will be performed similar to Time to Improvement of Grade 4 Neutropenia.

9.4.1.3 Time to Improvement of Grade 3 Anemia

Analyses will be performed similar to Time to Improvement of Grade 4 Neutropenia.

9.4.2 Duration of Blood Count Improvement

Duration of blood count improvement will be analyzed for subjects who achieved bone marrow blast clearance (CR/CRi/MLFS).

9.4.2.1 Duration of Improvement of Grade 4 Neutropenia Present at the Time of Blast Clearance

For subjects whose ANC lab value is <0.5× 10^9/L at the time of blast clearance with a subsequent improvement, the duration of improvement of Grade 4 Neutropenia present at the time of blast clearance is defined as number of days from the first date of ANC lab value recovered to ≥0.5 × 10^9/L following blast clearance to the first date when ANC lab value dropped back to <0.5 × 10^9/L.

9.4.2.2 Duration of Improvement of Grade 4 Thrombocytopenia Present at the Time of Blast Clearance

Analyses will be performed similar to Duration of Improvement of Grade 4 Neutropenia.

9.4.2.3 Duration of Improvement of Grade 3 Anemia Present at the Time of Blast Clearance

Analyses will be performed similar to Duration of Improvement of Grade 4 Neutropenia.

9.4.3 Rates of CR or CRi in molecular subtypes

Rates of CR/CRi in molecular subtypes (FLT3-ITD/TKD, IDH1, IDH2, IDH1/2, TP53, NPM1, CEBPA, TET2, ASXL1, DNMT3A, Other) identified per institutional practices will be summarized using summary statistics (N, mean, standard deviation, median, range) for each of the treatment groups.

9.5 Efficacy Subgroup Analysis

Rates of composite complete remission rates (CR + CRi) will be presented along with their exact 95% CI.

The subgroups defined below, not limited to, will be used for these analyses:

1. Gender (Male, Female)
2. Age (12– < 65 years, 65 – < 75 years, ≥ 75 years)

3. Baseline ECOG (Grade < 2, ≥ 2)
4. Type of AML (De Novo, Secondary, Therapy-related AML)
5. Cytogenetic risk (Intermediate, Poor, Favorable)
6. CYP3A inhibitors use leading to venetoclax dose reduction (Yes, No)
7. Antecedent hematologic history of MDS or MPN (Yes, No)

10.0 Safety Analysis

10.1 General Considerations

All analyses in this session will be presented for: venetoclax in combination with azacitidine, venetoclax in combination with decitabine, and all treated subjects combined.

10.2 Analysis of Adverse Events

10.2.1 Treatment-Emergent Adverse Events

Adverse events (AE) with onset or worsening on or after the first dose of study drug and no more than 30 days after the last dose of study drug are treatment emergent. All summaries of adverse events will include treatment-emergent events (TEAE) only unless specified otherwise.

Adverse event data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The version of the MedDRA dictionary that is current at the time of summarization will be applied to the codes prior to summarization. AE rates will then be summarized by system organ class (SOC) and preferred term (PT).

Within each summary the following AE rates will be presented:

- Overall rates: subjects who had at least one AE,
- SOC rates: subjects who had a least one event falling in a given system organ class,

- PT rates: subjects who had at least one event with the given preferred term.

For summaries of AE by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) grade, at each level of summarization (overall, SOC, and PT) each subject is counted only once at the maximum grade level.

Summaries of SAE are described in Section 10.2.3.

The number and percentage of subjects experiencing at least one event for each of the following categories will also be summarized:

- Any TEAE
- TEAE with reasonable possibility of relationship to venetoclax per the investigator.
- TEAE with NCI grade 3 or higher
- TEAE with NCI grade 3 or 4
- TEAE leading to discontinuation of venetoclax
- TEAE leading to venetoclax dose interruption
- TEAE leading to venetoclax dose reduction
- TEAE with reasonable possibility of relationship to the HMA per the investigator
- TEAE leading to discontinuation of the HMA
- TEAE leading to HMA dose interruption
- TEAE leading to HMA dose reduction.

Overview tables with overall rates of each of the above AE types plus treatment-emergent death rates will be prepared for TEAE.

