1.0 Title Page

Clinical Study Protocol M15-656

A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy

Incorporating Amendments 1, 2, 2.01 (China Only), 3, 4, 5, 6, 7, and 8

AbbVie Investigational Product:	Venetoclax (ABT-199/GDC-0199)
Date:	01 July 2020
Development Phase:	3
Study Design:	This is a randomized, double-blind, placebo controlled, multicenter trial evaluating efficacy and safety of venetoclax in combination with azacitidine versus placebo in combination with azacitidine in treatment naïve subjects with AML who are ≥ 18 years of age and not eligible for standard induction therapy due to age or co-morbidities.
EudraCT Number:	2016-001466-28
Investigator:	Investigator information on file at AbbVie
Sponsor:	AbbVie Inc.
Sponsor/Emergency Contact:	[redacted] MD, FACP Senior Medical Director AbbVie 1 North Waukegan Road North Chicago, IL 60064 Phone: Cell: Fax: Email: Emergency 24 Hour Number: +1 973-784-6402

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	25 October 2016
Amendment 1	21 December 2016
Amendment 2	20 February 2017
Amendment 2.01 (China Only)	29 March 2017
Amendment 3	10 May 2017
Amendment 4	01 March 2018
Amendment 5	08 August 2018
Amendment 6	15 May 2019
Amendment 7	21 August 2019

The purpose of this amendment is to:

- Section 1.2 Synopsis and Section 5.1 Overall Study Design and Plan, update number of subjects enrolled to 443.

  Rationale: *To update the actual number of subjects enrolled on the study.*
- Update Section 1.2, Synopsis and Section 5.1.3, Treatment Period, text updated to clarify that subjects will continue to receive assigned study drug without cross over until discontinuation and to clarify that disease assessment will no longer be reviewed by IRC following the 75% OS interim analysis.

  Rationale: *The study has met its primary endpoints of overall survival based on the 75% OS interim analysis and response rates based on the previously performed interim analysis for CR/CRi.*
- Updates made throughout the protocol and Appendix C to incorporate necessary protocol modifications due to the COVID-19 pandemic.

  Rationale: *To allow flexibility for subject treatment during the COVID-19 pandemic*
- Update Section 5.1.4 Post Treatment Follow-Up, update to survival and post treatment follow up language.

Rationale: *To allow for more frequent assessment of subjects's survival status and post treatment follow up and clarify the Survival and Post Treatment Follow-up period.*

- Update Section 5.3.1.1 Study Procedures, sub-section Bone Marrow Aspirate and Biopsy for Disease Assessment update text to indicate that the IRC would no longer be completing disease assessments.

  Rationale: *To clarify that disease assessments would not be completed by the IRC following the 75% OS interim analysis.*

- Update Section 5.5.5.1 Blinding of Investigational Product, update to clarify unblinded team members.

  Rationale: *To clarify that limited AbbVie personnel have been unblinded to support data interpretation and that subjects currently on treatment who are unblinded by the investigator will be discontinued from study treatment.*

- Update Section 6.1.7 Toxicity Management and Appendix L, Venetoclax and Azacitidine Dose Modifications, update to guidance regarding delay of treatment cycle by adding clarity to the criteria defining count recovery.

  Rationale: *To further clarify count recovery to include 'and' in the guidance criteria specific to delay of treatment cycle "and/or platelet count* $\geq 50 \times 10^3/\mu L$."

- Update Section 7.0 Protocol Deviations, update study contact.

  Rationale: *Update to current alternate contact for protocol deviations.*

- Update Section 10.2 Case Report Forms, to update vendor information.

  Rationale: *Updated to current name of ePRO vendor.*

- Update Appendix B List of Protocol Signatories, to update and add signatories.

  Rationale: *To add additional signatories.*

- Update Appendix C, Multiple footnote section language updates.

  Rationale: *To clarify survival visits and post treatment follow up visits and update language for corresponding pathology reports.*

An itemized list of all changes made to the protocol under this amendment can be found in Appendix M.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-656
Name of Study Drug: Venetoclax (ABT-199/GDC-0199)	**Phase of Development:** 3
Name of Active Ingredient: ABT-199 (GDC-0199)	**Date of Protocol Synopsis:** 01 July 2020
Protocol Title: A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy	

Objectives:

Primary Objectives:

- To evaluate if venetoclax in combination with azacitidine will improve overall survival (OS) and composite complete remission rate (complete remission + complete remission with incomplete marrow recovery; CR + CRi) versus placebo in combination with azacitidine, in treatment naïve subjects with acute myeloid leukemia (AML).

Secondary Objectives:

- To evaluate if venetoclax in combination with azacitidine will improve the rate of CR.
- To evaluate if venetoclax in combination with azacitidine will improve the rate of CR and complete remission with partial hematologic recovery rate (CRh).
- To evaluate if venetoclax in combination with azacitidine will improve the proportion of subjects achieving composite complete remission (CR or CRi) by initiation of Cycle 2.
- To evaluate if venetoclax in combination with azacitidine will improve the transfusion independence rate.
- To evaluate if venetoclax in combination with azacitidine will improve the MRD response rate
- To evaluate if venetoclax in combination with azacitidine will improve the response rates and overall survival in molecular subgroups.
- To evaluate if venetoclax in combination with azacitidine reduces fatigue and improves global health status/quality of life (GHS/QoL) based on patient reported outcome (PRO) assessments (Patient Reported Outcomes Measurement Information System [PROMIS], Cancer Fatigue Short Form [SF] 7a and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core [EORTC QLQ-C30]).
- To evaluate if venetoclax in combination with azacitidine will improve, event-free survival (EFS).

Objectives (Continued):

Exploratory Objectives:

- Exploration of biomarkers predictive of venetoclax activity and duration of response may be performed. These analyses maybe part of a multi-study assessment to compare responses to the therapies and/or disease state. Potential analyses may include, but will not be limited to:
  - To evaluate BCL2 expression and outcome measures of overall survival and complete remission rate
- To evaluate the impact of venetoclax on remaining subscales/items from the EORTC QLQ-C30 and EQ-5D-5L.

Investigators: Investigator information on file at AbbVie

Study Sites: Approximately 180 sites

Study Population: Adult male and female subjects, with confirmed AML, who are treatment naïve for AML, with a projected life expectancy of at least 12 weeks and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age or co-morbidities.

Number of Subjects to be Enrolled: Approximately 400 to 412 subjects (Enrollment completed with 443 subjects)

Methodology:

This is a randomized, double-blind, placebo controlled, multicenter trial evaluating efficacy of venetoclax in combination with azacitidine versus placebo in combination with azacitidine in treatment naïve subjects with AML who are ≥ 18 years of age and not eligible for standard induction therapy due to age or co-morbidities. If a subject enrolled on any arm achieves complete remission with incomplete marrow recovery (CRi) or has a morphologic leukemia free bone marrow after completion of Cycle 1, venetoclax/placebo may be interrupted from Day 29 for up to 14 days or until recovery of ANC ≥ 500/μL. If venetoclax/placebo is interrupted, then Cycle 2 administration of azacitidine will also be delayed. Cycle 2 treatment with venetoclax/placebo and azacitidine will resume on the same day after the interruption. Subjects with resistant disease after end of Cycle 1 will need a bone marrow aspirate to evaluate response after completion of Cycle 2 or 3 if hematologic improvement is seen. **A bone marrow aspirate and biopsy will be done at the end of Cycle 4 and every 3 cycles after for subjects with resistant disease until two successive samples indicate CR or CRi.** For subjects with a response of CRi a repeat bone marrow aspirate must be performed to confirm a CR once peripheral blood count recovery is noted. For subjects who have not recovered ANC ≥ 500/μL within 14 days of drug interruption or require longer duration of interruption between treatment cycles, bone marrow aspirate may be performed per investigator discretion to assess disease status before resuming treatment with next Cycle. Blood and bone marrow samples will be collected for biomarker analysis and exploratory research at designated timepoints throughout the study.

Screening

Unless otherwise specified, screening procedures must be performed within 21 days prior to randomization. Once screening procedures are complete and eligibility is confirmed, subjects will be randomized using a 2:1 ratio to one of the following two arms:

- Arm A: Venetoclax plus Azacitidine
- Arm B: Placebo plus Azacitidine

Methodology (Continued):

Study Treatment

All subjects will receive venetoclax or placebo orally once daily (QD) plus Azacitidine QD beginning on Cycle 1 Day 1. Venetoclax or placebo should be taken within 30 minutes of food intake. Subjects will receive Azacitidine for 7 days from Day 1 of each cycle beginning with Cycle 1.

Cycle Length – 28 Days

- Venetoclax 400 milligram (mg) or Placebo Daily on Days 1 – 28
- Azacitidine 75 mg/m^2 Subcutaneous (SC) or IV Daily for 7 days

Subjects will continue their treatment assignment until documented disease progression per Investigator assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). Subjects will continue to receive the assigned study treatment without cross over until treatment discontinuation. All subjects will have a final visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. Baseline laboratory assessments will be obtained at Cycle 1 Day 1 prior to first dose of study treatment. Patient-reported outcome (PRO) measures should be completed after a blood sample is taken to confirm the subject is able to receive study treatment at the study visit, but prior to the performance of all other non-PRO assessments and the administration of study treatment. Disease assessments by IWG criteria will be performed at end of Cycle 1 (± 3 days) and every 3 cycles starting on Cycle 4 Day 1 and continuing until disease progression per the modified IWG criteria, or the subject withdraws consent. In addition to being reviewed by the Investigator and local hematopathologists, all disease assessment information will be sent to an Independent Review Committee (IRC) to provide response assessment. Interpretations from the IRC will not be shared with sites. Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets the following criteria within 21 days prior to randomization.

1. Subject must have confirmation of AML by WHO criteria, previously untreated and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age or co-morbidities.
2. Subject must be ≥ 18 years of age.
3. Subject must have a projected life expectancy of at least 12 weeks.
4. Subject must be considered ineligible for induction therapy defined by the following:
   - ≥ 75 years of age;
     OR
   - ≥ 18 to 74 years of age with **at least one** of the following co-morbidities:
     - ECOG Performance Status of 2 or 3;
     - Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina;
     - DLCO ≤ 65% or FEV1 ≤ 65%;
     - Creatinine clearance ≥ 30 mL/min to < 45 ml/min
     - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the AbbVie Therapeutic Area Medical Director (TA MD) during screening and before study enrollment

5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status:
   - of 0 to 2 for subjects ≥ 75 years of age.

   OR

of 0 to 3 for subjects ≥ 18 to 74 years of age.

6. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24 hours urine collection.
7. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 3.0 × ULN*
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN*
   - bilirubin ≤ 1.5 × ULN*
     * Unless considered to be due to leukemic organ involvement
     - Subjects who are < 75 years of age may have a bilirubin of ≤ 3.0 × ULN
8. Female subjects must be either postmenopausal defined as:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

     OR
   - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR

Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at Study Day 1 through at least 90 days after the last dose of study drug.

9. Male subjects who are sexually active, must agree, from Study Day 1 through at least 90 days after the last dose of study drug, to practice the protocol specified contraception. Male subjects must agree to refrain from sperm donation from initial study drug administration through at least 90 days after the last dose of study drug.
10. Female subjects of childbearing potential must have negative results for pregnancy test performed:
    - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
    - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.

11. Subject must voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. Subject has received treatment with the following:
   - A hypomethylating agent, venetoclax and/or any chemo-therapeutic agent for Myelodysplastic syndrome (MDS).
   - CAR-T cell therapy.
   - Experimental therapies for MDS or AML.
   - Current participation in another research or observational study
2. Subject has history of myeloproliferative neoplasm [MPN] including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukemia (CML) with or without *BCR-ABL*1 translocation and AML with *BCR-ABL*1 translocation.
3. Subject has:
   - Favorable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) as per the NCCN Guidelines Version 2, 2016 for Acute Myeloid Leukemia.
4. Subject has acute promyelocytic leukemia
5. Subject has known active CNS involvement with AML.
6. Subject has known HIV infection (due to potential drug-drug interactions between antiretroviral medications and venetoclax) HIV testing will be performed at Screening, only if required per local guidelines or institutional standards.
7. Subject is known to be positive for hepatitis B or C infection [HCV Ab indicative of a previous or current infection; and/or positive HBs Ag or detected sensitivity on HBV-DNA PCR test for HBc Ab and/or HBs Ab positivity] with the exception of those with an undetectable viral load within 3 months of screening. (Hepatitis B or C testing is not required). Subjects with serologic evidence of prior vaccination to HBV [i.e., HBs Ag-, and anti-HBs+] may participate.
8. Subject has received strong and/or moderate CYP3A inducers within 7 days prior to the initiation of study treatment.
   - Chinese AML subjects participating in the safety cohort per Appendix K are also excluded from receiving strong and/or moderate CYP3A inhibitors from 7 days prior to the initiation of study treatment through the entire dose limiting toxicity (DLT)/safety evaluation period.
9. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.
10. Subject has a cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
11. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, any other medical condition or known hypersensitivity to any of the study medications including excipients of azacitidine that in the opinion of the investigator would adversely affect his/her participating in this study.
12. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 13. Subject exhibits evidence of other clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial or fungal). 14. Subject has a history of other malignancies within 2 years prior to study entry, with the exception of: • Adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast; • Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin; • Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent: requires discussion with TA MD. 15. Subject has a white blood cell count > 25×10^9/L. (Hydroxyurea or leukapheresis are permitted to meet this criterion.)	
Investigational Product:	Venetoclax, 100 mg, 50 mg and 10 mg tablet
Dose:	Cycle 1: Day 1: 100 mg, Day 2: 200 mg, Day 3: 400 mg, Day 4 – Day 28: 400 mg Subsequent cycles: Day 1 – Day 28: 400 mg QD
Mode of Administration:	Oral
Reference Therapy:	Placebo (to match venetoclax 100 mg, 50 mg, and 10 mg tablet)
Dose:	Not Applicable
Mode of Administration:	Oral
Reference Therapy:	Azacitidine
Dose:	75 mg/m^2; Daily for 7 Days of all cycles, Cycle = 28 days QD
Mode of Administration:	Subcutaneous (SC) or IV as indicated in local label
Duration of Treatment: Subjects will receive venetoclax/placebo/azacitidine until documented disease progression, unacceptable toxicity or intolerance, withdrawal of consent, or the subject meets other criteria for discontinuation per study protocol (whichever occurs first).	

