1.0 Title Page

Efficacy Statistical Analysis Plan

Study M14-212

Study M14-358

Study M14-387

Venetoclax (ABT-199/GDC-0199) in Combination with LDAC (Low Dose Cytarabine) (LDAC) or HMA (Azacitidine or Decitabine) for the Treatment Subjects with Acute Myeloid Leukemia

Date: 02 Oct 2019

Version 4.0

2.0 Table of Contents

List of Tables

2.1 Summary of Versions

Version	Date of Completion	Summary
1.0	19 Dec 2017	First version (Appendix of Briefing Book of FDA Type C Meeting)
2.0	04 May 2018	Implemented comments from FDA
3.0	27 Nov 2018	Update the version date for 2nd interim CSR
4.0	02 Oct 2019	Update the version date for 3rd interim CSR

2.2 List of Abbreviations and Definitions of Terms

AE	Adverse event
AESI	Adverse Event of Special Interest
AML	Acute Myeloid leukemia
AST	Aspartate aminotransferase
HMA	Azacitidine or Decitabine
LDAC	Low dose cytarabine
MedDRA	Medical dictionary for regulatory activities
MPN	Myeloproliferative neoplasm
NCI	National Cancer Institute
NCI CTC	National Cancer Institute Common Terminology Criteria
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

3.0 Introduction

This efficacy SAP covers the statistical procedure for the efficacy analyses of the data from Studies M14-358 (R&D/17/1341) and M14-387 (R&D/17/1340). These analyses will support the efficacy assessment of venetoclax for AML. Analyses will be performed by personnel from Data and Statistical Sciences at AbbVie or their designees using SAS Version 9.3 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Objectives for Statistical Analysis Plan

This SAP provides the details of the statistical analyses planned to be performed for the efficacy assessment of Studies M14-358 and M14-387. The analyses will include all AML subjects who had at least one dose of venetoclax.

5.0 Studies/Protocols

A complete list of relevant clinical studies associated with venetoclax that will be contributed to the product efficacy assessment is listed in Table 1.

Table 1. Studies to be Included in Efficacy Summary

Study ID Phase (Status)	Number of Enrolled Subjects (Actual/Planned)	Location	Study Design	Primary Objective
M14-358 Phase 1b (Enrollment complete and follow-up is ongoing)	212/260	Australia, Germany, France, and US	Open-label study of venetoclax + azacitidine or decitabine in treatment naïve elderly (≥ 60 years) subjects with AML who are not eligible for standard induction therapy; 2 stages: dose escalation and dose expansion (both HMAs)	Evaluate the safety, PK, and efficacy of venetoclax + decitabine or azacitidine in the target population. The objective of the safety expansion is to confirm efficacy and safety of the intended dose for Phase 3 study.
M14-387 Phase 1/2 (Enrollment complete and follow-up is ongoing)	92/92	Australia, Germany, Italy, US	Open-label study of venetoclax + LDAC in treatment naïve subjects with AML who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy; 2 stages: dose escalation and safety expansion	Phase 1: Evaluate the safety, PK and determine the MTD and RPTD of venetoclax + LDAC. Phase 2: Estimate efficacy, including ORR, and characterize the toxicity of the combination at the RPTD. Cohort C: Evaluate the ORR for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated.

The venetoclax doses and regimens in the Studies listed in Table 1 are described in Table 2 below.

Table 2. Regimens Investigated in Venetoclax AML Studies

Study ID	Venetoclax Dose and Frequency	Treatment Regimen
M14-358	Venetoclax ***400*** mg QD, ***800*** mg QD, ***1200*** mg QD	Venetoclax in combination with HMA (Azacitidine or Decitabine)
M14-387	Venetoclax ***600*** mg QD, ***800*** mg QD	Venetoclax in combination with LDAC (Low dose cytarabine)

6.0 Analysis Sets

6.1 Definition of Analysis Sets and Rationale

This efficacy SAP provides details of statistical analyses that are to be performed for the efficacy assessment of Studies M14-358 and M14-387. The analyses for Studies M14-358 and M14-387 will not be pooled and three analysis sets will be prepared for summaries of efficacy as detailed in Table 3. The reason for not pooling the Studies M14-358 and M14-387 is that the different treatment regimens (venetoclax monotherapy, venetoclax in combination with azacitidine, venetoclax in combination with decitabine, and venetoclax in combination with LDAC) are expected to have different efficacy profiles. Thus, it is not appropriate to pool data across these studies to assess the efficacy of venetoclax.

Table 3. Definition of the Analysis Sets

Analysis Data Sets	Studies Included	Study Population	Treatment Groups
1. Venetoclax in combination with HMA	M14-358	Subjects who received at least one dose of venetoclax	• venetoclax 400 mg QD + azacitidine (N = 84) • venetoclax 800 mg QD + azacitidine (N = 37) • overall of venetoclax + azacitidine (N = 127) • venetoclax 400 mg QD + decitabine (N = 31) • venetoclax 800 mg QD + decitabine (N = 37) • overall of venetoclax + decitabine (N = 73) • DDI venetoclax 400 mg QD (N = 12)
2. Venetoclax in combination with LDAC	M14-387	Subjects who received at least one dose of venetoclax	• venetoclax 600 mg QD + LDAC (N = 82) • venetoclax 600 mg QD + LDAC without MPN (N = 78) • All Subjects (venetoclax 600 mg QD + LDAC or Venetoclax 800 mg QD + LDAC) (N = 92)

1) Venetoclax in combination with HMA Analysis Set

This analysis set includes subjects who received at least one dose of venetoclax in Study M14-358. This analysis dataset will be used to provide a comprehensive summary of efficacy of venetoclax in combination with HMA (azacitidine 75 mg/m^2 daily administered intravenously or subcutaneously [Days 1 - 7] or decitabine 20 mg/m^2 daily administered intravenously [Days 1 - 5] during each 28 day cycle).

2) Venetoclax in combination with LDAC Analysis Set

This analysis set includes subjects who received at least one dose of venetoclax in Study M14-387.

This analysis dataset will be used to provide a comprehensive summary of efficacy of venetoclax in combination with LDAC (20 mg/m^2 daily administered subcutaneously [Days 1 - 10]). Patients with an antecedent history of myeloproliferative neoplasm (MPN) including polycythemia vera, myelofibrosis, essential thrombocythemia, or chronic myelogenous leukemia were excluded from the study in Study M14-387 Protocol

Amendment 2 because emerging evidence suggested that patients with JAK2 mutated MPN may not benefit from treatment with venetoclax in combination with LDAC. To explore the efficacy of venetoclax in combination with LDAC both including and excluding those patients with a history of MPN will be presented.

Unless otherwise stated, data included in efficacy analyses is subjected to the cutoff date which is determined at each interim analysis.

6.2 Planned Efficacy Analyses for Each Analysis Dataset

A list of contents of efficacy analyses described in the Statistical Methods section (Section 8.0) is provided below. The list of analyses will be performed for all three analysis datasets separately. Data will not be pooled across studies.