10.2.2 SAEs (Including Deaths)

Treatment-emergent serious adverse event rates will be summarized by MedDRA system organ class and preferred term as done for adverse events in general. The summaries of SAE data will include tabulations of the following rates:

- All treatment-emergent SAE
- Adverse events resulting in hospitalization
- Adverse events resulting in death.

Treatment Emergent Deaths

Rates of deaths that occur within 30 days of start of treatment and within 30 days following the last dose of study drug will also be summarized.

10.2.3 Selected AEs

Selected AEs will be identified through the search criteria provided in table below and summarized by MedDRA system organ class and preferred term.

Table 1. Selected Adverse Events

Selected Adverse Events	Search Criteria
Tumor Lysis Syndrome* (AE) occurring within 7 days from the first dose study drug	SMQ – "Tumor Lysis Syndrome" (narrow)
Neutropenia*	PT terms – "neutropenia," "neutrophil count decreased," "febrile neutropenia*," "agranulocytosis," "neutropenic infection," and "neutropenic sepsis"
Thrombocytopenia*	PT terms – 'Thrombocytopenia' and 'platelet count decreased'
Anemia*	PT terms – 'Anaemia' and 'Haemoglobin decreased'
Grade ≥3 infections	SOC of 'infections and infestations'
Hemorrhages	SMQ - 'Haemorrhages' (narrow)

*Considered as AESI in the protocol.

10.2.4 Listing of SAEs and Deaths

A listing of serious adverse events will be provided. All data from the adverse event records will be compiled into the data listing. A listing of reports of treatment-emergent deaths will also be provided.

10.3 Analysis of Laboratory Data

10.3.1 Variables and Criteria Defining Abnormality

Where applicable, lab test data will be graded according to National Cancer Institute Common Terminology Criteria (NCI CTCAE) version 4.03.

The NCI criteria are ranges of test values that are to be graded from one to four. Lab test results that do not fall into the grade one to four ranges, generally those that are in the normal range for the lab or else are abnormal in the direction opposite the test, will be assigned a grade of zero.

10.3.2 Statistical Methods

For each lab test for which NCI criteria exist, shift tables will be generated that cross tabulate the number of subjects with baseline values of Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4 versus maximum post-baseline of Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. All treated subjects will be included in the cross tabulation regardless whether baseline or post-baseline measurements are collected.

Separate laboratory shifts tables based on the two criteria below will be generated for each laboratory tests related to CTCAE:

- Shifts from Grade 0 (Normal) at baseline to Grade 1 - 4 Post-baseline (maximum) and worsening from an abnormal baseline value of at least one grade up post-baseline (maximum)
- Shifts from Grade 0 - 2 at baseline to Grade 3 or 4 Post-baseline (maximum) and from Grade 3 at baseline value to Grade 4 post-baseline (maximum).

The maximum NCI grade value is the value with highest NCI grade collected after the first dose of study drug and within 30 days following the last dose of study drug. In cases where multiple values are collected on the same day, the maximum grade value and minimum grade value will be selected as the value for that day for the post-baseline grade value and for the baseline grade value, respectively.

Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

The number and percentage of subjects with liver Enzyme value meeting the criteria for potential drug-induced liver injury (ALT > 3 × ULN or AST > 3 × ULN and TBILI > 2 × ULN within 72 hours [3 days if time stamp is not collected] of each other) will be presented.

The number and percentage of subjects meeting the Howard criteria for TLS will be presented. The Howard Criteria for TLS is defined as two or more of the following treatment-emergent lab changes within a 24-hour period. The evaluation period for TLS is after 1st dose of study drug to 7 days from the 1st dose of study drug.

- uric acid > 475.8 mcmol/l,
- potassium > 6 mmol/l,
- inorganic phosphorus > 1.5 mmol/l
- calcium < 1.75 mmol/l.

11.0 Summary of Changes Between the Previous Version of SAP and the Current SAP

1. From version 1 to version 2, clarify transfusion independence and conversion rate in Section 4.3.2.

2. From version 1 to version 2, clarify molecular marker in Section 7.1 and Section 9.3.

3. From version 1 to version 2, updated selected AE in Section 10.2.3.

4. From version 1 to version 2, updated Section 9.4.