Criteria for Evaluation:

Efficacy:

Bone marrow biopsies and aspirates must be performed at screening for all subjects. Cytogenetic and molecular profiling will be done at a local lab during screening. Samples for molecular markers and baseline disease assessment for MRD evaluation must be collected at screening for confirmation at central lab. Bone marrow aspirate and biopsy must be performed at the end of Cycle 1. For subjects with resistant disease at the end of Cycle 1 a repeat bone marrow aspirate and biopsy must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to assess response. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles thereafter (± 1 week). Bone marrow will be performed until two successive samples indicate CR or CRi. For subjects with a response of CRi on two successive bone marrow samples an additional bone marrow aspirate and biopsy must be performed to confirm a CR once peripheral blood count recovery is noted. Subsequently, disease assessments are based on laboratory results and physical examination. A bone marrow aspiration and biopsy is required if relapse is suspected or at the Final Visit. All subjects will have response assessment according to the modified IWG criteria for AML. Progressive disease is defined per European LeukemiaNet recommendations. If additional treatments are needed to optimize subjects' medical care, they can be performed following institutional standards and procedures. Subject's disease assessment is based on the most recent physical examination, bone marrow results and recent hematology values. For subjects who require a delay in next cycle of study treatment for blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks or pre-dose labs from Day 1 of the next cycle can be used to determine the IWG response.

All subjects who completed at least one cycle of study treatment will be assessed by the investigators using the modified IWG criteria for AML as described below. Subjects who have discontinued study treatment prior to completion of Cycle 1 will be deemed non-evaluable for response assessment.

Criteria for Evaluation (Continued):

Efficacy (Continued):

CR:	Absolute neutrophil count > 10^3/μL, platelets > 10^5/μL, red cell transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRi:	All of the criteria for CR except for residual neutropenia ≤ 10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). Red blood cell transfusion (RBC) dependence is also defined as CRi.
PR:	All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
MLFS:	Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of circulating blasts and extramedullary disease without peripheral blood count recovery that meet the thresholds for either CR or CRi.
RD:	Failure to achieve CR, CRi, PR or MLFS; only for subjects surviving at least 7 days following completion of Cycle 1 treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
MR:	Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
PD:*	• 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 10^9/L [500/μL], and/or platelet count to > 50 × 10^9/L [50 000/μL] non-transfused); or • 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L (> 25 000/μL); or • New extramedullary disease

CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission; MLFS = morphologic leukemia free state; RD = resistant disease; MR = morphologic relapse

* PD = Progressive disease as defined by ELN criteria.

In addition to the response assessment using the above response criteria, each subject will also be evaluated for complete remission with partial hematologic recovery rate (CRh) based on the bone marrow and hematologic parameters.

Pharmacokinetic:

Sparse pharmacokinetic (PK) samples will be collected and analyzed for venetoclax and azacitidine. Venetoclax results may be incorporated into a population PK analysis to estimate parameters such as clearance.

Criteria for Evaluation (Continued):

Safety:

Adverse event (AE) monitoring, vital signs, physical examination, and laboratory values. If any additional diagnostic testing performed as clinically indicated will be assessed. Note: All subjects will be hospitalized for the first 4 days of dosing during Cycle 1 and longer as needed per standard of care for peripheral blood count recovery and management of disease related complications during the escalation of venetoclax dose from 100 to 400 mg.

Patient-Reported Outcomes:

PROs will be evaluated using the following measures at specific time points throughout the study: PROMIS Cancer Fatigue SF 7a, GHS/QoL as assessed by EORTC QLQ-C30, and EQ-5D-5L.

Statistical Methods:

Efficacy:

Primary and Secondary Efficacy Endpoints:

Overall Survival (OS):

Overall survival will be defined as the number of days from the date of randomization to the date of death. Subjects that have not died will be censored at the last known date to be alive.

Composite Complete Remission Rate:

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRi) will be calculated based on current IWG criteria for AML. Subjects who are randomized but have no IWG disease assessment will be considered as non-responders for CR + CRi rate.

Complete Remission (CR) Rate:

The proportion of subjects with complete remission (CR) will be calculated based on current IWG criteria for AML. Subjects who are randomized but have no IWG disease assessment will be considered as non-responders for CR rate.

CR + CRh rate

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRh) will be calculated. Subjects who are randomized but have no post-baseline disease assessment will be considered as non-responders for CR + CRh rate.

Composite Complete Remission Rate by the Initiation of Cycle 2:

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRi) by the initiation of Cycle 2 will be calculated based on the modified IWG criteria for AML. Subjects who are randomized but have no IWG disease assessment by the initiation of Cycle 2 will be considered as non-responders.

Post Baseline RBC Transfusion Independence Rate

Post baseline RBC transfusion independence rate will be calculated as the portion of subjects who achieved RBC transfusion independence post baseline. The RBC Transfusion independence is defined as a period of at least 56 days with no RBC transfusion between the first dose of study drug and the last dose of study drug + 30 days. All randomized subjects will be included to estimate the post-baseline transfusion independence rates.

Statistical Methods (Continued):

The Rate of Conversion (RBC)

The rate of conversion will be calculated as proportion of subjects being post-baseline transfusion independent from baseline RBC transfusion dependence.

The Rate of Conversion (Platelets)

The rate of conversion will be calculated as proportion of subjects being post-baseline Platelets transfusion independent from baseline platelets transfusion dependence.

MRD Response Rate

MRD response will be defined using a threshold of less than 0.1% of residual blasts per leukocytes as measured in bone marrow. Additional thresholds may also be explored and correlated with efficacy outcomes. Subjects who are randomized but have no MRD assessment will be considered as non-responders for the calculation of MRD response rate. The proportion of subjects (CR + CRi, or CR + CRh) achieving an MRD response will be calculated.

Event-Free Survival (EFS):

EFS will be defined as the number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure or death from any cause. If a specified event does not occur, subjects will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after randomization will be censored at the date of randomization.

Pharmacokinetic:

An analysis of venetoclax plasma concentrations may be performed using a nonlinear mixed effect population PK modeling approach.

Pharmacodynamic and Predictive Biomarker Analysis (Not Applicable for China):

Exploratory research may be conducted to find biomarkers predictive of venetoclax activity. Peripheral blood and bone marrow samples will be obtained at study specified time points. Biomarkers (e.g., cytogenetics, molecular markers, characterization of Bcl-2 family members and minimal residual disease status MRD) may be assessed to compare patient responses in the two arms in order to identify markers that may be predictive of venetoclax activity.

Safety:

A safety analysis will be performed for all dosed subjects unless otherwise indicated. For the study as a whole, AEs will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized as appropriate.

Patient-Reported Outcomes:

Fatigue as assessed by the PROMIS Cancer Fatigue SF 7a and GHS/QoL as assessed by the EORTC QLQ-C30 will be evaluated using a linear mixed effects regression model to test for differences between the two treatment arms. Exploratory research will also be conducted on the subscales and items from the PROMIS Cancer Fatigue SF 7a, EORTC QLQ-C30, and EQ-5D-5L.

Statistical Methods (Continued):

Sample Size:

For US and countries using the US as the reference country, the study includes single primary endpoint of overall survival. For Japan, EU and countries using EU as reference for obtaining approval, the study includes dual-primary endpoints of overall survival (OS) and CR + CRi rate. The sample size calculation is based on the following assumptions:

- The significance level (two-sided 0.05) will be split to give a 0.01 significance level to the CR + CRi rate analysis and an overall 0.04 significance level to the OS analysis.
- Median OS of 10.4 months for placebo plus azacitidine arm
- Median OS of 14.9 months for venetoclax plus azacitidine arm (hazard ratio of 0.7)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary
- 2:1 randomization ratio to venetoclax plus azacitidine, and placebo plus azacitidine arm, stratified by age (18 – < 75, ≥ 75), cytogenetics (intermediate risk, poor risk) and region (US, EU, China, Japan, Rest of world)

With the above assumptions, a total of 360 death events will provide 86.7% power to detect statistically significant difference in OS between treatment arms at alpha level of 0.04. A total of approximately 400 subjects (267 in venetoclax in combination with azacitidine arm, and 133 in placebo with azacitidine arm) will be randomized into the study to obtain the 360 death events. A total of approximately 412 subjects including the open label Chinese safety cohort may be enrolled.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (also called SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASD	Amorphous solid dispersion
AST	Aspartate aminotransferase (also called SGOT)
AZA	Azacitidine
Bcl	B-Cell Lymphoma
BCRP	Breast Cancer Resistant Protein
BM	Bone Marrow
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CD-ROM	Compact Disc – Read Only Memory
CHF	Congestive Heart Failure
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CMH	Cochran Mantel Haenszel
CNS	Central Nervous System
CR	Complete Remission
CRF	Case Report Form
CRh	Complete Remission with partial hematologic recovery
CRi	Complete Remission with Incomplete Blood Count Recovery
CRp	Complete Remission with Incomplete Platelet Recovery
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19

CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-Free Survival
ELN	European LeukemiaNet
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life
EQ-5D-5L	EuroQol EQ-5D-5L
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FFPE	Formalin-Fixed Paraffin-Embedded
FSH	Follicle-Stimulating Hormone
GHS/QOL	Global Health Status/Quality Of Life
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HDPE	High Density Polyethylene
HIV	Human Immuno-Deficiency Virus
HMA	Hypomethylating agent
HNSTD	Highest Non-severely Toxic Dose
HR	Hematologic Response
hr	Hour
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IMP	Investigational Medical Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
IWG	International Working Group
JP	Japan
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LTLS	Laboratory Tumor Lysis Syndrome
MTD	Maximum Tolerated Dose
MCL	Mantle Cell Lymphoma
MD	Medical Director
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Morphologic Relapse
µg	Microgram
mg	Milligram
mL	Milliliter
µM	Micromolar
MLFS	Morphologic leukemia free state by bone marrow
MPN	Myeloproliferative Neoplasm
MRD	Minimal Residual Disease
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCS	Not clinically significant
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar

ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Remission
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcome Measurement Information System
PT	Prothrombin Time
PD	Progressive Disease
QD	Once Daily
QTcF	QT interval measurement corrected by Fridericia's formula
RBC	Red Blood Cell
RD	Resistant Disease
RNA	Ribonucleic Acid
RPTD	Recommended Phase 2 Dose
R/R	Relapse/Refractory
SAE	Serious Adverse Event
SC	Subcutaneous
SF	Short Form
SGOT	Serum Glutamic-oxaloacetic Transaminase (also called AST)
SGPT	Serum Glutamic-pyruvic Transaminase (also called ALT)
SLL	Small Lymphocytic Lymphoma
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STD	Severely Toxic Dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Therapeutic Area
TLS	Tumor Lysis Syndrome
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization

Pharmacokinetic and Statistical Abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to Hour 24
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity
CL/F	Apparent oral clearance
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
IC_{50}	Half maximal inhibitory concentration
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration
V/F	Apparent volume of distribution

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3.0 Introduction

Venetoclax Activity and Preclinical Pharmacokinetic Profile

Hematologic malignancies are highly dependent upon the anti-apoptotic protein BCL-2 for survival. Over-expression of BCL-2 is associated with tumor initiation, disease progression, and drug resistance, and is thus a compelling target for anti-tumor therapy. Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (K_i < 0.010 nM) than for BCL-X_L (Ki = 48 nm) or MCL-1 (K_i > 444 nM).[1] In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines, including acute myeloid leukemia (AML).[1] Venetoclax was especially potent against non-Hodgkin's lymphoma (NHL) cell lines expressing high levels of BCL-2 protein due to the t(14;18) chromosome translocation, amplification of the *BCL-2* gene locus, or aberrantly activated signaling mechanisms.