- Complete remission (CR) rate (Analysis datasets 1 - 3)
- Complete remission with partial hematologic recovery (CRh) rate (Analysis datasets 1 - 3)
- CR + CRh rate (Analysis datasets 1 - 3)
- CR + CRh rate by the initiation of Cycle 2 (Analysis datasets 1 - 3)
- Time to the first response of CR + CRh (Analysis datasets 1 - 3)
- Time to best response of CR + CRh (Analysis datasets 1 - 3)
- Duration of CR (Analysis datasets 2 - 3)
- Duration of CR + CRh (Analysis datasets 1 - 3)
- CR + CRi rate (Analysis datasets 2 - 3)
- CR + CRi rate by the initiation of Cycle 2 (Analysis datasets 2 - 3)
- Time to the first response of CR + CRi (Analysis datasets 2 - 3)
- Time to best response of CR + CRi (Analysis datasets 2 - 3)
- Duration of CRi (Analysis datasets 2 - 3)
- Duration of CR + CRi (Analysis datasets 2 - 3)
- Objective Response Rate (CR + CRi + PR) (Analysis datasets 2 - 3)
- Overall survival (OS) (Analysis datasets 2 - 3)

- Post baseline RBC/Platelet transfusion independence and duration of post baseline RBC/Platelet transfusion independence (Analysis datasets 1 - 3)
- Time to first RBC/platelet transfusion (Analysis datasets 2 - 3)
- Time to the first recurrent RBC/platelet transfusion (Analysis dataset 2 - 3)
- Time to first Grade 3 or above TEAE hemorrhage event (SMQ narrow) (Analysis datasets 2 - 3)
- Time to first Grade 3 or above TEAE SOC of "infections and infestations" event (Analysis datasets 2 - 3)
- Time to first hospitalization due to SAE (Analysis datasets 2 - 3)

7.0 Analysis Conventions

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to

- Venetoclax and HMA (Study M14-358)
- Venetoclax and LDAC (Study M14-387)

Definition of Last Dose of Study Drug + 30 Days

Last dose of study drug + 30 days is defined as the last of dose of venetoclax, HMA, or LDAC + 30 days on or prior to data extraction dates.

Definition of Baseline

Unless otherwise stated, baseline for a given variable will be defined as the last non-missing value for that variable obtained prior to the first dose of any component of study drug.

Definition of Study Day

Study Day is defined as the number of days since (positive numbers) or prior to (negative numbers) the first dose of study drug. 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 defined as Study Day –1; there is no Study Day 0.

Definition of Final Observation

The final observation is defined as the last non-missing observation collected.

Full Analysis Set

The full analysis set includes all subjects who received at least one dose of venetoclax.

Safety Analysis Set

The safety analysis set includes all subjects who received at least one dose of venetoclax.

8.0 Statistical Methods

Unless otherwise specified, all summaries/analyses of three analysis datasets will be presented separately. Disposition, demographic, prior and concomitant medication, prior disease history including AML, and study drug exposure summary will be performed as described in the safety SAP.

8.1 Efficacy Analyses

Unless otherwise specified, all summaries/analyses of efficacy data will be presented for all treatment groups of the analysis datasets 1 – 3 specified in Table 3 separately. There will be no pooled analyses across the three analysis datasets. All subjects who have received at least one dose of venetoclax will be included in the efficacy analyses. Unless otherwise stated, the data cutoff date will be applied to efficacy analyses for Study M14-358 and Study M14-387 (Analysis dataset 2 - 3).

8.1.1 Complete Remission (CR) Rate

Complete Remission (CR) is a response based on investigator report using modified IWG criteria for AML.

Complete Remission (CR) rate will be defined as the proportion of subjects who achieve a complete remission at any time point during the study per the modified IWG criteria for AML. Subjects who never achieve CR or have no IWG disease assessment will be considered to be non-responders in the calculation of CR rate. In addition to the CR rate, the 95% confidence interval for CR rate based on the binomial distribution (Clopper-Pearson exact method) will be provided. The disease assessment collected after the post-treatment therapy will be excluded.

8.1.2 CRh Rate

CRh (Complete remission with partial hematologic recovery) is a derived response based on bone marrow blast and hematology lab values. A Subject achieves a CRh when meeting the following criteria:

- Bone marrow with < 5% blasts and
- Peripheral blood neutrophil count of $> 0.5 \times 10^3/\mu L$ and
- Peripheral blood platelet count of $> 0.5 \times 10^5/\mu L$ and
- A 1 week ($\geq$ 7 days) platelet transfusion-free period prior to the hematology lab collection.

For a bone marrow sample collected before the last cycle of study treatment, the hematology lab results collected from the date of the bone marrow sample collection up to the Day 1 of a subsequent cycle of study treatment will be used for CRh analysis.

For a bone marrow sample collected during or after the last cycle of study treatment, the hematology lab results collected within 14 days after bone marrow sample collection date will be used for CRh analysis.

CRh rate will be defined as the proportion of subjects who achieve CRh as the best response at any time point during the study. Subjects who never achieve CRh or have not had disease assessment or hematology data will be considered to be non-responders in the calculation of CRh rate. In addition to the CRh rate, the 95% confidence interval for CRh rate based on the binomial distribution (Clopper-Pearson exact method) will be provided. The disease assessment collected after the post-treatment therapy will be excluded for above analyses.

8.1.3 CR + CRh Rate

CR + CRh rate will be defined as the proportion of subjects who achieve CR or CRh at any time point during the study. Subjects who never achieve CR/CRh or have no disease assessment will be considered to be non-responders in the calculation of CR + CRh rate. In addition to the CR + CRh rate, the 95% confidence interval for CR + CRh rate based on the binomial distribution (Clopper-Pearson exact method) will be provided.

The time to the 1st response of CR + CRh is defined as number of days from the 1st date of study drug to the 1st response of CR + CRh. The time to the best response of CR + CRh is defined as number of days from the 1st date of study drug to the 1st date of best response of CR + CRh.

The medians and ranges of time to the 1st response of CR + CRh and time to the best response of CR + CRh for all subjects, as well as for subjects with best response CR or best response of CRh will be summarized.

The disease assessment collected after the post-treatment therapy will be excluded for above analyses.

8.1.4 CR + CRh Rate by Initiation of Cycle 2

CR + CRh rate by initiation of Cycle 2 will be defined as the proportion of subjects who achieve CR or CRh by initiation of Cycle 2 of study treatment. Subjects who never achieve CR or CRh or have not had disease assessment by initiation of Cycle 2 will be

considered to be non-responders in the calculation of CR + CRh rate by initiation of Cycle 2. In addition to the CR + CRh rate by initiation of Cycle 2, the 95% confidence interval for CR + CRh rate by initiation of Cycle 2 based on the binomial distribution (Clopper-Pearson exact method) will be provided.

The disease assessment collected after the post-treatment therapy will be excluded for above analysis.

8.1.5 Duration of CR

Duration of CR is defined as number of days from date that subject achieved CR to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. If a subject is still responding at the data cutoff date, then the subject's data will be censored. The disease assessment data after the onset of any post-treatment therapy will not be included in the duration of CR analysis. The detailed censoring rule is described in Table 4. For each analysis dataset, the distribution of duration of CR will be estimated using Kaplan-Meier methodology. Median duration of CR with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

Table 4. Event/Censor and Corresponding Event/Censor Time for Duration of CR or CR + CRh

Situation	Event/Censor	Event Time/Censor Time
IWG disease progression (PD) or Clinical disease progression (CPD) on or prior to any post-treatment therapy and data cutoff date, whichever is earliest	Event	Earliest PD date
Death due to disease progression on or prior to data cutoff date regardless whether it occurred after any new post-treatment	Event	Death date
Neither PD nor CPD nor Death due to disease progression and without post-treatment therapy on or prior to the data cutoff date	Censor	Last disease assessment date (bone marrow or hematology lab collection date) on or prior to the data cutoff date
Neither PD nor CPD nor Death due to disease progression but having post-treatment therapy on or prior to the data cutoff date	Censor	Start of post-treatment therapy

8.1.6 Duration of CR + CRh

Duration of CR + CRh is defined as number of days from date that subject achieved CR + CRh to the first date of relapse, clinical disease progression or death due to disease progression, whichever occurred earliest. If a subject is still responding at the data cutoff date, then the subject's data will be censored. The disease assessment data after the onset of any post-treatment therapy will not be included in the duration of CR + CRh analysis. The detailed censoring rule is described in Table 4. For each analysis dataset, the distribution of duration of CR + CRh will be estimated using Kaplan-Meier methodology. Median duration of CR + CRh with the corresponding 95% CI will be provided from Kaplan-Meier estimation. Duration of CR + CRh will be summarized for all subjects, subjects achieving CR, and subjects achieving CRh.

8.1.7 Overall Survival (OS)

Time to death for a given subject will be defined as the number of days from the date of first dose of study drug to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died on or before the "Cutoff" date, and there is any data (survival follow-up, study visit, death date, etc.) confirming that the subject is still alive or dies after the "Cutoff" date, the data will be censored at the "Cutoff" date; otherwise the data will be censored at the date when the subject was last known to be alive.

For each analysis datasets, the distribution of OS will be estimated using Kaplan-Meier methodology. Median survival time with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

OS will be summarized for all subjects, subjects achieving CR, subjects achieving CRh, and non-CR/non-CRh subjects.

8.1.8 Post Baseline Transfusion Independence Rate (RBC/Platelet) and Duration of Post Baseline Transfusion Independence

The transfusion data was designed to be collected during the treatment period and until the 30 day follow-up visit. Therefore, the evaluation period for the post baseline transfusion independence is from the first dose of study drug to the last dose of study drug + 30 days, disease progression (including clinical progression), or death, whichever is earlier. Thus, post baseline transfusion independence is defined as a period of at least 56 days (≥ 56 days) with no RBC or platelet transfusion during the evaluation period.

Post baseline transfusion independence rate will be estimated as the proportion of subjects known to achieve transfusion independence during the evaluation period. The corresponding 95% CI for transfusion independence rate will be provided based on the binomial distribution (Clopper-Pearson exact method).

In addition, the baseline transfusion independence rate, which is defined as the proportion of subjects who received no transfusion within 56 days prior to the first dose of study drug (Studies M14-358 and M14-387) or 28 days (Study M14-212) prior to the first dose of study drug, will also be summarized. An analysis based on the definition of baseline transfusion independence as 28 days on or prior to the first dose of study drug will also be performed for all studies.

Number and percentage of subjects who were transfusion dependent at baseline and then become transfusion independent during the evaluation period will be provided. Number and percentage of subjects who were transfusion-independent at baseline and remain transfusion-independent during the evaluation period will also be provided.

In addition to the transfusion independence rate, the duration of transfusion independence will also be summarized. The duration of transfusion independence is defined as the 1st time period that a subject receives no RBC/platelet transfusions for at least 56 days during the evaluation period. The descriptive statistics (median and range) will be provided for duration of transfusion independence.

All transfusion data available in the extracted database will be used in the analyses of transfusion independence rate and duration of transfusion independence. The above analyses will also be performed separately for

- RBC transfusion
- Platelet transfusion.

8.1.9 Time to the First Event

For each analysis set, the distribution of time to event for each parameter described in below sections will be estimated using Kaplan-Meier methodology. Median time to the first event for each parameter listed below with the corresponding 95% CI will be provided from Kaplan-Meier estimation. All data available in the extracted database will be used for the analyses described in Section 8.1.9.

8.1.9.1 Transfusion

The transfusion data was designed to be collected during the treatment period and until the 30 day follow-up visit. Thus, the data included in this section is from the first dose date of study drug to the last dose of study drug + 30 days. Transfusion data will be summarized as RBC transfusion and platelet transfusion separately.

Time to 1st RBC/Platelet Transfusion After Achieving CR

Time to 1st RBC/platelet transfusion after achieving CR will be defined as number of days from achieving CR to the first RBC/platelet transfusion. If a subject did not have any RBC/platelet transfusion events, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR will be included in the analysis.

Time to 1st RBC/Platelet Transfusion After Achieving CRh

Time to 1st RBC/platelet transfusion after achieving CRh will be defined as number of days from achieving CRh to the first RBC/platelet transfusion. If a subject did not have any RBC/platelet transfusion events, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CRh will be included in the analysis.

Time to 1st RBC/Platelet Transfusion After Achieving CR/CRh

Time to 1st RBC/platelet transfusion after achieving CR/CRh will be defined as number of days from achieving CR/CRh to the first RBC/platelet transfusion. If a subject did not have any RBC/platelet transfusion, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR/CRh will be included in the analysis.

Time to the 1st RBC/Platelet Transfusion Before Achieving CR

Time to the 1st RBC/platelet transfusion before achieving CR will be defined as number of days from the 1st date of study drug to the 1st RBC/platelet transfusion before achieving CR. If a subject did not have any RBC/platelet transfusion before achieving CR, the subject's data will be censored at the date that CR is first achieved. Only subjects who achieve CR will be included in the analysis.

Time to the 1st RBC/Platelet Transfusion Before Achieving CRh

Time to the 1st RBC/platelet transfusion before achieving CRh will be defined as number of days from the 1st date of study drug to the 1st RBC/platelet transfusion before achieving CRh. If a subject did not have any RBC/platelet transfusion before achieving CRh, the subject's data will be censored at the date that CRh is first achieved. Only subjects who achieve CRh will be included in the analysis.

Time to the 1st RBC/Platelet Transfusion Before Achieving CR/CRh

Time to the 1st RBC/platelet transfusion before achieving CR/CRh will be defined as number of days from the 1st date of study drug to the 1st RBC/platelet transfusion before achieving CR/CRh. If a subject did not have any RBC/platelet transfusion before achieving CR/CRh, the subject's data will be censored at the date that CR/CRh is first achieved. Only subjects who achieve CR/CRh will be included in the analysis.

Time to 1st RBC/Platelet Transfusion from 60 Days After the First Dose of Study Drug

Time to 1st RBC/platelet transfusion from 60 days after the first dose of study drug will be defined as number of days from 60 days after first dose date of study drug to the first RBC/platelet transfusion. If a subject did not have any RBC/platelet transfusion, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to First RBC/Platelet Transfusion from 1st Date of Study Drug

Time to 1st RBC/platelet transfusion from 1st date of study drug will be defined as number of days from first dose date of study drug to the first RBC/platelet transfusion. If a subject did not have any RBC/platelet transfusion, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

8.1.9.2 Time to the First Hospitalization due to SAE

Analyses of adverse events will include only "treatment-emergent" events. "Treatment emergent adverse events" are defined as any adverse events that first occur on or after the date of first dose of study drug and with an onset date no more than 30 days after the last dose date of study drug. Thus, the data included in this section is from first dosing of study drug to last dose date of study drug + 30 days.

Time to 1st Hospitalization After Achieving CR

Time to the 1st hospitalization after achieving CR will be defined as number of days from achieving CR to the first hospitalization. If a subject did not have any hospitalization, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR will be included in the analysis.

Time to 1st Hospitalization After Achieving CRh

Time to the 1st hospitalization after achieving CRh will be defined as number of days from achieving CRh to the first hospitalization. If a subject did not have any hospitalization, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CRh will be included in the analysis.

Time to the 1st Hospitalization After Achieving CR/CRh

Time to the 1st hospitalization from achieving CR/CRh will be defined as number of days from achieving CR/CRh to the 1st hospitalization. If a subject did not have any hospitalization, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR/CRh will be included in the analysis.