BCL-2 over-expression has also been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. In addition, high levels of BCL-2 were associated with poor survival in a subset of patients with this disease.[2,3] The BCL-2/BCL-X_L inhibitor ABT-737 has been shown to kill AML cells, including leukemic stem/progenitor cells, as both a single agent and in combination with cytarabine[2] or 5-azacitidine.[3] To further define the role of BCL-2 in this disease, panels of AML cell lines and primary patient samples were cultured in the presence of venetoclax. Twelve of 24 AML cell lines tested were sensitive to venetoclax, with cell killing IC_{50} values of < 1.0 µM. The sensitivity of primary AML subject samples was comparable to that observed for primary CLL samples, with a median IC_{50} = 0.010 µM (n = 57) for AML[4] versus a median IC_{50} = 0.003 µM (n = 35) for CLL (AbbVie R&D/10/1025, AbbVie R&D/12/538). Venetoclax has also demonstrated killing of AML leukemic stem/progenitor cells ex vivo and antitumor efficacy in vivo, inhibiting the growth of AML cell lines or AML patient-derived primary cells systemically engrafted into immunocompromised mice.[4] Single agent venetoclax is currently being studied in

relapsed/refractory (R/R) AML and was found to induce rapid reduction in blast counts in some patients indicating activity in subject with this disease. However, not all AML cell lines, primary patient samples, or subjects treated with single agent venetoclax were found to be sensitive, and there is biologic rationale for combining venetoclax with certain chemotherapeutic agents in the treatment of AML. The MCL-1 protein can act as a resistance factor for Bcl-2 family inhibitors[5,6] including in AML.[2] Therapeutic agents such as the DNA methyltransferase inhibitor azacitidine,[3] the DNA synthesis inhibitor cytarabine[7] and the anthracycline doxorubicin[8] have shown an ability to down-regulate MCL-1, indicating that they might combine well with BCL-2 inhibitors. In support of this, ABT-737 has demonstrated synergistic killing of AML cell lines when combined with cytarabine or doxorubicin.[2] Likewise, the combination of ABT-737 and azacitidine demonstrated synergistic killing of 7 of 8 primary AML patient samples and completely inhibited the engraftment of human CD45 + AML cells into immunocompromised mice.[3] Combinations of venetoclax and chemotherapeutic agents commonly used in the treatment of AML were recently tested against a panel of 20 AML cell lines. While most combinations resulted in additive cell killing, venetoclax combined with cytarabine or azacitidine showed synergistic effects on several AML cell lines. These data suggest that BCL-2 inhibition alone may be sufficient for the synergistic effects that have been observed between ABT-737 and cytarabine or azacitidine, and thus provides a rationale for testing these combinations with venetoclax in subjects with AML. In mouse, rat, monkey, and dog, the venetoclax pharmacokinetic profile was characterized by low plasma clearance (CLp = 0.02 to 0.27 L/hr•kg) and low volumes of distribution (V_{ss} = 0.3 to 1.1 L/kg). Half-lives ranged from 2.2 hours in monkey to 12.0 hours in dog. Formulation-dependent oral bioavailability was noted in all species. Studies in both rat and dog have defined the behavior of the amorphous solid dispersion (ASD) for both toxicology and first-in-human evaluation. Plasma concentrations obtained from fed dogs were 30% to 50% higher than those obtained from fasted animals.

Venetoclax and M27 metabolite are predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Venetoclax is also substrate for P-glycoprotein (P-gp)

and breast cancer resistance protein (BCRP) transporters. No active uptake of venetoclax was observed in cells overexpressing organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3. Based on in vitro results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (IC_{50} > 30 µM); and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 µM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Venetoclax Preclinical Toxicology

Toxicology studies completed with venetoclax are general toxicology studies with periods of once-daily oral dosing ranging from 2 weeks to 6 months in mice, from 2 weeks to 13 weeks in rats, and from 1 week to 9 months in dogs, in vitro and in vivo genetic toxicology, dose range-finding in mice and rats to support dose selection for possible carcinogenicity assessments, embryo-fetal development in mice and rabbits, fertility and early embryonic development in male and female mice, dose range-finding in juvenile mice, and phototoxicity in mice. Other studies were in vitro genetic toxicity testing of the M27 major human metabolite and in vitro and in vivo impurity qualification. Reversibility of venetoclax-related changes was assessed in the 4-week study in mice and in the 2- and 4-week studies in dogs.

The primary toxicities associated with repeat-dose administration of venetoclax are effects on the hematologic system (decreased lymphocytes and red blood cell mass in mice, rats and dogs), the male reproductive system (testicular germ cell depletion in dogs), and embryo-fetal toxicity in mice. Other noteworthy findings are epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs. Maximum venetoclax plasma exposures (mean $AUC_{0\text{-}24h}$, combined male and female values) achieved in the 4-week studies were 92 µg•hr/mL (at 600 mg/kg/day) in mice and 572 µg•hr/mL (at 150 mg/kg/day) in dogs. In the 6-month mouse and 9-month dog chronic toxicity studies, AUCs reached 34.1 µg•h/mL (at 300 mg/kg/day) in mice and 85.6 µg•h/mL (at 20 mg/kg/day) in dogs. In rats, exposures were higher in females than

in males; at dosages of 150 and 400 mg/kg/day in the 13-week maximum tolerated dose study, exposures ranged up to 83.1 to 127.8 µg•h/mL in females and up to 26.4 to 44.3 µg•h/mL in males.

Venetoclax produced generally dose-related decreases in lymphocytes in the peripheral blood (up to –75% in mice, –64% in rats, and –81% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacology of venetoclax (a selective Bcl-2 inhibitor).[9]

Following a 4-week recovery period, lymphocyte counts remained minimally decreased by –21% to –26% in mice, indicating that reversibility was occurring but was not complete. In dogs, the recovery of decreases in peripheral blood total lymphocytes and lymphocyte subsets (CD4+ T-cells and CD8+ T-cells and [CD21+] mature B cells) was prolonged, requiring up to 18 weeks after a single dose or after completion of 2 weeks of dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> –90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs, but as with peripheral blood lymphocytes, required up to 18 weeks in dogs. Decreases in lymphocyte counts can be readily monitored in clinical trial subjects.

In the 4-week mouse and dog studies, dose-related reversible decreases in red blood cell (RBC) mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached –21% in mice at 600 mg/kg/day and –23% in dogs at 150 mg/kg/day, and were considered to be adverse based on a criterion of –20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached 30% to 49% at ≥ 150 mg/kg/day in female rats. Hematologic parameters are readily monitored in clinical trial subjects.

No effects of venetoclax have been identified on the female reproductive tract of mice, rats, and dogs. However, in dogs venetoclax produced adverse, non-dose-related microscopic findings of testicular germ cell loss at all dosages tested (2 to

150 mg/kg/day). In the 4-week study, testicular spermatogonia were decreased at the end of the dosing period, and their loss was consistent with the observed depletion of all germ cell types at the end of the 4-week recovery period. There were no testicular effects in mice or rats; in these animal species, exposures overlapped those in dogs. Venetoclax-induced testicular changes may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[10-12] There are currently no data assessing the effect of venetoclax on human spermatogenesis, and the actual risk to humans for testicular findings similar to those observed in dogs remains unknown. In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies.

In the mouse embryo fetal development study, increased post-implantation loss and decreased fetal body weights occurred at the highest dosage administered (150 mg/kg/day); the NOAEL was defined at the mid dosage of 50 mg/kg/day. No fetal toxicity was observed in rabbits, but exposures were approximately one-tenth those in mice. Venetoclax was not teratogenic in mice or rabbits, and there were no other effects on development or fertility.

Additional effects of venetoclax were white hair coat discoloration in dogs at ≥ 6 mg/kg/day and single-cell necrosis in multiple epithelial tissues at ≥ 2 mg/kg/day in dogs.

Hair coat discoloration (increased amount of hair that was white) was observed in the dog after approximately 3 months of dosing in the 9-month chronic toxicity study. This change was consistent with loss of pigment in the hair and correlated histopathologically with decreased pigment in hair follicle bulbs. A change to gray coat color was also seen in NZBWF1 mice treated daily with 33 or 100 mg/kg venetoclax, but not at lower dosages. Evidence from Bcl-2 knockout mouse (Bcl-2 -/-) studies indicates that hair hypopigmentation occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[13] In the dog, pigmentation of the skin and in the eye (particularly in the pigmented iris and fundus) appeared unaffected; this was confirmed by the absence of

associated histopathologic findings in skin (other than in hair follicles) and in the eye. The risk of hair graying in clinical trial subjects treated with venetoclax is unknown. Single cell necrosis occurred in the gallbladder, exocrine pancreas, epididymides, prostate, and stomach of dogs. These changes were minimal except for non-dose-dependent minimal to mild single cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9-month study. After 4 weeks of dosing and a 4-week recovery period, reversibility was observed in the gallbladder and exocrine pancreas, but minimal single cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed microscopically. Single cell necrosis was not found in the mouse or rat; maximum achieved exposures were comparable to or greater than the lowest exposures at which this finding occurred in dogs.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity (tested in vivo in hairless mice). Venetoclax administration in dogs in the 4-week study was associated with dose related, transient post-dose emesis, increased salivation, and fecal alterations (unformed or watery feces) at dosages of ≥ 5 mg/kg/day. These clinical signs were present throughout the dosing phase, but were not dose-limiting and were not observed in the recovery phase. In the 9-month dog study, non-adverse decreases in mean body weight and body weight gain, associated with decreases in food consumption, were present at ≥ 2 mg/kg/day.

Dogs at the high dosage of 150 mg/kg/day in the 4-week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in three dogs the swelling reaction was observed after the first dose. The clinical signs were limited to the 150 mg/kg/dosage, were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis.

M27 is a major human metabolite observed at steady state in chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL) patient plasma samples. It is present at significantly lower exposure levels (0.04- and 0.06-fold, respectively) in the mouse and dog, and therefore is a disproportionate metabolite. M27 was negative in Ames and chromosome aberration in vitro assays, has at least 58-fold less in vitro potency than venetoclax, and demonstrates low off-target toxicity potential based on in vitro secondary pharmacology assays. Taken together, these nonclinical results suggest that M27 does not represent a significant safety risk, and does not change the benefit/risk ratio for clinical trial subjects with advanced hematologic malignancies treated with venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the central nervous system (CNS)/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest oral dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 μg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (C_{max} = 16 μg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (–6% to –13%) and cardiac output (–11% to –19%) at plasma concentrations of ≥ 16 μg/mL and ≥ 32 μg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average C_{max} = 6.09 μg/mL at the 1200 mg/day dose).

On the basis of nonclinical toxicology and safety pharmacology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia,[14] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Although no effects of venetoclax on female reproductive tissues have been observed in general repeat-dose toxicology studies, embryo-fetal toxicity studies in animals have identified a fetal toxicity risk. Thrombocytopenia has not been a significant finding in toxicology studies in mice

and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-X_L sparing) inhibitor. Consequently, thrombocytopenia is not expected to be dose limiting.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current Investigator's Brochure.[14]

Acute Myeloid Leukemia

Acute myeloid leukemia is the most common form of acute leukemia in adults and is characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood and extra medullary tissues. It is a heterogeneous disease, encompassing a large number of distinctly different subtypes that may have different clinical presentations and differing responses to treatment. AML is defined by World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow.[17] The estimated number of new cases is 19,950 and 10,430 deaths in 2016 in the United States.[18] The incidence is approximately 36,000 cases worldwide. The median age of diagnosis is 67 years, with 55% of the patients diagnosed at 65 years or older, and approximately a third of them are diagnosed over the age of 75. Standard treatment for newly diagnosed AML for patients who are medically fit consists of remission induction therapy with cytarabine as the backbone combined with an anthracycline, usually daunorubicin or idarubicin (7 + 3) followed by consolidation therapy. Elderly AML is a biologically and clinically distinct disease with a diminished response to chemotherapy with low remission rates and short disease-free and overall survival. Higher proportion of unfavorable cytogenetics, higher frequency of antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype accounts for the poor outcomes associated with current therapy. Additionally, the presence and severity of comorbid conditions, compromised end organ function that enhance the toxicity of induction chemotherapy, and functional incapacity all decrease the ability for the elderly patient to tolerate induction chemotherapy and survive life-threatening infections often associated with AML therapy.[19] While some elderly patients are able to receive standard induction or intensive chemotherapy, the majority are treated with less intensive therapies such as hypomethylating agents, low

dose cytarabine or best supportive care. Similarly, younger patients with significant cardiac, pulmonary or other comorbidities may not be eligible to receive standard induction therapy. Several studies have also demonstrated the benefits of induction therapy over supportive care only, with respect to survival and quality of life, suggesting that treatment should be offered to all patients diagnosed with AML.[20]

Venetoclax Clinical Data

As of 28 November 2015, based on the data available in the AbbVie and Genentech/Roche clinical databases, a total of 1509 subjects have been exposed to at least 1 dose of venetoclax in the oncology development program. Of these, data are available for 1498 subjects; 102 had AML, 935 subjects had CLL/SLL, 346 subjects had NHL, and 115 subjects had MM. An additional 66 subjects were healthy volunteers who participated in the DDI studies. Based on the available data, a total of 564 oncology subjects received the drug as monotherapy and 933 subjects received the drug in combination with other therapies.

Based on the mechanism of action and nonclinical and clinical data available to date, the safety profile of venetoclax is well described. The most common adverse drug reactions across all indications are nausea, diarrhea, hematological effects, and serious and/or opportunistic infections. Hematologic effects include neutropenia/febrile neutropenia, thrombocytopenia, anemia, and lymphopenia. Upper respiratory tract infections are among the most common infections. TLS is an important identified risk and is predominantly seen in the CLL population with high tumor burden. Based on pre-clinical data, decreased spermatogenesis has been identified as a potential risk for venetoclax.

Clinical Data in AML

As of 09 March 2016 a total of 102 subjects with AML have been treated in the venetoclax oncology clinical program: 32 subjects with R/R and in unfit AML received venetoclax as a single agent (Study M14-212) and 70 subjects received venetoclax in combination with other therapeutic agents including 45 subjects with HMAs (Study M14-358) and 25 subjects with low-dose cytarabine (LDC) (Study M14-387). To

date, the adverse events observed occurred at an incidence that appeared to be consistent with what would be expected in the AML patients both in monotherapy and combination studies. Neutropenia is being closely monitored.

Overview of Phase 2 Study M14-212: Venetoclax Monotherapy in AML

This is a completed study with single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study.[21] The most common adverse events observed in ≥ 30% of the subjects in Study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment.

Efficacy data for Study M14-212 are available for all 32 subjects, the majority (30, 94%) of the subjects had R/R AML and a few (2, 6%) were deemed unfit for intensive therapy. The ORR was 19% (6 of 32 subjects), with complete remission (CR) in 2 (6%) and complete remission with incomplete marrow recovery (CRi) in 4 (13%) subjects. Anti-leukemic activity was observed in an additional 7 (22%) subjects, with ≥ 50% bone marrow reduction with hematologic recovery in 4 of these subjects. Increase activity was observed in patients with a high percentage of BCL2 expressing cells and low percentage of BCLxL expressing cells by flow cytometry.