Time to the 1st Hospitalization Before Achieving CR

Time to the 1st hospitalization before achieving CR will be defined as number of days from the 1st date of study drug to the 1st hospitalization before achieving CR. If a subject did not have any hospitalization event, the subject's data will be censored at date that CR is first achieved. Subjects who achieve CR will be included in the analysis.

Time to the 1st Hospitalization Before Achieving CRh

Time to the 1st hospitalization before achieving CRh will be defined as number of days from the 1st date of study drug to the 1st hospitalization before achieving CRh. If a subject did not have any hospitalization event, the subject's data will be censored at date that CRh is first achieved. Subjects who achieve CRh will be included in the analysis.

Time to the 1st Hospitalization Before Achieving CR/CRh

Time to the 1st hospitalization before achieving CR/CRh will be defined as number of days from the 1st date of study drug to the 1st hospitalization before achieving CR/CRh. If a subject did not have any hospitalization event, the subject's data will be censored at date that CR/CRh is first achieved. Subjects who achieve CR/CRh will be included in the analysis.

Time to the 1st Hospitalization from 60 Days After the First Dose of Study Drug

Time to the 1st hospitalization from 60 days after the first dose of study drug will be defined as number of days from 60 days after first dose date of study drug to the

1st hospitalization. If a subject did not have any hospitalizations, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to the 1st Hospitalization After 1st Date of Study Drug

Time to the 1st hospitalization after 1st date of study drug will be defined as number of days from first dose date of study drug to the 1st hospitalization. If a subject did not have any hospitalizations, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

8.1.9.3 Time to First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ)

Analyses of adverse events will include only "treatment-emergent" events. "Treatment emergent adverse events" are defined as any adverse events that first occur on or after the date of first dose of study drug and with an onset date no more than 30 days after the last dose date of study drug. Thus, the data included in this section is from first dosing of study drug to last dose date of study drug + 30 days.

Time to First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) from Achieving CR

Time to the first event of Grade 3 or above TEAE of Haemorrhages from achieving CR will be defined as number of days from achieving CR to the first event of Grade 3 or above TEAE of Haemorrhages. If a subject did not have any Grade 3 or above TEAE of Haemorrhages, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR will be included in the analysis.

Time to First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) from Achieving CRh

Time to the first event of Grade 3 or above TEAE of Haemorrhages from achieving CRh will be defined as number of days from achieving CRh to the first event of Grade 3 or above TEAE of Haemorrhages. If a subject did not have any Grade 3 or above TEAE of Haemorrhages, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) from Achieving CR/CRh

Time to the first event of Grade 3 or above TEAE of Haemorrhages from achieving CR/CRh will be defined as number of days from achieving CR/CRh to the first event of Grade 3 or above TEAE of Haemorrhages. If a subject did not have any Grade 3 or above TEAE of Haemorrhages, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR/CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) Before Achieving CR

Time to the 1st first event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ) before achieving CR will be defined as number of days from the 1st date of study drug to the 1st Grade 3 or above haemorrhages event before achieving CR. If a subject did not have any Grade 3 or above TEAE of Haemorrhages (narrow SMQ), the subject's data will be censored at date that CR is first achieved. Subjects who achieve CR will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) Before Achieving CRh

Time to the 1st event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ) before achieving CRh will be defined as number of days from the 1st date of study drug to the 1st Grade 3 or above haemorrhages event before achieving CRh. If a subject did not have any Grade 3 or above TEAE of Haemorrhages (narrow SMQ), the subject's data will be censored at date that CRh is first achieved. Subjects who achieve CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) Before Achieving CR/CRh

Time to the 1st event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ) before achieving CR/CRh will be defined as number of days from the 1st date of study drug to the 1st Grade 3 or above Haemorrhage event before achieving CR/CRh. If a subject did not have any Grade 3 or above TEAE of Haemorrhages (narrow SMQ), the subject's data will be censored at date that CR/CRh is first achieved. Subjects who achieve CR/CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) from 60 Days After the First Dose of Study Drug

Time to the first event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ) from 60 days after the first dose of study drug will be defined as number of days from 60 days after first dose date of study drug to the first event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ). If a subject did not have any events of Grade 3 or above TEAE of Haemorrhages (narrow SMQ), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to the First Event of Grade 3 or Above TEAE of Haemorrhages (Narrow SMQ) from the First Dose of Study Drug

Time to the first event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ) from first dose of study drug will be defined as number of days from first dose date of study drug to the first event of Grade 3 or above TEAE of Haemorrhages (narrow SMQ). If a subject did not have any events of Grade 3 or above TEAE of Haemorrhages (narrow SMQ), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to 1st serious Haemorrhages (narrow SMQ) will be performed using the same method if data is available.

8.1.9.4 Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC)

Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) from Achieving CR

Time to the first event of Grade 3 or above TEAE of infections/infestations (SOC) from achieving CR will be defined as number of days from achieving CR to the first event of Grade 3 or above TEAE of infections/infestations (SOC). If a subject did not have any Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR will be included in the analysis.

Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) from Achieving CRh

Time to the first event of Grade 3 or above TEAE of infections/infestations (SOC) from achieving CRh will be defined as number of days from achieving CRh to the first event of Grade 3 or above TEAE of infections/infestations (SOC). If a subject did not have any

Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CRh will be included in the analysis.

Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) from Achieving CR/CRh

Time to the first event of Grade 3 or above TEAE of infections/infestations (SOC) from achieving CR/CRh will be defined as number of days from achieving CR/CRh to the first event of Grade 3 or above TEAE of infections/infestations (SOC). If a subject did not have any Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Subjects who achieve CR/CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) Before Achieving CR

Time to the 1st first event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CR will be defined as number of days from the 1st date of study drug to the 1st event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CR. If a subject did not have any Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at date that CR is first achieved. Subjects who achieve CR will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) Before Achieving CRh

Time to the 1st event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CR will be defined as number of days from the 1st date of study drug to the 1st event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CRh. If a subject did not have any Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at date that CRh is first achieved. Subjects who achieve CRh will be included in the analysis.

Time to the First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) Before Achieving CR/CRh

Time to the 1st event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CR/CRh will be defined as number of days from the 1st date of study drug to the 1st event of Grade 3 or above TEAE of infections/infestations (SOC) before achieving CR/CRh. If a subject did not have any Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at date that CR/CRh is first achieved. Subjects who achieve CR/CRh will be included in the analysis.

Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) from 60 Days After the First Dose of Study Drug

Time to the first event of Grade 3 or above TEAE of infections/infestations (SOC) from 60 days after the first dose of study drug will be defined as number of days from 60 days after first dose date of study drug to the first event of Grade 3 or above TEAE of infections/infestations (SOC) during the treatment period. If a subject did not have any events of Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to First Event of Grade 3 or Above TEAE of Infections/Infestations (SOC) from the First Dose of Study Drug

Time to the first event of Grade 3 or above TEAE of infections/infestations (SOC) from first dose of study drug will be defined as number of days from first dose date of study drug to the first event of Grade 3 or above TEAE of infections/infestations (SOC). If a subject did not have any events of Grade 3 or above TEAE of infections/infestations (SOC), the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. This analysis will be performed for subjects who achieve CR, achieve CR/CRh, and don't achieve CR or CRh separately.

Time to 1st serious infections/infestations (SOC) will be performed using the same method if data is available.

8.1.10 Time to the 1st Recurrent Transfusion Event from the 1st Transfusion Event

Transfusion data will be summarized by RBC transfusion and platelet transfusion separately.