Overview of Ongoing Phase 1b Study (M14-358): Venetoclax in Combination with HMA in Treatment Naïve AML

As of 09 March 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m^2 intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m^2 intravenously or subcutaneously on Days 1 – 7 once every 28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.[22]

The most common adverse events for all subjects in Study M14-358 were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutrophil count decreased (31.1%), platelet count decreased, cough, and fatigue (28.9% each), edema peripheral and hypokalemia (26.7% each). Events grade 3 and above were reported for the majority (91.1%) of subjects; the most common event was febrile neutropenia (40.0%). Serious adverse events were reported for 27 (60.0%) subjects, including febrile neutropenia (11 subjects), malignant neoplasm progression (3 subjects) atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis, bone pain (2 subjects each). All other events occurred in 1 subject each. The combination of venetoclax with decitabine and azacitidine demonstrates a tolerable safety profile.

As of 09 March 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia-free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

The maximum tolerated dose has not been reached in either arm and dose escalation stage has completed enrollment. Enrollment into safety expansion at 400 mg and 800 mg dose of venetoclax in combination with both HMAs is ongoing.

Overview of Ongoing Phase 1/2 Study M14-387: Venetoclax in Combination with low Dose Cytarabine in Treatment Naïve AML

As of 28 November 2015, a total of 25 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled; 18 subjects were enrolled into the Phase 1 portion of the study and a RPTD of 600 mg has been identified. Enrollment into the subsequent Phase 2 portion with approximately 50 subjects is ongoing to evaluate the RPTD for efficacy and safety. Preliminary efficacy data for Study M14-387 are available for 18 subjects with AML as of 28 November 2015. The ORR was 44.4% including 4 (22.2%) subjects achieving CR and 4 (22.2%) subjects achieving CRi.

Of the 25 subjects enrolled in study the most common adverse events were nausea (68.0%), anemia (52.0%), and febrile neutropenia (36.0%). Events grade 3 and above were reported for all but one subject (96.0%) of subjects; the most common event was anemia (48.0%). Serious adverse events were reported for 19 (76.0%) subjects, including febrile neutropenia (7 subjects), pyrexia, hyponatremia, and malignant neoplasm progression (2 subjects each). All other events occurred in 1 subject each. Fatal adverse events occurred in 5 (20.0%) subjects: 2 events of malignant neoplasm progression and 1 event each of acute hepatic failure, Candida pneumonia, and lung infection.

Additional safety and efficacy data are described in more detail in the current version of the Investigator's Brochure.[14]

3.1 Differences Statement

This is the first randomized study comparing venetoclax in combination with azacitidine versus placebo in combination with azacitidine in subjects with AML who are treatment naïve and are considered ineligible for standard induction therapy.

3.2 Benefits and Risks

Venetoclax was evaluated as a single agent (Study M14-212) in patients with R/R AML or frontline in patients with AML who are unfit to receive intensive chemotherapy demonstrating clinical activity. Venetoclax in combination with hypomethylating agents (decitabine or azacitidine) in treatment naïve patients ≥ 65 years of age who were ineligible to receive standard induction therapy (Study M14-358) is an ongoing study again demonstrating an acceptable benefit risk profile. Data from Study M14-358 demonstrate favorable safety profile and promising clinical activity in subjects with untreated AML who are unfit to receive standard induction therapy.

Currently there are no approved therapies in the US for patients with AML who are not candidates for conventional induction treatment. In Europe, decitabine and azacitidine are approved as single agents for patients with treatment naïve AML. However, the reported overall response (CR + CRp) rate in a randomized trial was 17.8% and the median overall survival was 7.7 months with decitabine compared with 7.8% and 5.0 months in treatment choice arm consisting of either subcutaneous low dose cytarabine (88.5% of patients) or supportive care (11.5% of patients).[23] The reported overall response (CR+CRi) rate and median overall survival were 27.8% and 10.4 months with azacitidine versus 25.1% and 6.5 months, respectively, in the conventional care regimens arm consisting of best supportive care, low dose cytarabine or intensive chemotherapy.[24] Both of these trials in AML patients are ≥ 65 years of age demonstrate lower response rates and survival than standard induction therapy. These data highlight the need for novel approaches that offer greater improvements in survival for those patients who are not eligible for treatment with standard induction therapy.

Rapid cell death in patients with AML can result in tumor lysis syndrome (TLS) during initial dosing. To mitigate the risk of TLS in AML patients the regimen is designed to escalate the dose of venetoclax rapidly and safely with standard doses and schedule of azacitidine to optimize the opportunity for achieving a response and enable close subject monitoring.

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. No additional risk to study subjects is anticipated with the use of venetoclax/placebo in this population with limited treatment options for their underlying AML.

For additional safety and efficacy data please refer to the current Investigator Brochure.[14]

4.0 Study Objectives

4.1 Primary Objective

The primary objective is:

- To evaluate if venetoclax in combination with azacitidine will improve overall survival (OS) and composite complete remission rate (complete remission + complete remission with incomplete marrow recovery; CR + CRi) versus placebo in combination with azacitidine, in treatment naïve subjects with acute myeloid leukemia (AML).

4.2 Secondary Objectives

The secondary objectives are:

- To evaluate if venetoclax in combination with azacitidine will improve the rate of CR.
- To evaluate if venetoclax in combination with azacitidine will improve the rate of CR and complete remission with partial hematologic recovery rate (CRh).
- To evaluate if venetoclax in combination with azacitidine will improve the proportion of subjects achieving composite complete remission (CR or CRi) by initiation of Cycle 2.
- To evaluate if venetoclax in combination with azacitidine will improve the transfusion independence rate.
- To evaluate if venetoclax in combination with azacitidine will improve the MRD response rate.

- To evaluate if venetoclax in combination with azacitidine will improve the response rates and overall survival in molecular subgroups.
- To evaluate if venetoclax in combination with azacitidine reduces fatigue and improves global health status/quality of life (GHS/QoL) based on patient reported outcome (PRO) assessments (Patient Reported Outcomes Measurement Information System [PROMIS], Cancer Fatigue Short Form [SF] 7a and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core [EORTC QLQ-C30]).
- To evaluate if venetoclax in combination with azacitidine will improve, event-free survival (EFS).

4.3 Exploratory Objectives

The exploratory objectives are:

- Exploration of biomarkers predictive of venetoclax activity and duration of response may be performed. These analyses maybe part of a multi-study assessment to compare responses to the therapies and/or disease state. Potential analyses may include but not limited to:
  - To evaluate BCL2 expression and outcome measures of overall survival and complete remission rate
- To evaluate the impact of venetoclax on the remaining subscales/items from the EORTC QLQ-C30 and EQ-5D-5L.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo controlled, multicenter trial evaluating efficacy and safety of venetoclax in combination with azacitidine versus placebo in combination with azacitidine in treatment naïve subjects with AML who are ≥ 18 years of age and not eligible for standard induction therapy due to age or

comorbidities. Subjects will be randomized to one of the two treatment Arms in a 2:1 ratio, both of which will have treatment cycles of 28 days.

- Arm A: Venetoclax 400 mg orally QD on Days 1 – 28 plus Azacitidine 75 mg/m^2 SC or IV (per local label) Daily for 7 days
- Arm B: Placebo orally QD on Days 1 – 28 plus Azacitidine 75 mg/m^2 SC or IV (per local label) Daily for 7 days

443 subjects were randomized to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

This study is sponsored by AbbVie in collaboration with Roche/Genentech.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 during the period from the Screening Visit up to dosing on Cycle 1 Day 1, and will record the results of this assessment and the details of the informed consent process in the subject's medical records.

Eligible subjects have up to 21 days to complete screening procedures. Once screening procedures are completed and eligibility is confirmed, subjects will be randomized. After being randomized, subjects will have up to 5 days to initiate Cycle 1 Day 1 however this window cannot exceed the allotted 21 day Screening period.

5.1.2 Rescreening

Due to the acute nature of AML, subjects who have failed to meet the eligibility criteria during screening period will not be permitted to re-screen.

5.1.3 Treatment Period

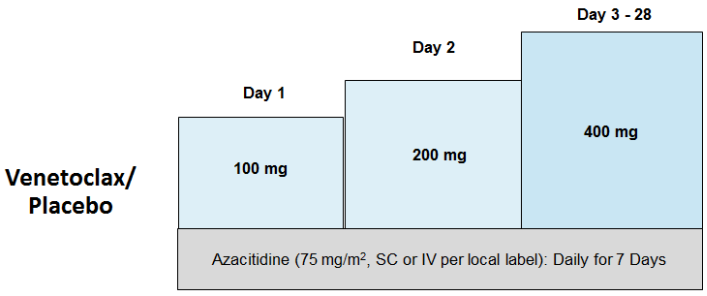
After meeting the eligibility criteria, subjects will be enrolled via IRT into a treatment arm. All subjects will begin study drugs (investigational product and reference therapy) on Cycle 1 Day 1. Subjects in Arm A will receive venetoclax orally QD plus Azacitidine (SC or IV per local label instructions) QD beginning on Cycle 1 Day 1. Venetoclax should be taken within 30 minutes after completion of a meal (preferably breakfast). Subjects in Arm B will receive placebo orally QD plus Azacitidine (SC or IV per local label instructions) QD beginning on Cycle 1 Day 1. Placebo should be taken within 30 minutes after completion of a meal (preferably breakfast). Subjects will receive Azacitidine for 7 days of each cycle, beginning on Day 1 of each cycle.

Dosing Schedule Overview – For Venetoclax/Placebo

Venetoclax or placebo for venetoclax will be administered with a 3-day ramp up beginning with 100 mg dose on Day 1 to reach the final dose of 400 mg on Day 3 of Cycle 1. Venetoclax or placebo for venetoclax will be continued at 400 mg daily thereafter.

Figure 1. (Dosing Schematic)

Figure 1. Cycle 1 Dosing Schematic



Subjects will be hospitalized during the venetoclax ramp-up period during Cycle 1 (e.g., Days –1 through Day 4).

Cycle Length – 28 Days

- Venetoclax 400 mg or Placebo QD on Days 1 – 28
- Azacitidine75 mg/m^2 SC or IV (per local label) Daily for 7 Days

Subjects will continue their study treatment until documented disease progression per Investigator assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). Subjects will continue to receive the assigned study treatment without cross over until treatment discontinuation. Azacitidine administration starting with Cycle 5 and subsequent cycles may be administered in a non-hospital/clinic environment, as allowed per local regulations. Baseline laboratory assessments will be obtained at Cycle 1 Day 1 prior to first dose of study treatment. PRO measures scheduled for administration should be completed after a blood sample is taken to confirm the subject is able to receive study treatment at the study visit, but prior to the performance of all other non-PRO assessments and the administration of study treatment. All subjects will have a Final Visit performed when treatment is discontinued unless subject has withdrawn consent to participate in the study. All subjects will be followed for survival information (i.e., date and cause of death) unless the subject requests to be withdrawn specifically from this study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

Disease assessments by the modified IWG criteria[15] will be performed at end of Cycle 1 (± 3 days) and every 3 cycles starting on Cycle 4 Day 1 and continuing until disease progression as defined per ELN criteria[16] or the subject withdraws consent. In addition to being reviewed by the Investigator and local hematopathologists, all pertinent information for disease assessment will be reviewed by an Independent Review Committee (IRC) to provide response assessment. Interpretations from the IRC will not be shared with sites. Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC. A charter will outline the review process for the IRC's determination of response. An Independent Data Monitoring Committee (IDMC)

will periodically review safety and efficacy data per the IDMC Charter. Details regarding the IDMC are provided in Section 5.5.5.2.

5.1.4 Post Treatment Follow-Up

Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected (e.g., via telephone calls and/or clinical visits) every 2 months after the last study visit or as needed to allow for more frequent survival analyses until end of study, defined as last subject last visit.

Post treatment follow up for subjects who discontinue study drugs for reasons other than disease progression, hematology and disease assessments data will be collected every 2 months or as needed to allow for more frequent survival analyses until end of study, defined as last subject last visit.

All subjects will be followed for survival information (i.e., date and cause of death) unless the subject requests to be withdrawn specifically from this study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator. In such instances, sites may enter confirmation of death using source documentation from publicly available records such as death certificates or funeral notices.

For subjects that are considered lost to follow-up but have not withdrawn consent, reasonable attempts must be made to obtain information on the survival status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent and documented in the subject's source documents.

30 Day Safety Follow-Up Visit

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety

assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event is achieved.

A Safety Follow-Up Visit does not need to be performed for subjects who had a Final Visit conducted > 30 days after discontinuation of study drug and did not require additional adverse event follow-up. If the subject refuses or is unable to attend the Safety Follow-Up Visit, this should be noted in the subject's source documentation.

5.2 Selection of Study Population

The study population consists of treatment naïve subjects with AML who are considered ineligible for standard induction therapy. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Subject must have confirmation of AML by WHO criteria, previously untreated and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities.
2. Subject must be ≥ 18 years of age.
3. Subject must have a projected life expectancy of at least 12 weeks.
4. Subject must be considered ineligible for induction therapy defined by the following:
   - ≥ 75 years of age;

   OR

   - ≥ 18 to 74 years of age with **at least one** of the following co-morbidities:
     - ECOG Performance Status of 2 or 3;
     - Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina;
     - DLCO ≤ 65% or FEV1 ≤ 65%;

- Creatinine clearance ≥ 30 mL/min to < 45 ml/min;
- Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN;
- Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the AbbVie TA MD during screening and before study enrollment.

5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status:

   - 0 to 2 for subjects ≥ 75 years of age.

   OR

   - 0 to 3 for subjects ≥ 18 to 74 years of age.

6. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hours urine collection.

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet (\text{Weight in kg}) \bullet [0.85 \text{ if Female}]}{72 \bullet \text{Serum Creatinine (mg/dL)}}$$

Or, if serum creatinine is in µmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet (\text{Weight in kg}) \bullet [1.23 \text{ if Male, } 1.04 \text{ if Female}]}{\text{Serum Creatinine (µmol/L)}}$$

7. Subject must have adequate liver function as demonstrated by:

   - aspartate aminotransferase (AST) ≤ 3.0 × ULN*
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN*
   - bilirubin ≤ 1.5 × ULN*

     * Unless considered due to leukemic organ involvement.