Time to 1st Recurrent RBC/Platelet Transfusion from the 1st Transfusion After Achieving CR

Time to 1st recurrent RBC/platelet transfusion from the 1st transfusion after achieving CR will be defined as number of days from the 1st transfusion after achieving CR to the first recurrent RBC/platelet transfusion. If a subject only has one RBC/platelet transfusion after achieving CR, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Only subjects with best response CR with at least one subsequent transfusion will be included in the analysis.

Time to 1st Recurrent RBC/Platelet Transfusion from the 1st Transfusion After Achieving CRh

Time to 1st recurrent RBC/platelet transfusion from the 1st transfusion after achieving CRh will be defined as number of days from the 1st transfusion after achieving CRh to the first recurrent RBC/platelet transfusion. If a subject only has one RBC/platelet transfusion after achieving CRh, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Only subjects with best response CRh with at least one subsequent transfusion will be included in the analysis.

Time to 1st Recurrent RBC/Platelet Transfusion from the 1st Transfusion After Achieving CR/CRh

Time to 1st recurrent RBC/platelet transfusion from the 1st transfusion after achieving CR/CRh will be defined as number of days from the 1st transfusion after achieving CR/CRh to the first recurrent RBC/platelet transfusion. If a subject only has one RBC/platelet transfusion after achieving CR/CRh, the subject's data will be censored at 30 days after the last dose date of study drug or death of any cause, whichever occurs earlier. Only subjects with best response CR/CRh with at least one subsequent transfusion will be included in the analysis.

Time to 1st Recurrent RBC/Platelet Transfusion from the 1st Transfusion for non-CR/CRh Subjects

Time to 1st recurrent RBC/platelet transfusion from the 1st transfusion will be defined as number of days from the 1st RBC/platelet transfusion to the first recurrent RBC/platelet transfusion. If a subject only has one RBC/platelet transfusion, the subject's data will be censored at last dose of study drug + 30 days or death of any cause, whichever occurs earlier. Only subjects with best response of non-CR/CRh and with at least one subsequent transfusion will be included in the analysis.

8.1.11 Additional Sensitivity Analyses of Efficacy Variables

Duration of Response

Sensitivity analyses for duration of CR + CRh, duration of CRh, and duration of CR will be provided based on different censoring methods.

1. For subjects who had post treatment therapy before disease progression events or death due to disease progression, two methods will be performed:
    - Method 1: this subject data will be censored at the date of last disease assessment before starting post treatment therapy;

- Method 2: this subject's data will be considered as an event at the date of last disease assessment before starting post treatment therapy.

2. For subjects who are lost to follow-up without disease progression or death due to disease progression documented, last disease assessment (bone marrow and hematology lab collations) will be considered as an event.

3. If a disease progression or death due to disease progression event occurred more than 91 days (3 cycles) from the last disease assessment (bone marrow collection or hematology lab collection), this subject will be censored at the date of last disease assessment prior to the disease progression or death due to disease progression event.

Details of the censoring method for sensitivity analyses of duration of response are provided below in Table 5.

Table 5. Censoring Methods for Analyses of CR + CRh, CR, and CRh

Situation	Date of Progression/Date of Censor	Outcome
Post-treatment therapy initiated with no disease progression documented	Date of last disease assessment before initiating post-treatment therapy (bone marrow or hematology lab)	Method 1) Censored
Post-treatment therapy initiated with no disease progression documented	Date of last disease assessment before initiating post-treatment therapy (bone marrow or hematology lab)	Method 2) Event
Loss to follow-up without disease progression or death due to disease progression documented	Date of last disease assessment (bone marrow or hematology lab)	Event
Death or disease progression occurred after missing a scheduled disease assessments (disease progression or Death due to disease progression occurred > 91 days of last disease assessment)	Date of last disease assessment (bone marrow or hematology lab)	Censored

Overall Survival

Sensitivity analyses for OS will be provided based on different censoring methods as shown in Table 6. OS analysis including all deaths collected in the extracted database will also be performed.

Table 6. Censoring Methods for Analyses of OS

Situation	Date of Progression/Date of Censor	Outcome
Withdrawal consent for survival follow-up	Last known alive date	Event
Post-treatment therapy	Start date of post-treatment therapy	Censored

8.1.12 Exploratory Analysis of MRD Data

The MRD data is collected at baseline, the end of Cycle 1, and every 3 cycles thereafter when bone marrow is collected in Study M14-358 and Study M14-387. The MRD data collected after the first dose of study drug to the last dose of study drug + 7 days, disease progression, clinical progression, the start of new post-treatment therapy, death, or cutoff date, whichever occurs earlier, will be included in the post-baseline MRD analyses.

The MRD analyses include MRD records meeting the following criteria:

1. CD45 value ≥ 100,000 and MRD value < 0.1%; or
2. MRD value ≥ 0.1%.

Zero is imputed if MRD value is 'less than LLoQ.' Missing MRD is assigned if MRD value is 'too few CD45+ cell.'

The best post-baseline MRD (the lowest) value will be defined as the smallest MRD collected after the first dose of study drug to the last dose of study drug + 7 days, disease progression, clinical progression, the start of new post-treatment therapy, death, or cutoff date, whichever occurs earlier. The median and range will be presented for subjects who

achieved CR, CR + CRh or CR + CRi. The best MRD value will also be categorized to three groups < 0.1%, ≥ 0.1%, and Unknown/Missing MRD value. The summary of the best MRD value will be performed among subjects who achieved CR, CR + CRh, or CR + CRi.

OS will also be summarized by the best MRD value (< 0.1%, ≥ 0.1%, Unknown/Missing if any) for subjects achieved CR + CRh or CR + CRi. Median survival time with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

OS will also be summarized by the best MRD value (< 1%, ≥ 1%, Unknown/Missing if any) for subjects achieved CR + CRh or CR + CRi. Median survival time with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

Duration of CR + CRh will also be summarized by the best MRD value (< 0.1%, ≥ 0.1%, Unknown/Missing if any) for subjects achieved CR + CRh. Median duration of CR + CRh with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

Duration of CR + CRi will also be summarized by the best MRD value (< 0.1%, ≥ 0.1%, Unknown/Missing if any) for subjects achieved CR + CRi. Median duration of CR + CRi with the corresponding 95% CI will be provided from Kaplan-Meier estimation.

8.1.13 Subgroup Assessment of Efficacy Variables

The subgroup analyses will be performed for Studies M14-358 and M14-387 including the following treatment groups.

Study M14-358:

1. overall of venetoclax + azacitidine (N = 127)
2. venetoclax 400 mg + azacitidine (N = 84)
3. overall of venetoclax + decitabine (N = 73)

Study M14-387:

1. venetoclax 600 mg QD + LDAC or venetoclax 800 mg QD + LDAC (N = 92)
2. venetoclax 600 mg QD + LDAC (N = 82)
3. venetoclax 600 mg QD + LDAC and without MPN (N = 78).

No subgroup analyses will be performed for Study M14-212 due to relative small number of patients in this study.

CR rate, CR + CRh rate, post-baseline transfusion independence rate, duration of CR, duration of CR + CRh, and OS will be assessed for the subgroups within each treatment group as defined below.

- Gender (Male, Female)
- Age (< 75 years, ≥ 75 years)
- By modified Ferrara Criteria (Y, N)
- By Cytogenetics (Intermediate risk, poor risk)
- Type of AML (primary, secondary)
- AML MDS related changes (Yes, No)
- Prior HMA use (Yes, No) (only for Study M14-387)
- Biomarker mutation (TP53, FLT3, IDR1/2, NPM1)
- Moderate/Strong CYP3A inhibitors (Y, N)

In addition, number of percentage of CR/CRh subjects went on post-treatment therapy will be summarized.