     - Subjects who are < 75 years may have a bilirubin of ≤ 3.0 × ULN

8. Female subjects must be either postmenopausal defined as:

   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

     OR
   - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

     OR

   Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at Study Day 1 through at least 90 days after the last dose of study drug.

9. Male subjects who are sexually active, must agree, from Study Day 1 through at least 90 days after the last dose of study drug, to practice the protocol specified contraception. Male subjects must agree to refrain from sperm donation from initial study drug administration through at least 90 days after the last dose of study drug.

10. Female subjects of childbearing potential must have negative results for pregnancy test performed:

    - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
    - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.

11. Subject must voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

1 – 7	To select the appropriate subject population for the evaluation
8 – 10	The impact of venetoclax on pregnancy is unknown
11	In accordance with Harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Subject has received treatment with the following:
   - A hypomethylating agent, venetoclax and/or chemo therapeutic agent for Myelodysplastic syndrome (MDS).
   - CAR-T cell therapy.
   - Experimental therapies for MDS or AML.
   - Current participation in another research or observational study
2. Subject has history of myeloproliferative neoplasm [MPN] including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukemia (CML) with or without *BCR-ABL*1 translocation and AML with *BCR-ABL*1 translocation.
3. Subject has the following:
   - Favorable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) as per the NCCN Guidelines Version 2, 2016 for Acute Myeloid Leukemia.
4. Subject has acute promyelocytic leukemia.
5. Subject has known active CNS involvement with AML.
6. Subject has known HIV infection (due to potential drug-drug interactions between antiretroviral medications and venetoclax) HIV testing will be performed at Screening, only if required per local guidelines or institutional standards.
7. Subject is known to be positive for hepatitis B or C infection [HCV Ab indicative of a previous or current infection; and/or positive HBs Ag or detected sensitivity on HBV-DNA PCR test for HBc Ab and/or HBs Ab positivity] with the exception of

those with an undetectable viral load within 3 months of screening. (Hepatitis B or C testing is not required). Subjects with serologic evidence of prior vaccination to HBV [i.e., HBs Ag-, and anti-HBs+] may participate.

8. Subject has received strong and/or moderate CYP3A inducers within 7 days prior to the initiation of study treatment.
   - Chinese AML subjects participating in the safety cohort per Appendix K are also excluded from receiving strong and/or moderate CYP3A inhibitors from 7 days prior to the initiation of study treatment through the entire dose limiting toxicity (DLT)/safety evaluation period.
9. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.
10. Subject has a cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
11. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, any other medical condition or known hypersensitivity to any of the study medications including excipients of azacitidine that in the opinion of the investigator would adversely affect his/her participating in this study.
12. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
13. Subject exhibits evidence of other clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial or fungal).
14. Subject has a history of other malignancies within 2 years prior to study entry, with the exception of:

- Adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast;
- Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
- Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent; requires discussion with TA MD.

15. Subject has a white blood cell count > 25×10^9/L. (Hydroxyurea or leukapheresis are permitted to meet this criterion.)

Rationale for Exclusion Criteria

1 – 10	To select the appropriate subject population for the evaluation
11 – 15	For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medications, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be documented in source documents and electronic case report forms (eCRFs) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency.

The AbbVie TA MD or designee (refer to Section 6.1.5) should be contacted if there are any questions regarding prior and concomitant therapies.

General guidelines regarding excluded, cautionary and allowed medications are summarized in Table 1 and Appendix H.

Table 1. Excluded Food/Medications

Excluded Food (From 3 Days Prior to Study Administration Until Last Day of Treatment)
• Grapefruit and grapefruit products • Seville Oranges (including marmalade containing Seville oranges) • Starfruit
Excluded Medications
• **Strong CYP3A Inducers** – during ramp up and throughout the study
Cautionary, Additional Guidance Noted
• **Strong and Moderate CYP3A inhibitors^** Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 2-fold for moderate inhibitors and at least 8-fold for strong inhibitors during co-administration (see Table 2). • **Moderate CYP3A inducers^** Exclude during the ramp-up phase and consider alternative medications. If subject requires use of these medications, use with caution and contact AbbVie TA MD or designee (refer to Section 6.1.5) for guidance. • **P-gp inhibitors** Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 2-fold (see Table 2).
Cautionary
• Warfarin* • Coumarin derivatives* e.g., phenprocoumon • P-gp substrates** • BCRP substrates • OATP1B1/1B3 substrates • BCRP inhibitors

^ Chinese AML subjects enrolled in the safety cohort are prohibited to take strong CYP3A inhibitors, moderate CYP3A inhibitors and inducers from the initiation of study treatment through the entire dose limiting toxicity (DLT)/safety evaluation period.

* Closely monitor International Normalized Ratio (INR).

** If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

Table 2. Dose Modifications for Venetoclax: Moderate and Strong CYP3A Inhibitor Use

Venetoclax Dose	Modified Venetoclax Dose if Co-Administered with a Moderate CYP3A or P-gp Inhibitor	Modified Venetoclax Dose if Co-Administered with a Strong CYP3A Inhibitor
100 mg (Cycle 1 Day 1 ONLY)	50 mg	10 mg
200 mg (Cycle 1 Day 2 ONLY)	100 mg	20 mg
400 mg	200 mg	50 mg

Note: After discontinuation of the inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the previous dose level. Ramp-up is not required upon discontinuation of the inhibitor.

A sample list of excluded medications and cautionary medications that fall into the categories within section can be found in Appendix H. It is not possible to produce a 100% exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate local product label and/or FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

If the investigator determines that such a medication is medically necessary without an available alternative, the investigator will notify the AbbVie TA MD prior to administration and discuss the investigator's use of these medications and the investigator's plans to medically monitor the subject. Commonly used anti-infective agents for prophylaxis have CYP3A inhibitory properties and dose reductions of venetoclax/placebo are required. When feasible, administration of such a medication should be planned prior to beginning ramp up or beginning of a cycle to prevent dose reductions during a treatment cycle.

Steroid therapy during study participation should be limited to lower dose and short duration if medically indicated. Exceptions can be inhalational steroids for the treatment of asthma or COPD, topical steroids and for prevention and/or treatment of transfusion related reactions.

Intrathecal chemotherapy or radiation therapy for CNS prophylaxis is not permitted during study participation.

5.2.4 Contraception Recommendations

While participating in this research study, female subjects should not become pregnant or breastfeed a baby. Male subjects should not father a baby.

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 90 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1. Also, subjects must use a barrier method during this study from initial study drug administration to 90 days after the last dose of study drug as drug.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1. Also, subjects must use a barrier method during this study from initial study drug administration to 90 days after the last dose of study drug.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, vasectomy occurred more than 3 months prior to screening and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence

(e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 90 days after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Additionally, male subject agrees not to donate sperm from Study Day 1 through at least 90 days after the last dose of study drug.

5.3 Pharmacokinetic, Biomarker, Exploratory Research, Safety and Efficacy, Assessments/Variables

5.3.1 Safety and Efficacy Measurements Assessed and Flow Chart

This study is designed to assess Pharmacokinetic, Biomarker, Exploratory Research, and Safety data. Exploratory efficacy analyses will be performed on all subjects enrolled unless otherwise specified. Study procedures described in this protocol are summarized in Appendix C.

5.3.1.1 Study Procedures

All study procedures outlined in Appendix C are discussed in detail in this section, with the exception of adverse event information (discussed in Section 6.0). All study data will be recorded on eCRFs.

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. Every effort should be made to ensure the safety of subjects, while

maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the details in this section and Appendix C on how to proceed.

Procedures performed at Screening will serve as baseline, unless repeated on Cycle 1 Day 1 prior to dosing; in which case the latter will serve as baseline. Any abnormal laboratory or vital sign assessment between screening and prior to administration of study drug will be recorded in the subject's medical history and will also serve as the subject's baseline. Record highest grade of cytopenias in medical history, including any transfusion support, prophylaxis received regardless if screening value indicates a lesser grade.

A subject who has signed the informed consent, has had at least one study procedure conducted, and is determined to be a screen failure, will not proceed into the study.

Informed Consent

Signed informed consent form will be obtained from the subject or the subject's legally acceptable representative in order to participate in this study. The IRB approved informed consent form must be signed and dated by each subject prior to undergoing any study procedures or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent will also be required for the optional exploratory research sampling portion of the study. Refer to Section 9.3 for details on obtaining and documenting informed consents.

Due to the COVID-19 pandemic, modifications to the protocol procedures may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, drug delivery method, etc.). Documentation of this notification and verbal consent should be maintained at the site. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible.

Medical and Oncologic History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Detailed oncology history including:
  - Date of diagnosis of AML and subtype
  - Date of diagnosis of any previous malignancy and/or antecedent hematologic disorder
  - Histology
  - Any surgical procedures
  - Treatments administered (including dates and type of modality)
  - Transfusion of blood products within 8 weeks
- Prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken.

On Cycle 1 Day 1, any changes observed from the Screening assessments (prior to dosing and not related to study specific required procedures) will be recorded in the subject's medical history. At each visit, including the Final Visit and the 30-Day Safety Follow-Up Visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded on the adverse event eCRF.

Adverse Event and Prior/Concomitant Medication Assessment

All concomitant medications (prescription or over-the-counter, including vitamins and/or herbal supplements) and AE assessments will be performed per Appendix C. On Cycle 1 Day 1, any events observed from the time of signing of the informed consent but prior to initial study drug administration will be recorded as a serious or non-serious adverse event, if considered by the Investigator to be causally related to the study-required procedures.

Cytogenetic Assessment

Cytogenetic (chromosomal) analysis must be performed locally from diagnostic bone marrow (preferred) or from peripheral blood if adequate number of circulating blasts ($> 10^9$/L) are present. Fluorescence-in-situ hybridization (FISH) analysis can be performed to exclude favorable risk cytogenetic risk category (per NCCN Guidelines listed in Appendix F) where available during screening to avoid undue delay of enrollment, however, cytogenetic analysis must be completed for all subjects and the results must be available prior to randomization. Historic cytogenetic data will be accepted if done within 1 month prior to screening.

Molecular Markers

Profiling of common genetic abnormalities in AML may be explored on a mandatory bone marrow sample at a central laboratory designated by AbbVie.

Patient-Reported Outcome (PRO) Variables

PRO assessments include PROMIS Cancer Fatigue SF 7a, EORTC QLQ-C30, and EQ-5D-5L. These assessments will be collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, per Appendix C, including Final Visit. PRO assessments will be self-administered by subjects using the electronic tablets supplied by the sponsor and site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. PRO assessments should generally be completed prior to any other procedures and clinical assessments and prior to dosing; however, they may be administered following confirmation that the subject is able to receive study treatment at the visit.

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO instruments over the phone as needed. Delegated site staff may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date

and time of PRO data collection should be recorded along with who collected the information. Subject responses will be entered into Trialmax, the Electronic Patient Reported Outcome (ePRO) system, instead of the electronic tablet, by the site staff. IRB/EC approval should be obtained prior to completing PROs by phone interview.

PROMIS Cancer Fatigue SF 7a

PROMIS® is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being.[25] PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. Fatigue will be assessed using the PROMIS Cancer Fatigue SF that has been developed for use in oncology populations.[26,27] PROMIS Cancer Fatigue SF 7a is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. The recommended minimum important difference range is 3 – 5 points; the lower bound (3) is being used as the minimum important difference in this study.[28] All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always.

EORTC QLQ-C30

Health-related quality of life (HRQoL) and symptoms will be assessed with the EORTC-QLQ-C30 version 3.[29] The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language-cultural groups. A change of 5 to 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference. A change of ≥ 10 to < 20 points is considered a moderate change.

EQ-5D-5L

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations.[30,31] The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scores for the 5 dimensions are used to compute a single utility index score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health. The minimum important difference for the EQ-5D-5L utility index score in cancer patients is 0.08, and the minimum important difference for EQ-5D VAS is 7.[32,33]

Table 3. Patient-Reported Outcome Assessments

Administration Order	Test	Administration Time
1	PROMIS Cancer Fatigue SF 7a	Approximately 5 minutes
2	EORTC QLQ-C30	Approximately 12 minutes
3	EQ-5D-5L	Approximately 5 minutes
	Total Admin Time: Approximately 22 minutes	

Physical Examination

Physical examinations (full and targeted exams), including body weight, will be performed per Appendix C. These will be measured at:

- Screening
- Day 1 of every cycle
- Prior to discharge from hospital
- Final Visit
- 30-Day Safety Follow-up

The targeted physical exam includes an assessment of heart, lung, and abdomen, and any body system, guided by the examiner's observations or subject complaints on new or

changed conditions, symptoms, or concerns. Targeted exams can be performed by the Principal Investigator (PI) or delegated to qualified medical staff (e.g., a sub-Investigator, nurse, etc.).

If the screening physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the exam on Cycle 1 Day 1 unless clinically indicated. Physical examinations after screening may be performed within 3 days before the scheduled visit. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Screening Visit only. For height and weight, subject should not wear shoes and wear lightweight clothing.

Vital Signs

Body temperature, weight, sitting blood pressure, pulse, and respiratory rate will be measured at all visits prior to blood collections and prior to dosing with venetoclax/placebo and azacitidine per Appendix C. These will be measured at:

- Screening
- Cycle 1 Day 1 and Day 1 of every cycle
- Final Visit
- 30-Day Safety Follow-up

It is recommended that vital signs should be assessed after the subject has been seated quietly for at least 5 minutes.

ECOG Performance Status

The ECOG performance status per Appendix C will be assessed at:

- Screening
- Cycle 1 Day 1 and Day 1 of every cycle
- Final Visit

- 30-Day Safety Follow-up

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self -care. Totally confined to bed or chair.

12-Lead Electrocardiogram (ECG)

A single 12-lead resting ECG per Appendix C will be obtained at:

- Screening
- Final Visit (May be obtained within ± 2 days of the visit)
- As clinically indicated

Electrocardiograms will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit radiofrequency signals in the room.

Each ECG will be evaluated by an appropriately qualified physician at the study site (the "local reader") who will determine if any findings outside normal physiological variation are clinically significant. The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and subject discontinuation from the study.

The local reader will sign and date the safety ECG and provide a global interpretation using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of ECGs will be entered into the electronic case report forms (eCRFs). If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate using Fridericia's formula (QTcF) will be calculated for all ECGs and documented only if the QT interval is determined to be prolonged by the local reader.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

Multiple Gated Acquisition Scan (MUGA)/2D Echocardiogram with Doppler

Assessment of ejection fraction will be made at Screening per Appendix C by either a MUGA (preferred method) or 2D echocardiogram with Doppler only if needed to determine eligibility for subjects ≥ 18 to 74 years of age with cardiac disease. Findings will be documented on the appropriate eCRF. Subsequent MUGAs/echocardiograms will be performed whenever clinically necessary. It is preferred that the same method of assessment is used for a given subject.

The original MUGA/echocardiogram report with physician assessment will be retained in the subject's records at the study site. If necessary, AbbVie may request that copies of MUGA/echocardiogram reports be sent in for further analysis.

Pulmonary Function Tests

Assessment of lung function by diffusion capacity of lung (DLCO) or forced expiratory volume during the first second (FEV1) will be made at Screening per Appendix C only if needed to determine eligibility for subjects ≥ 18 to 74 years of age with respiratory disease.

Bone Marrow Aspirate and Biopsy For Disease Assessment

Bone marrow aspirates and biopsies per Appendix C will be obtained for local assessment at the following time points until two successive samples indicate CR or CRi:

- Screening
- End of Cycle 1 (must be performed within ± 3 days of Cycle 1 Day 28 and resulted prior to the administration of treatment for Cycle 2)
- For subjects with resistant disease at end of Cycle 1 a repeat bone marrow must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to assess for a response of CR/CRi.
- For subjects with a response of CRi on two successive bone marrow samples an additional bone marrow aspirate and biopsy must be performed to confirm a CR once peripheral blood count recovery is noted.
- For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week).
- Upon concern for relapse.
- Final Visit (If no BM collected within last 6 – 8 weeks, or if relapse of disease has already been confirmed).

Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis could be used as baseline assessment to satisfy eligibility criteria as long as the samples were taken 30 days prior to randomization. A bone marrow aspirate and biopsy must be performed for all subjects during screening to collect mandatory samples for biomarker assessments *(biomarker collections are not applicable to subjects enrolled in China)*.

Bone marrow aspirates and/or biopsies performed in addition to those required per protocol as standard of care throughout the study should also be captured on an eCRF.

A sufficient bone marrow aspirate and bone marrow core biopsy must be collected for all subjects at each of the disease assessments for local pathology assessment and mandatory biomarker assessments. The bone marrow core biopsy sample collection is mandatory; it is considered an optional procedure only for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects if the marrow aspirate sample is inadequate or un-evaluable for disease assessment, another bone marrow aspirate and biopsy sample must be performed within 7 days. The corresponding local laboratory pathology/bone marrow report should be sent to the central laboratory for each local disease assessment. The local laboratory's pathology/bone marrow report will be used by the IRC during their assessment of disease response. Detailed collection instructions for the local laboratory pathology/bone marrow report which is to be utilized by the IRC will be provided by the Sponsor. Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

Clinical Laboratory Tests

All subjects will undergo the laboratory assessments listed in Table 4 per the schedule in Appendix C. Certified local laboratories will be utilized to process and provide results for all of the tests listed in Table 4. These data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories.

Due to travel restrictions and other changes in local regulations in light of the COVID-19 pandemic, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible for subject safety and to determine the next cycle of study treatment.

If laboratory samples cannot be obtained, study drug administration cannot be continued unless the investigator has reviewed all prior laboratory results as close to the planned new cycle of study treatment, confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within approximately 3 days from the scheduled visit.

Table 4. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Blast count (if detected)	Blood urea nitrogen (BUN) or Urea Creatinine Calculated or Measured creatinine clearance Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid or Urate Total protein Glucose Albumin Lactate dehydrogenase (LDH) Bicarbonate or Carbon dioxide	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination (as clinically indicated)
Coagulation		
Prothrombin time (PT) or International Normalized Ratio (INR) Activated partial thromboplastin time (aPTT)		

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator may repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.

- A laboratory test value that requires a subject to be discontinued from the study, requires a subject to receive treatment, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or the investigator considers clinically significant will be recorded as an adverse event.

Chemistry and Hematology

Chemistry and hematology per Appendix C will be performed at:

- Screening
- Cycle 1 Days 1, 2, 3, 4, 5,* 8, 15, 22
- Day 1 of Cycle 2 and Day 1 of every cycle thereafter. Starting with Cycle 3 Day 1 may be performed within 3 days prior to the scheduled visit.**
- Final Visit
- 30-Day Safety Follow-up
- As needed throughout study

* Additional laboratory assessments may be performed per investigator discretion, up to 48 hours after reaching final dose if clinically indicated.

** For cycles with bone marrow assessments, hematology and chemistry labs should be performed on the same day as the bone marrow assessment. If the disease assessment occurs outside of the visit window, then the hematology and chemistry labs should be repeated prior to dosing.

Additional hematology and chemistry laboratory assessments will be performed based on the clinical indications per institutional guidelines and regional standards between Cycle 1 to the beginning of Cycle 2 Day 1 and after subsequent treatment cycles.

For chemistry labs performed for TLS prophylaxis and monitoring during dose ramp up period during Cycle 1, refer to Section 6.1.7.1, Management of Tumor Lysis Syndrome, and Appendix I, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS), for specific requirements.

Coagulation

Prothrombin time (PT) or International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) samples per Appendix C will be collected at:

- Screening
- Cycle 1 Day 1
- Final Visit

Urinalysis

Urinalysis samples per Appendix C will be collected at:

- Screening
- Cycle 1 Day 1
- Final Visit

Documentation of Non-Childbearing Status and Pregnancy Testing

For each female subject, the Investigator will document non-childbearing status (surgically sterile or post-menopausal for at least 1 year) or potential childbearing status.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

For all female subjects of childbearing potential, pregnancy testing must be performed as follows:

- Screening – with serum sample obtained within 14 days prior to the first study drug administration.
- Cycle 1 Day 1 – if it has been > 7 days since obtaining the serum pregnancy results (performed by either urine or serum pregnancy testing),
- Subjects with borderline pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

- Day 1 of each subsequent cycle, until all study drugs are permanently withdrawn (performed by either urine or serum pregnancy testing)

Subject Calendar/Diaries

Subject calendars/diaries will be provided at the time of discharge from the hospital. Subjects will be instructed to bring their calendars/diaries back to the site to be reviewed at each visit, including at any visit at which a dose level change may be required.

Subjects will be instructed to record the date and time each dose of study drug is taken, (indicating if any doses of study drug are missed) and whether or not doses were taken within 30 minutes after the completion of a meal.

Subjects will also be instructed to record adverse events and concomitant medications in the subject calendars/diaries.

The calendars/diaries are to be reviewed at each visit and relevant pages are to be photocopied by study staff. By the end of the subject's participation in the study, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

Randomization and Subject (Screening) Number Assignment

Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number only after the subject has signed the informed consent and prior to any study-specific procedures being performed (e.g., labs are drawn). Screening numbers will be a unique 5 – digit number and will begin with 10001 with the first three digits representing the investigative site, and the last two digits representing the subjects at that site. Subjects who meet all Inclusion Criteria and none of the Exclusion Criteria after Screening will proceed to being randomized. The site will contact the IRT to complete the randomization process and obtain study drug assignment. Subjects will be enrolled as described in Section 5.5.3 and will receive a separate unique 6-digit randomization

number that will be automatically recorded in the eCRF through the IRT system. This randomization number will be used only by AbbVie for loading the treatment schedule into the database. Study treatment should start within 5 days after randomization, however this window cannot exceed the allotted 21 day Screening period. All subsequent drug assignments and changes in subject status (e.g., treatment completion) will be registered in the IRT.

Dispensing Venetoclax/Placebo

Randomized subjects will receive sufficient quantities of venetoclax/placebo for 28 days in each 28-day cycle during all cycles. The IRT will assign kit of venetoclax/placebo to be dispensed to a subject. Prior to each drug dispensation, site personnel must contact IRT for kit number assignment. **Venetoclax/placebo cannot be dispensed without contacting the IRT.** AbbVie or designee (refer to Section 7.0) will provide specific instructions on the use of IRT.

Subjects will be provided with venetoclax/placebo self-administration instructions. Subjects will be instructed to store venetoclax/placebo according to specific directions included in Section 5.5.2.1. Subjects are required to return bottles of venetoclax/placebo (empty, partially filled, or full) to the study site prior to the start of the next cycle and at the Final Visit.

Dispensing Azacitidine

The IRT will assign every vial of azacitidine which was supplied by AbbVie to be dispensed for use by the site. Prior to each drug dispensation, site personnel must contact IRT for vial number assignment. AbbVie supplied Azacitidine cannot be dispensed without contacting the IRT. AbbVie or designee (refer to Section 7.0) will provide specific instructions on the use of IRT.

Azacitidine which is to be supplied locally will be dispensed and tracked per the normal practices of those sites.

5.3.1.2 Collection and Handling of Biomarker and Exploratory Research Samples (Not Applicable for China)

Whole blood, plasma, bone marrow aspirate, and bone marrow core biopsy tissue will be collected per Appendix D. In addition to the mandatory biomarker research specimens, subjects will also have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in the optional exploratory research. Specimens collected for these purposes may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. All samples should be prepared, labeled, and shipped as outlined in the study-specific laboratory manual. The biomarker rationale is discussed in the Biomarker Research Variables Section (Section 5.3.6).

AbbVie (or people or companies working with AbbVie) will store the mandatory and optional biomarker and exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Mandatory Samples for Biomarker Analysis

Blood Collections:

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M15-656 Laboratory Manual.

Blood Collection for Plasma:

Approximately 4 mL or 20 mL of blood will be collected prior to dose at:

- Screening or prior to first dose of study drug (4 mL)
- End of Cycle 1 (20 mL)

- Response assessments: every 3 cycles after end of Cycle 1 assessment (20 mL)
- Final Visit/Time of Relapse (20 mL)

Bone Marrow Aspirate and Biopsy Collections

Bone marrow aspirates should be drawn into appropriately labeled tubes in conjunction with the disease assessments. A portion of the aspirate must be processed according to the institutional standard procedures for diagnostic evaluation (locally); however, approximately 6 to 7 mL of the bone marrow aspirate should be collected for biomarker assessments, which will be shipped to the central laboratory. Detailed processing will be outlined in the most current version of the Study M15-656 Laboratory Manual for the following:

Bone Marrow Collection for Disease Assessment/MRD by Flow Cytometry

NOTE: This should be the first tube drawn from the bone marrow aspirate collection.

Approximately 1 to 2 mL of bone marrow aspirate at:

- Screening visit
- End of Cycle 1
- Response assessments: every 3 cycles after end of Cycle 1 assessment
- Final Visit/Time of Relapse

Bone Marrow Collection for AML Mutational Profiling

Approximately 1 mL of bone marrow aspirate at:

- Screening visit
- Final Visit/Time of Relapse

Bone Marrow Collection for Translational Research:

- Screening visit (4 mL)

- End of Cycle 1 and every 3 cycles after end of Cycle 1 for response assessment (1 mL)
- Final Visit/Time of Relapse (4 mL)

For subjects, where bone marrow aspirates are no longer required for response assessments, the biomarker samples will also not be collected.

Bone Marrow Biopsy for Bcl-2 Family Protein Analysis

Either an FFPE tissue block or approximately 6 to 10 slides from the bone marrow core biopsy should be collected at:

- Screening visit
- Final Visit/Time of Relapse

5.3.1.3 Samples for Optional Pharmacogenetic Exploratory Research (Not Applicable for China)

Optional whole blood samples for DNA and RNA isolation will be collected on Cycle 1 Day 1 (pre-dose), Cycle 3 Day 1 and Final/Relapse Visit from each subject who consents to provide samples for exploratory research. Pharmacogenetic samples should be prepared, labeled, and shipped as outlined in the most current Study M15-656 laboratory manual.

5.3.1.4 Meals and Dietary Requirements

Each dose of venetoclax/placebo will be taken orally once daily with approximately 240 mL of water within approximately 30 minutes after the completion of a meal (preferably after breakfast). Tablets must be swallowed whole and must not be broken, chewed, or crushed.

Subjects may not consume the following: grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is

completed due to possible CYP3A mediated metabolic interaction. It is expected that sites record if excluded food products are consumed by the subject during the study.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assays of venetoclax, azacitidine and their possible metabolites will be collected by venipuncture at each study visit indicated in Appendix E. Blood samples must be protected from direct sunlight during collection, processing and storage. A total of approximately 7 blood samples (3 ml) for venetoclax will be collected per subject. A total of approximately 5 blood samples (6 mL) for azacitidine will be collected from approximately 75 subjects. The total number of venetoclax pharmacokinetic samples planned is 2800 and at minimum 375 azacitidine pharmacokinetic samples for analysis. Additionally, intensive pharmacokinetic samples will be obtained on Cycle 2 Day 4 for the Chinese AML safety cohort subjects from China mainland sites, as indicated in Appendix K.

5.3.2.2 Handling/Processing of Samples

Blood Samples for Venetoclax PK Assay

Detailed sample collection and processing instructions for the venetoclax PK will be provided in the current Study M15-656 laboratory manual.