9.0 Sample Size

For the non-randomized Phase 1/2 Studies M14-358 and M14-387, there is no formal statistical testing and study-wise sample size justification planned. Sample size justification for the Expansion 1 and Expansion 2 cohorts of Study M14-358 based on

CR + CRi rate and the Phase 2 portion of Study M14-387 based on ORR rate can be found in each study protocol. The full analysis set of Study M14-358 and Study M14-387 includes both dose escalation and dose expansion. The sample size justification using CR rates at the recommended Phase 2 venetoclax dose level for Study M14-358 and Study M14-387 and historical CR rates are summarized in Table 7.

Table 7. Sample Size Justification

	N	Targeted CR Rate (95% CI)	Historical CR Rate of LDAC Alone (%)[1]	Historical CR Rate of AZA Alone (%)[1]	Historical CR Rate of DEC Alone (%)[2]
Study M14-387 venetoclax 600 mg QD + LDAC	82	21% (13%, 31%)	7.9%	NA	NA
Study M14-358 venetoclax 400 mg QD + AZA	84	36% (27%, 48%)	NA	19.5%	NA
Study M14-358 venetoclax 400 mg QD + DEC	31	39% (22%, 58%)	NA	NA	15.7%

Based on the enrolled sample sizes in Studies M14-358 and M14-387, the lower limit of the 95% confidence intervals for the target CR rates are higher than the historical CR rates from previously conducted clinical trials of azacitidine, decitabine and LDAC, and represent a clinically meaningful improvement for subjects.

10.0 References

1. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. Blood. 2015;126(3):291-9.
2. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients

with newly diagnosed acute myeloid leukaemia. J Clin Oncol. 2012;30(21):2670-7.

1.0 Title Page

Safety Statistical Analysis Plan

Study M14-212

Study M14-358

Study M14-387

Venetoclax (ABT-199/GDC-0199) in Combination with LDAC (low dose Cytarabine) or HMA (Azacitidine and Decitabine) for the Treatment Subjects with Acute Myeloid Leukemia

Date: 21 Dec 2018

Version 3.0

2.0 Table of Contents

List of Tables

2.1 Summary of Versions

Version	Date of Completion	Summary
1.0	13 Dec 2017	First version (Appendix of Briefing Book of FDA Type C Meeting)
2.0	04 May 2018	Final version for Interim 1 CSR
3.0	27 Nov 2018	Update MEDDRA version for Interim 2 CSR

2.2 List of Abbreviations and Definitions of Terms

AE	Adverse event
AESI	Adverse Event of Special Interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AML	Acute Myeloid leukemia
AST	Aspartate aminotransferase
HMA	Azacitidine or Decitabine
ISS	Integrated summary of safety
LDAC	Low dose cytarabine
MedDRA	Medical dictionary for regulatory activities
MPN	Myeloproliferative neoplasm
NCI	National Cancer Institute
NCI CTC	National Cancer Institute Common Terminology Criteria
PT	Preferred term
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

3.0 Introduction

This safety statistical analysis plan (SAP) covers analyses of safety data from Studies M14-358 (R&D/17/1341), M14-387 (R&D/17/1340), and M14-212 (R&D/15/0200). These analyses will support the safety assessment of venetoclax for AML. Analyses will be performed by personnel from Data and Statistical Sciences at AbbVie or their designees using SAS Version 9.3 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Background

This SAP provides details of statistical analyses that are to be performed for the safety assessment of venetoclax treatment for AML. Safety analyses will be performed to assess the potential effect of venetoclax monotherapy or in combination with hypomethylating agents (HMA) or low dose cytarabine (LDAC) on adverse events (AEs), as well as clinical laboratory measurements and vital signs.

5.0 Studies Included

All AbbVie sponsored venetoclax AML studies to be included are described below in Table 1. All studies' results will be presented separately. Data will not be pooled across studies.

Table 1. List of Venetoclax Studies to be Included in the Safety Summary

Study ID Phase (Status)	Number of Enrolled Subjects (Actual/Planned)	Location	Study Design	Primary Objective
M14-212 Phase 2 (completed)	32/54	US	Open-label study of venetoclax in adults with relapsed or refractory AML, or untreated AML unfit for intensive therapy	Evaluate the preliminary efficacy of single agent venetoclax.
M14-358 Phase 1b (Enrollment complete and follow-up is ongoing)	212/260	Australia, Germany, France, and US	Open-label study of venetoclax + azacitidine or decitabine in treatment naïve elderly (≥ 60 years) subjects with AML who are not eligible for standard induction therapy; 2 stages: dose escalation and dose expansion	Evaluate the safety, PK, and efficacy of venetoclax + decitabine or azacitidine in the target population. The objective of the safety expansion is to confirm efficacy and safety of the intended dose for Phase 3 study.
M14-387 Phase 1/2 (Enrollment complete and follow-up is ongoing)	92/94	Australia, Germany, Italy, US	Open-label study of venetoclax + LDAC in treatment naïve subjects with AML who are ≥ 60 years of age and who are not eligible for standard anthracycline-based induction therapy; 2 stages: dose escalation and safety expansion	Phase 1: Evaluate the safety, PK and determine the MTD and RPTD of venetoclax + LDAC. Phase 2: Estimate efficacy, including ORR, and characterize the toxicity of the combination at the RPTD. Cohort C: Evaluate the ORR for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated.

The venetoclax doses and regimens in the studies listed in Table 1 are described in Table 2 below.

Table 2. Regimens Investigated in Venetoclax AML Studies

Study ID	Venetoclax Dose and Frequency	Treatment Regimen
M14-212	Venetoclax ***400*** mg QD, ***800*** mg QD, ***1200*** mg QD	Venetoclax monotherapy
M14-358	Venetoclax ***400*** mg QD, ***800*** mg QD, ***1200*** mg QD	Venetoclax in combination with HMA (Azacitidine or Decitabine)
M14-387	Venetoclax ***600*** mg QD, ***800*** mg QD	Venetoclax in combination LDAC (Low dose cytarabine)

6.0 Analysis Sets

6.1 Definition of Analysis Sets

Each of the three studies will represent a separate analysis set as detailed in Table 3 below. No pooled analysis sets are defined.

Table 3. Definition of the Analysis Sets

Analysis Data Sets	Study Included	Study Population
1. Monotherapy	M14-212	Subjects who received at least one dose of venetoclax
2. Venetoclax in combination with HMA	M14-358	Subjects who received at least one dose of venetoclax
3. Venetoclax in combination with LDAC	M14-387	Subjects who received at least one dose of venetoclax

6.2 Rationale for Analysis Sets

The reason for not pooling the Studies M14-212, M14-358, and M14-387 is that the different treatment regimens (venetoclax monotherapy, venetoclax in combination with HMA, venetoclax in combination with LDAC) are expected to have different safety

profiles. Thus, it is not appropriate to pool data across these studies to assess the safety of venetoclax in combination with HMA or venetoclax in combination with LDAC.

1) Monotherapy Analysis Set

This analysis set includes AML subjects who have been treated with venetoclax in Study M14-212. This analysis dataset will be used to provide a comprehensive summary of safety of venetoclax monotherapy in AML subjects. Safety summaries will be presented for all subjects (N = 32).

2) Venetoclax in Combination with HMA Analysis Set

This analysis set includes subjects who received at least one dose of venetoclax in Study M14-358. This analysis dataset will be used to provide a comprehensive summary of safety of venetoclax in combination with HMA (azacitidine 75 mg/m^2 or decitabine 20 mg/m^2). Safety summaries will be presented for the following nine groups:

1. venetoclax 400 mg QD + azacitidine (N = 84);
2. venetoclax 800 mg QD + azacitidine (N = 37);
3. venetoclax 1200 mg QD + azacitidine (N = 6);
4. overall of venetoclax + azacitidine (N = 127);
5. venetoclax 400 mg QD + decitabine (N = 31);
6. venetoclax 800 mg QD + decitabine (N = 37);
7. venetoclax 1200 mg QD + decitabine (N = 5);
8. overall of venetoclax + decitabine (N = 73);
9. DDI (drug-drug interaction) venetoclax 400 mg QD (N = 12).

3) Venetoclax in Combination with LDAC Analysis Set

This analysis set includes subjects who received at least one dose of venetoclax in Study M14-387. This analysis dataset will be used to provide a comprehensive summary of safety of venetoclax in combination with LDAC (20 mg/m^2 subcutaneously given Days 1 – 10). Patients with an antecedent history of myeloproliferative neoplasm (MPN) including polycythemia vera, myelofibrosis, essential thrombocythemia, or chronic myelogenous leukemia were excluded from the study in Study M14-387 Protocol Amendment 2 because emerging evidence suggested that patients with JAK2 mutated MPN may not benefit from treatment with venetoclax in combination with LDAC. To explore the safety of venetoclax in combination with LDAC both including and excluding those patients with a history of MPN, safety summaries will be presented for the following three groups:

1. All subjects (N = 92)
2. venetoclax 600 mg QD (N = 82)
3. venetoclax 600 mg QD without MPN (N = 78).

7.0 Statistical Methods

The methods described here apply to the analysis on the analysis sets described in Section 6.2.

7.1 Analysis Conventions

All data available in the extracted database will be used in the safety analyses.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to

- Venetoclax (Study M14-212)
- Venetoclax and HMA (Study M14-358)

- Venetoclax and LDAC (Study M14-387)

Definition of Baseline

All baseline summary statistics and analyses will be based on characteristics prior to the initiation of any component of study drug. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of any component of study drug.

Definition of Study Day

Study Day is defined as the number of days since (positive numbers) or prior to (negative numbers) the first dose of study drug. 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 defined as Study Day –1; there is no Study Day 0.

Definition of Final Observation

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

7.2 Subject Disposition

The number and percentage of subjects will be provided for analysis data sets 2 – 3 specified in Table 3 for the following summaries. The summary of subject disposition for Study M14-212 is in study CSR.

- Subjects by country
- Subjects discontinued for each reported primary reason (e.g., due to AE, due to disease progression, due to withdrew consent, etc.).

7.3 Study Drug Exposure

Exposure to venetoclax will be characterized in the following ways for summarization:

- Treatment duration: time from the first dose to the last dose of study drug (days)
- Treatment cycle: number of cycles that subjects are exposed to venetoclax
- Dose Intensity due to reduction: the ratio of actual total venetoclax dose and the planned total venetoclax. Days without venetoclax are not included in the planned total venetoclax dose.
- Dose Intensity due to reduction and interruption: the ratio of actual total venetoclax dose and the planned total venetoclax dose in the time period between first dose of venetoclax to the last dose of venetoclax. Days without venetoclax are included in the planned total venetoclax dose.

Dose intensity is also summarized for subjects who are moderate or strong CYP3A inhibitor users. The moderate or strong CYP3A inhibitor users are defined as subjects who take moderate or strong CYP3A inhibitors with venetoclax for a period with at least 7 days.

Exposure to LDAC and HMA will be characterized in the following ways for summarization:

- Treatment cycle: The number of cycles that subjects are exposed to LDAC or HMA

7.4 Demographics and Baseline Disease Related Characteristics

The following demographics and baseline disease related characteristics will be summarized for Analysis Data Sets 1 – 3 specified in Table 3.

Demographics:

- Gender (Male, Female)
- Age (< 75 years, ≥ 75 years)
- Race (White, Non-white)

- Weight (< 75 kg, ≥ kg)
- Region (US and Non-US)

Baseline and Disease-Related Characteristics:

	Study M14-212	Study M14-358	Study M14-387
Baseline Bone Marrow Blast (%) (mean, SD, median, range)	√	√	√
Baseline Bone Marrow Blast (< 30%, 30 – 50%, ≥ 50%)	√	√	√
ECOG Performance Status (0, 1, 2, 3)	√	√	√
Subjects with secondary AML (Yes, No)		√	√
Cytogenetics (Intermediate, Poor)		√	√
AML Disease Type (Primary, Secondary)		√	√
Subjects receiving prior HMA for MDS (Yes, No)		N/A	√
Antecedent hematologic history (Yes, No)		√	√
History of oncological surgery (Yes, No)		√	√
Prior oncological therapy (Yes, No)		√	√
History of radiation therapy (Yes, No)		√	√
Transfusion independence at baseline (Yes, No)		√	√
Prior MPN (Yes, No)		√	√
Prior Hydoxyurea Use (Yes, No)		√	√
Fulfilling Modified Ferrara Criteria (Yes, No)		√	√
Comorbidities (Yes, No) if data is available		√	√

For demographic and baseline characteristics: categorical data will be summarized with the number of subjects and corresponding percentage – the number and percentage of subjects with missing information will also be summarized; continuous data will be summarized with sample size, mean, standard deviation, median, and range.

7.5 Prior and Concomitant Medications

Prior medications include all medications administered prior to the first dose of study drug. Concomitant medications include all medications administered (started treatment or continued treatment) during the treatment period defined as the day of the first dose of study drug through the day of the final dose of study drug.

The number and percentage of subjects that received at least one concomitant medication ("Any Concomitant Medication") will be summarized. Additionally, the number and percentage of subjects who received concomitant medications will be summarized by the World Health Organization (WHO) generic drug names according to the WHO-DRUG dictionary. Similar summaries will be presented for prior medications.

For summaries of concomitant medications, if an incomplete start date was collected for a medication, the medication will be assumed to be a concomitant medication unless there is evidence that confirms that the medication was not a concomitant medication (e.g., the medication end date was prior to the first dose of study drug).

A subject who reports the use of two or more medications 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. Similar rules apply to prior medications as well.

Concomitant medications will be summarized for analysis data sets 2 – 3 specified in Table 3. The summary for prior and concomitant medications of Study M14-212 is in study CSR.

In addition, post-treatment therapy will be summarized for analysis data sets 2 – 3.

7.6 Adverse Events

All summaries/analyses involving AEs will include treatment-emergent AEs (TEAE) only, unless otherwise specified. TEAEs are defined as any event with onset or worsening after the first dose of study drug and no more than 30 days after the last dose of

study drug. If an incomplete onset date was collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of study drug).

All adverse event summaries will be summarized for analysis sets 2 – 3 specified in Table 3.

7.6.1 Analysis of Treatment Emergent Adverse Events

Adverse event data will be summarized using system organ classes (SOCs) and preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or later for Studies M14-358 and M14-387. Adverse events were coded and summarized in MedDRA Version 18.1 for the Study M14-212 CSR.

For each AE summary, the number and percentage of subjects experiencing at least one AE will be presented (overall) for each dosing group. Subjects reporting more than one AE within a SOC will be counted only once for that SOC. Subjects reporting more than one AE for a PT will be counted only once for that PT.