Blood Samples for Azacitidine PK Assay (Only Australia, Canada, France, Germany, Japan and US)

Detailed sample collection and processing instructions for the azacitidine PK will be provided in the current Study M15-656 laboratory manual.

5.3.2.3 Disposition of Samples

The frozen plasma pharmacokinetic samples for venetoclax and azacitidine assays will be packed in dry ice sufficient to last during transport and shipped from the study site to a central lab designated by AbbVie. An inventory of the samples included will accompany

the package. Please refer to current Study M15-656 laboratory manual for complete shipping instructions.

5.3.2.4 Measurement Methods

Plasma concentrations of venetoclax and azacitidine will be determined under the supervision of the Drug Analysis Department at AbbVie. Plasma concentration of possible venetoclax metabolite(s) may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

Efficacy Assessments

Responses will be evaluated based on the revised guidelines by the International Working Group (IWG) for AML. Progressive disease is defined per European LeukemiaNet recommendations. Subject's response is based on most recent physical examination, bone marrow results and recent hematology values. For subjects who require a delay in next cycle of study treatment for peripheral blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks from the bone marrow evaluation or pre-dose labs from Day 1 of the next cycle can be used to determine the IWG response. As a significant number of the subjects in this study might have antecedent hematologic illnesses, hematologic response including transfusion independence will also be evaluated.

Criteria for evaluation are as follows:

- CR: Absolute neutrophil count > 10^3/μL, platelets > 10^5/μL, red cell transfusion independence, and bone marrow with < 5% blasts, absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease
- CRi: All criteria as CR except for residual neutropenia ≤ 10^3/μL (1000/μL) or thrombocytopenia ≤ 10^5/μL (100,000/μL). Red blood cell transfusion (RBC) dependence is also defined as CRi.
- PR: All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.

- MLFS: Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of circulating blasts and extramedullary disease without peripheral blood count recovery that meet the thresholds for either CR or CRi.
- RD: Failure to achieve CR, CRi, PR or MLFS; in subjects surviving at least 7 days following completion of Cycle 1 treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
- MR: Bone Marrow blasts ≥ 5% after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
  * In cases with bone marrow blast percentages of 5% – 10%, a repeat marrow should be performed 1 week later to distinguish relapse from bone marrow regeneration.
- PD:
  - > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5×10^9/L [500/μL], and/or platelet count to > 50×10^9/L [50 000/μL] non-transfused); or
  - 50% increase in peripheral blasts (WBC × % blasts) to > 25×10^9/L (> 25 000/μL); or
  - New extramedullary disease

Reporting of Results

All dosed subjects will be assessed for response to treatment based on the published guidelines. Assessments will be performed at the end of Cycle 1 and every 3 cycles thereafter for response assessment. Subject will be assigned to one or more of the following categories by the investigators:

1. complete remission;
2. complete remission with incomplete blood count recovery;
3. partial remission;

4. morphologic leukemia free state;
5. resistant disease;
6. progressive disease;
7. indeterminate (not assessable, insufficient data);
8. morphologic relapse;

MRD status if performed at investigator site for subjects who achieve CR or CRi:

1. minimal residual disease negative;
2. minimal residual disease positive.

5.3.4 Safety Variables

The safety of venetoclax or placebo plus azacitidine will be assessed by evaluating study drug exposure, adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters.

5.3.5 Pharmacokinetic Variables

Values for the PK parameters of venetoclax, including the apparent clearance (CL/F), may be determined using a population PK approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Biomarker and Optional Exploratory Research Variables (Not Applicable for China)

Blood and bone marrow specimens will be collected to conduct exploratory biomarker analyses. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Evaluations may include the identification of common molecular aberrations at baseline, the assessment of minimal residual disease levels present after therapy, and analyzing biomarkers related to the pathway(s) targeted

by the study drug or believed to be related to the disease or to drug response. For example, inhibition of BCL-2 by Venetoclax induces apoptosis in AML cell lines and patient derived blasts suggesting that BCL-2 levels may be predictive of response. Therefore, we may evaluate the relationships between BCL-2 (protein, activity and/or gene expression) at baseline and patient responses to therapy (i.e., overall survival and complete response rates) for correlations with efficacy. The information learned from analyzing these samples may be used to investigate factors impacting response to treatment, scientific questions related to AML or in the development of new therapies. The results of biomarker analysis are exploratory in nature, may not be conducted in GLP laboratories, and the results may not be included with the clinical study report.

Blood and bone marrow samples collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study. The samples may also be used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) continues but no longer than 20 years after study completion.

Overall, the goals of the biomarker analyses described in this section are to 1) determine the relationship between drug concentration and disease status (pharmacodynamics) and 2) identify responsive patient populations (based on subject characteristics at baseline and relapse).

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects from Treatment

Each subject has the right to withdraw from the study at any time. In addition, the investigator will discontinue a subject from the study treatment at any time if the investigator considers it necessary for any reason including:

- The investigator believes it is in the best interest of the subject;

- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease as defined per ELN criteria while on study drug;
- Treatment failure, defined as failure to achieve CR, CRi, PR, or MLFS after at least 6 cycles of study treatment;
- The subject experiences toxicities related to study drug that require more than a 4-week (1 cycle) dose interruption of venetoclax or azacitidine, in the absence of clinical benefit;
- The subject requires any radiotherapy or chemotherapy agents during the study period (with the exception of hydroxyurea allowed during Cycle 1);
- The occurrence of an adverse event that precludes further azacitidine drug administration;
- Noncompliance with the protocol.
- The subject becomes pregnant while on study drug.

The investigator or the study site personnel will inform AbbVie prior to discontinuing a subject from the study by contacting the AbbVie TA MD as identified in Section 7.0. All subjects will be included for analysis of safety data.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study and the primary reason will be recorded and a Final Visit along with all necessary procedures per Appendix C (will be performed as soon as possible after discontinuation from the study). The subject would then enter Post Treatment Follow Up as outlined in Section 5.1.4 and follow all necessary procedures per Appendix C.

Subjects with disease progression or relapse may continue to receive study treatment if the investigator considers it to be in the best interest of the subject. Disease assessment will be captured in EDC per protocol criteria. The subject will be monitored per study procedures described in Section 5.3.1.1 or more often if the investigator considers it necessary.

Due to the COVID-19 pandemic, temporary study drug interruption may occur. Refer to the Section 5.3.1.1, Study Procedures and Appendix C for details on how to handle study activities/procedures accordingly. Study drug interruptions due to COVID-19 restrictions should be captured in EDC.

At the end of the subject's participation in the study, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

If, in the judgment of the investigator and AbbVie, the continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. The following procedures for discontinuation will be followed:

- If the sponsor has decided to prematurely discontinue the study, the sponsor will promptly notify in writing the investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- The investigator must promptly notify the IEC/IRB and give detailed reasons for the discontinuation.

The investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered

Subjects will take daily venetoclax 400 mg or placebo orally in the form of tablets. Venetoclax or placebo should always be given before azacitidine when administered for 7 days of every cycle, starting on Day 1 of each cycle. Subjects will self-administer Venetoclax or placebo by mouth QD. Tablets must be swallowed whole and must not be broken, chewed, or crushed.

Azacitidine must be prepared as per the applicable Summary of Product Characteristics (SmPC), and administered by the route indicated in the package insert or prescribing information. Subjects should be pre-medicated with anti-emetics for nausea and vomiting.

5.5.2 Identity of Investigational Products

Table 5. Identity of Investigational Product and Non-Investigational Products

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax Film-Coated Tablet	N/A	100 mg	Oral	AbbVie
Venetoclax Film-Coated Tablet	N/A	50 mg	Oral	AbbVie
Venetoclax Film-Coated Tablet	N/A	10 mg	Oral	AbbVie
Matching Placebo for Venetoclax 100 mg Film-Coated Tablet	N/A	0 mg	Oral	AbbVie
Matching Placebo for Venetoclax 50 mg Film-Coated Tablet	N/A	0 mg	Oral	AbbVie
Matching Placebo for Venetoclax 10 mg Film-Coated Tablet	N/A	0 mg	Oral	AbbVie
Azacitidine	Vidaza	100 mg powder for injection	SC or IV	Celgene or generic

AbbVie will provide venetoclax, and placebo for venetoclax for the study. AbbVie will provide azacitidine for selected countries.

Identity of Non-Investigational Product

Sites may be responsible for obtaining azacitidine in countries where it is approved for AML. For operational or regulatory purposes, AbbVie may provide azacitidine depending on local requirements. Azacitidine should be obtained from a licensed pharmacy or wholesaler.

Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and/or lot numbers for all azacitidine dispensed by the site.

Packaging and Labeling

Venetoclax tablets or placebo for venetoclax tablets will be packaged in high density polyethylene (HDPE) plastic bottles. The Venetoclax 100 mg or placebo bottle will contain 140 tablets, 50 mg or placebo bottle will contain 28 tablets, and 10 mg or placebo bottle will contain 5 tablets. The bottles will be labeled as per local regulatory requirements.

Azacitidine which is supplied by AbbVie will be provided as 100 mg lyophilized powder per single use vial. Each vial and carton will be labeled per local regulatory requirements. Each vial must be reconstituted and administered by the route as per the local azacitidine label.

5.5.2.1 Storage and Disposition of Study Drug(s)

Venetoclax or placebo for venetoclax study drug must be stored at 15° to 25°C (59° to 77°F). Azacitidine must be stored between 15° to 25°C (59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

5.5.3 Method of Assigning Subjects to Treatment Groups

The IRT will randomize subjects into the 2 treatment arms in a 2:1 ratio (venetoclax + azacitidine or placebo + azacitidine). A bottle (kit) number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IRT vendor. Subject randomization will be stratified by age (18 – < 75, ≥ 75), cytogenetics (intermediate risk, poor risk) and region (US, EU, China, Japan, Rest of world).

5.5.4 Selection and Timing of Dose for Each Subject

Venetoclax/placebo will be administered orally once daily (QD) Days 1 through 28, of a 28-day cycle, with a designated dose of 400 mg daily after ramp up in Cycle 1. During Cycle 1 Days 1 – 3, the dose will ramp up from 100 mg on Day 1, 200 mg on Day 2, and 400 mg on Day 3.

Azacitidine (75 mg/m^2) should be given QD following administration of venetoclax or placebo for 7 days of every cycle, starting on Day 1 of each cycle.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

The Investigator, the study site personnel, AbbVie site monitoring team and the subject will remain blinded to each subject's treatment with venetoclax/placebo throughout the course of the study. Limited AbbVie personnel have been unblinded following the planned second interim analysis, including AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team.

The Chinese subjects in mainland China who are participating in the AML safety cohort will receive open label venetoclax during the participation, as described in Appendix K.

All subjects will be treated with open-label azacitidine.

The IRT system can provide access to blinded subject treatment information during the study. AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

If the blind is broken for a subject currently on study treatment by the investigator, that subject would need to be discontinued from study treatment and post treatment or survival follow-up would commence.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An IDMC will review safety and efficacy data for this study in an un-blinded fashion and provide recommendations to AbbVie as per the IDMC charter. Details of the IDMC, including IDMC membership, which will include individuals with experience in treatment of patients with AML, and member responsibilities, will be outlined in the IDMC Charter. Clinical safety data will be reviewed at pre-determined intervals throughout the course of the study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

An interactive response system (IRT) will assign every bottle and/or kit of venetoclax/placebo and AbbVie supplied azacitidine to be dispensed to a subject during the study. Prior to each scheduled visit, site personnel must contact IRT for the next bottle or kit number(s) assignment. AbbVie or its designee will provide specific instructions on the use of IRT.

Depending on local regulations due to the COVID-19 pandemic, provision of study drug for direct-to-patient (DTP) and direct-from□patient (DFP) transfer will be available upon request. AbbVie has contracted with a third party vendor, Marken, for sites to ship study

drug DTP and DFP. Sites will be able to use Marken and/or another local courier for drug shipment, as needed. If necessary, notify AbbVie if DTP and/or DFP shipping will be used.

Sites will be responsible to:

- Meet IRB/IEC reporting requirements and submit the booking form (which will be provided) to the local IRB/IEC, as applicable.
- Submit the booking form at least 72 business hours before the drug needs to be picked up.
- Discuss the DTP and DFP process with the subject including:
  - Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
  - Obtain results of required safety procedures (e.g., urine pregnancy testing) before registering subject dispensation of study drug in IRT.
  - Confirm the subject will be available to accept delivery.
  - Confirm the subject will maintain the drug containers, as well as any unused drug for return to site.
- Follow up with the subject after shipment is received.
- Retain documentation of the shipment for IP accountability and monitoring.

To document compliance with the treatment regimen, subjects will be instructed to return all unused tablets and/or bottles (even if empty) and any other study-related items as necessary to the study coordinator at scheduled study visits. Compliance will be monitored and documented by the designated study site personnel on the appropriate form. The designated study site personnel will question the subject regarding adherence to the dosing regimen, record the number of tablets and/or bottles returned, the date returned and determine treatment compliance before dispensing new study drug to the subject. Compliance below 80% may require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document. The investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed to the subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the study site closeout visit. Upon completion or termination of the study, all original containers (containing partially used or unused venetoclax/placebo) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If pre-arranged between AbbVie and the site, destruction of used and unused venetoclax or placebo bottles will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a multicenter, randomized, double blind study to evaluate the efficacy and safety of venetoclax plus azacitidine compared to an active control of placebo plus azacitidine. The choice of the control group allows for a double blind assessment of the contribution of venetoclax to the safety and efficacy of the backbone regimen azacitidine.