For summaries of AEs by the National Cancer Institute Common Toxicity Criteria (NCI CTC) grade, at each level of summation (overall, SOC, and PT) each subject is counted only once at the maximum grade level. The number and percentage of subjects experiencing at least one event for each of the following events will be summarized (but not limited to):

- Any TEAE.
- Any TEAE with reasonable possibility related to venetoclax by the investigator.
- Any TEAE with NCI toxicity (CTCAE V4.0) Grade 3, 4, or 5 adverse events.
- Any TEAE with NCI toxicity (CTCAE V4.0) Grade 3 or 4 adverse event.
- Any treatment-emergent serious AE (SAE).
- Any TEAE leading to discontinuation of venetoclax.

- Any TEAE leading to venetoclax dose interruption.
- Any TEAE leading to venetoclax dose reduction.
- Any TEAE leading to hospitalizations.
- Any TEAE of special interest (AESI) (Section 7.6.2).
- Any TEAE leading to death.
- Any TEAE with reasonable possibility related to HMA (Study M14-358) or LDAC (Study M14-387) by the investigator.
- Any TEAE leading to discontinuation of HMA (Study M14-358) or LDAC (Study M14-387).
- Any TEAE leading to HMA (Study M14-358) or LDAC (Study M14-387) dose interruption.
- Any TEAE leading to HMA (Study M14-358) or LDAC (Study M14-387) dose reduction.

7.6.2 Selected Treatment-Emergent Adverse Events

The selected TEAEs will be summarized by following the search criteria Table 4.

Table 4. Selected Adverse Events

Selected Adverse Events	Search Criteria
Tumor Lysis Syndrome (AE)	SMQ – "Tumor Lysis Syndrome" (narrow)
Grade ≥ 3 neutropenia	PT terms – "neutropenia," "neutrophil count decreased," "febrile neutropenia," "agranulocytosis," "neutropenic infection," and "neutropenic sepsis"
Grade ≥ 3 infection, including opportunistic infections	SOC of "infections and infestations"
Haemorrhages (SMQ)	SMQ – "Haemorrhages" (narrow)

AE = adverse events; PT = preferred term; SMQ = Standardised MedDRA Query; SOC = system organ class

7.6.3 Hospitalization Due to Serious Adverse Events

Hospitalization due to serious adverse events will be summarized for analysis data set 2 – 3. The number of days of hospitalization during the treatment period will be

summarized with descriptive statistics. The treatment period is defined as from the first date of study drug to 30 days after last date of study drug. This analysis will be performed for analysis dataset 2 – 3.

7.6.4 Transfusion During the Treatment Period

Transfusion during the treatment period will be summarized for analysis dataset 1 – 3. The number of transfusions for each type of transfusion (RBC and Platelet) during the treatment period will be summarized with descriptive statistics.

7.6.5 Subgroup Assessment of Adverse Events for Overall Treatment Groups

TEAE, grade 3 or above TEAEs, and SAEs, will be assessed for the subgroups defined below in analysis datasets 2 – 3.

- Gender (Male, Female)
- Age (< 75 years, ≥ 75 years)
- Race (White, Non-white)
- Geographic region (US, Non-US)
- Best response (CR, CRh, CR/CRh, non-CR/CRh)
- Baseline Weight (< 75 kg, ≥ 75 kg)
- Baseline Renal Function (Normal, Mild impairment, Moderate impairment, sever impairment)
- Baseline Hepatic Function (Normal, Mild impairment, Moderate impairment, sever impairment)
- Moderate or Strong CYP3A inhibitors Users during treatment period

Study M14-358:

1. overall of venetoclax + azacitidine (N = 127);
2. venetoclax 400 mg QD + azacitidine (N = 84);
3. overall of venetoclax + decitabine (N = 73);

Study M14-387:

1. All subjects venetoclax 600 mg QD + LDAC or venetoclax 800 mg QD + LDAC (N = 92)
2. venetoclax 600 mg QD + LDAC (N = 82)
3. venetoclax 600 mg QD + LDAC and without MPN (N = 78).

7.7 Laboratory Parameters

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses. All values will be assessed based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 4.0). The highest grade will be used if lab results are collected on the same date.

All laboratory parameters will be summarized for analysis sets 2 – 3 specified in Table 3. The laboratory parameters summaries for Study M14-212 are available in the CSR.

7.7.1 Assessment of Shifts from Baseline in Clinical Laboratory Parameters

For shifts relative to NCI CTCAE grading, baseline and post-baseline laboratory observations will be categorized as Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4 according to NCI CTCAE grade version 4.0. For each parameter, 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 final observations of Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. Additionally, for each parameter, the number and percentage of subjects that have a baseline observation that is categorized as a Grade 0 to Grade 2 and have a Grade 3 or 4 final observations will be presented. In addition to the final observation, a similar summary will be produced for the maximum post-baseline NCI CTCAE grade.

7.7.2 Laboratory Abnormalities

Abnormal laboratory values will be summarized by following the search criteria in Table 5.

Table 5. Laboratory Abnormalities

Laboratory Abnormalities	Search Criteria
Tumor Lysis Syndrome (Howard Criteria) (Howard SC et al. 2011)	≥ 2 of the following metabolic abnormalities within 24 hours of each other (applicable to post-dose laboratory values only): Uric Acid > 476 µmol/L or 8.0 mg/dL; Potassium > 6.0 mmol/L; Inorganic Phosphorus > 1.5 mmol/L or 4.5 mg/dl; corrected Calcium < 1.75 mmol/L or 7.0 mg/dl
Potential Drug-Induced Liver Injury	Post-dose laboratory ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN that occur within 72 hours of each other

ALT = alanine aminotransferase; AST = aspartate aminotransferase; L = litre; µmol = micromole; mg/dL = milligram/deciliter; mmol = millimole; mEq = milliequivalent; ULN = upper limit of normal

7.7.3 Subgroup Assessment of Shifts from Baseline in Clinical Laboratory

Shifts from baseline Grade 0 – 2 to post baseline Grade 3 – 4 for the maximum grade in clinical laboratory variables will be assessed for the subgroups defined below:

- Gender (Male, Female)
- Age (< 75 years, ≥ 75 years)
- Race (White, Non-White)
- Region (US, Non-US)

Study M14-358:

1. overall of venetoclax + azacitidine (N = 127);
2. venetoclax 400 mg QD + azacitidine (N = 84);
3. overall of venetoclax + decitabine (N = 73).

Study M14-387:

1. All subjects venetoclax 600 mg QD + LDAC or venetoclax 800 mg QD + LDAC (N = 92)
2. venetoclax 600 mg QD + LDAC (N = 82)
3. venetoclax 600 mg QD + LDAC and without MPN (N = 78).

7.8 Vital Signs Parameter

The vital sign variables that will be assessed are systolic blood pressure, diastolic blood pressure, pulse and temperature. All vital sign summaries will be summarized for analysis sets 2 – 3 specified in Table 3. The vital signs variables summary for Study M14-212 is in study CSR.

7.8.1 Assessment of Potentially Clinically Significant Vital Signs Parameters

For selected vital signs parameters, a listing of all observations collected will be generated for subjects that had at least one post-baseline observation meeting pre-defined criteria for potentially clinically significant values. The number and percentage of subjects in each treatment group who have at least one post-baseline observation meeting the pre-defined criteria for potentially clinically significant values will be provided for each variable.

Pre-defined criteria for potentially clinically significant vital signs parameters are given in Table 6 below:

Table 6. Criteria for Potentially Clinically Significant Vital Signs Parameters

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart Rate	Low	Value ≤ 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value ≤ 36°C
	High	Value ≥ 38.5°C