Azacitidine is a low intensity therapy for AML and is currently approved in Europe as a single agent for patients with AML who are not candidates for standard induction chemotherapy or HSCT. The response rate in patients who were treated with azacitidine as monotherapy are substantially lower than what is seen in Study M14-358 in combination with venetoclax, a novel agent with BCL-2 inhibition. This combination would be a reasonable therapeutic regimen to be studied as an active comparator in a randomized, controlled study designed to evaluate the therapeutic value of a novel

investigational agent added to a hypomethylating agent that is currently used standard of care in this population.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard and validated.

The PRO measures chosen for this study have been validated in cancer patients. The specific symptoms and functional aspects assessed by these measures are considered to be among the most impactful to AML patients.[34,35]

5.6.3 Suitability of Subject Population

Subjects who have histological confirmation of acute myeloid leukemia who are treatment naïve, greater than or equal to 18 years of age, considered ineligible for treatment with a standard induction regimen due to age and comorbidity, and appropriate for azacitidine control arm may be enrolled. Study M14-358, which provides the experimental arm projections, enrolled a similar patient population.

5.6.4 Selection of Doses in the Study

The selected dosage of venetoclax is based on the results from Study M14-358, an ongoing Phase 1b study of escalating doses of venetoclax in combination with hypomethylating agents (HMA) i.e., decitabine and azacitidine in treatment naïve AML subjects greater than or equal to 65 years of age, and ineligible for treatment with a standard cytarabine and anthracycline induction regimen. The ORR of CR/CRi/PR was higher than the reported ORR from the Phase 3 monotherapy HMA trials in this population as reported in Section 3.0. While the efficacy and safety data at both 400 mg and 800 mg dose of venetoclax in combination with HMAs was comparable, prolonged neutropenia is reported in subjects receiving 800 mg dose of venetoclax after achieving a CR/CRi compared to subjects receiving 400 mg dose.

An exposure-response analysis of the efficacy from Study M14-358 indicated that the predicted probability of achieving CRi or better was approximately 70% at exposures associated with both the 400 mg and 800 mg daily dosage regimen of venetoclax in combination with the HMAs. The Maximum Tolerated Dose (MTD) of venetoclax was not reached in Study M14-358 at the highest tested dose of venetoclax (1200 mg daily). Only short-term safety and efficacy data are available at the 1200 mg dose. The emerging safety data with doses at 1200 mg daily, demonstrated increase in gastrointestinal adverse events of nausea (≥ 80%) and diarrhea (≥ 50%) in both of the HMA combination arms. Both safety and efficacy were taken into consideration for the selection of a maximum 400 mg daily dose of venetoclax to be used in combination with azacitidine for this study.

The dosing regimen for azacitidine is the dose specified for treatment of adult patients with AML in the EU SmPC and for treatment of myelodysplastic syndrome in the US prescribing information. Subjects will be treated for a minimum of 6 cycles. Failure to achieve CR, CRi or MLFS after at least 6 cycles of study treatment is considered as treatment failure. Treatment will be continued as long as the patient continues to derive clinical benefit or until documented disease progression or develops unacceptable toxicity.

5.6.4.1 Dose Adjustments for Venetoclax Upon Co-Administration with Anti-Fungal Agents

Patients with AML are at high risk for febrile neutropenia and life threatening fungal infections. Azoles, all of which are CYP3A inhibitors, are widely used in these patients for prophylaxis and treatment of invasive fungal infections.[36] As venetoclax is predominantly metabolized by CYP3A, co-administration with antifungal agents which are strong or moderate CYP3A inhibitors are expected to increase venetoclax exposures.

The effect of two strong CYP3A inhibitors (posaconazole and ketoconazole) on the pharmacokinetics of venetoclax was evaluated in two separate studies. Study M13-364 was conducted to evaluate the effect of ketoconazole given once daily on pharmacokinetics of a single dose of venetoclax in 12 subjects with NHL,[37] and a cohort of 12 untreated elderly AML subjects in Study M14-358 was enrolled to assess the effect

of posaconazole given twice daily on exposures of venetoclax given once daily.[38] Furthermore, prior studies indicated venetoclax bioavailability to be dependent on both food and dose. To account for the effect of covariates such as food and dose non-linearity on the bioavailability of venetoclax, a population PK model was used to simulate exposures of venetoclax in presence of strong CYP3A inhibitors.

The ramp-up scheme for venetoclax when given alone is 100 mg on Day 1, 200 mg on Day 2 and 400 mg QD from Day 3 onwards. To match the exposures (AUC) from these doses, venetoclax doses of 10 mg on Day 1, 20 mg on Day 2 and 50 mg QD from Day 3 onwards were chosen when co-administered with strong CYP3A inhibitors to mitigate any possible risk for TLS and ensure safety. Predicted venetoclax exposures when administered alone and in presence of strong CYP3A inhibitors at the recommended dose reductions are shown in Table 6.

Table 6. Predicted Geometric Mean (and 90% CI) AUC_{24} Exposures of Venetoclax When Administered Alone and in Presence of Strong CYP3A Inhibitor

	Venetoclax Alone				Venetoclax + Strong CYP3A Inhibitor			
	Ramp-Up			Steady-State	Ramp-Up			Steady-State
PK Parameter	Day 1 100 mg	Day 2 200 mg	Day 3 400 mg	Day 28 400 mg	Day 1 10 mg	Day 2 20 mg	Day 3 50 mg	Day 28 50 mg
AUC_{24} (µg•hr/mL)	4.23 (3.65 – 4.84)	8.86 (7.69 – 10.1)	15.9 (13.8 – 18.3)	20.5 (17.24 – 24.29)	1.20 (1.04 – 1.38)	3.17 (2.77 – 3.62)	7.01 (6.12 – 7.97)	26.4 (22.3 – 31.3)

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution. Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other cause of the event." For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic

medical intervention, meet protocol specific criteria (see Section 6.1.7) regarding toxicity management) or if the Investigator considers them to be adverse events.

Hospitalization of a subject to allow observation and management (e.g., for IV hydration) for the purpose of TLS prophylaxis will not be captured as a serious adverse event (SAE), unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

A treatment-emergent adverse event is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of venetoclax/placebo or azacitidine is administered until 30 days have elapsed following discontinuation of venetoclax/placebo and Azacitidine administration.

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event **within 24 hours** of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. Deaths related to disease progression will not be recorded as adverse events.

6.1.1.3 Adverse Events Commonly Associated with AML Study Population and/or Progression of AML

Certain adverse events are anticipated to occur in the study population (AML) at some frequency independent of drug exposure. These are discussed here as Adverse Events commonly associated with AML or progression of AML. Such events include known consequences of the underlying disease under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population).

These adverse events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol. An Independent Data Monitoring Committee will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of AML. Persistent cytopenias at the same CTCAE grade as at baseline are not to be reported as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the investigator had an identifiable cause other than the underlying disease. Record highest grade of cytopenias in medical history, including transfusion support and prophylaxis administered, regardless if screening value indicates a lesser CTCAE grade. Any clinically relevant abnormal laboratory assessment between screening and prior to administration of Venetoclax will be recorded in the patient's medical history.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, these Serious Adverse Event commonly associated with AML or progression of AML should be **reported to AbbVie as a serious adverse event *within 24 hours* of the site being made aware of the serious adverse event** (as defined in this Section).

6.1.1.4 Adverse Events Expected due to Study Related Endpoints

6.1.1.4.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol specified adverse event collection period (Section 6.1.4) that are attributed by the investigator solely to progression of AML should be recorded only on the Death eCRF and the Study Completion Form eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (Section 6.1.5).

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03). When applicable, once the diagnosis is confirmed the medical term should be reported for an event rather than the abnormal lab result as identified in CTCAE. If a reported adverse event increases in severity, the initial adverse event should be given final outcome date and a new adverse event must be reported to reflect the change in severity such that the dates on these AE's cannot overlap. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

For adverse events not captured by the Common Terminology Criteria, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life-threatening requiring urgent intervention (severe).

Grade 5 The adverse event resulted in death of the subject (severe).

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

The Investigator will assess the relationship of each adverse event to venetoclax/placebo, and to azacitidine. Some events may be reasonably related to more than one drug or to none. For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated to study drug.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the Investigator for the serious adverse event.

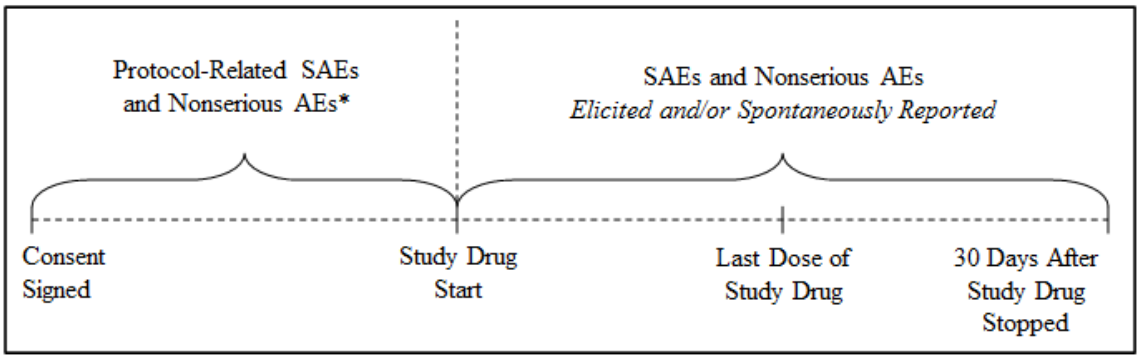
6.1.4 Adverse Event Collection Period

Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of venetoclax/placebo, or azacitidine will be collected only if they are considered by the Investigator to be causally related to the study-required procedures.

In addition, all serious and nonserious adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847)-938-0660

For safety concerns, contact the Oncology Safety Management Team at:

Oncology Safety Management
Dept. R48S, Bldg. AP30
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Safety Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

AbbVie Therapeutic Area Medical Director:

[redacted] MD, FACP
Senior Medical Director
Oncology Development
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Fax: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of the DSUR reporting period serves as the RSI during the reporting period. For follow up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

Due to the COVID-19 pandemic and evolving local regulations, urgent safety measures may need to be employed in order to protect participating subjects from any immediate hazard. Such events and measures should be reported to the sponsor emergency medical contact listed above immediately.

6.1.6 Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancy in a subject's partner will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

Management of Cytopenias and Infections

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in subjects with AML. Subjects with baseline neutropenia or those with secondary AML might be particularly at high risk.

Anti-infective prophylaxis for bacterial, viral and fungal infections are required for all subjects with ANC of < 500/µL. Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of these agents should be based on regional guidelines or institutional standards. Potential for drug-drug interactions should be considered. Please refer to Table 1, Table 2 and Appendix H for list of excluded and cautionary medications and implement dose reductions for venetoclax/placebo as necessary.

If a subject achieves CRi or has a morphologic leukemia free bone marrow (MLFS) (i.e., bone marrow blasts < 5%) after completion of Cycle 1, venetoclax/placebo should be interrupted to allow for ANC recovery from Day 29 until ANC ≥ 500/µL or up to 14 days. Cycle 2 administration of azacitidine will also be delayed until ANC ≥ 500/µL. Both venetoclax/placebo and azacitidine will resume on the same day after the interruption. If a subject presents with new onset Grade 4 neutropenia for more than 1 week during subsequent cycles, unless it is thought to be due to the underlying disease, venetoclax/placebo dosing should be interrupted until ANC is ≥ 500/µL. After Cycle 3, for subjects in CR/CRi who required interruption or delay of study drug administration for cytopenias (neutropenia [≤ 500/µL] or thrombocytopenia [≤ 50×10^3/µL]) venetoclax/placebo should be administered for 21 days out of 28 days during each of the subsequent cycles. Treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/µL and/or platelet count ≥ 50×10^3/µL or for up to 14 days whichever occurs earlier.

Subjects with ANC of 1000/µL **and** platelet count > 100 × 10^3/µL at end of C1 may proceed to C2D1 study treatment before the results of the bone marrow aspirate and biopsy preformed at end of C1 become available.

Subjects with resistant disease after Cycle 1 should receive subsequent cycles of study treatment with no dose interruption/delay until a repeat bone marrow assessment demonstrates CRi or MLFS. Once this response is achieved, dose interruptions and reduction in duration of venetoclax administration for neutropenia should be implemented as described above beginning from the cycle where a CRi or MLFS is demonstrated. If hematologic recovery (ANC or platelets) is achieved within 14 days after completion of the cycle, the duration of venetoclax is reduced to 21 days of the subsequent 28-day cycle. During subsequent cycles, if hematologic recovery with more than 25% increase above the nadir is not seen by Day 28, reassess counts every 7 days. If a 25% increase has not been achieved within 14 days after the completion of a cycle, based on the bone marrow biopsy cellularity azacitidine dose adjustment can be made as follows:

Table 7. Azacitidine Dose Modification

	% Dose in the Next Cycle if Recovery is Not Achieved Within 14 Days	
Bone Marrow Cellularity	**Recovery ≤ 21 Days**	**Recovery > 21 Days**
15 – 50%	100%	50%
< 15%	100%	33%

These are provided in Appendix L. If additional dose reductions or modifications that are thought to be necessary by the investigator a discussion with the AbbVie medical monitor (TA MD) is required. Subjects experiencing delays for a medical event unrelated to study treatment may delay study treatment up to 4 weeks. Delays greater than 21 days must be discussed with the AbbVie TA MD or a designee.

6.1.7.1 Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

There is a potential risk for TLS in subjects with AML, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment LDH levels, renal dysfunction, and dehydration.[39,40] In addition, on-target effect of venetoclax could lead to rapid cell death and pose a risk of TLS. To mitigate the risk for TLS all subjects enrolled in to the study will need TLS prophylaxis and monitoring. For subjects at higher risk for TLS, additional mitigation measures with more intensive laboratory monitoring and intervention should be implemented. Lower starting dose of venetoclax/placebo may be considered. Prophylactic reductions of potassium, inorganic phosphorus or uric acid above normal range are recommended prior to beginning study treatment and continue based on the ongoing risk of TLS.

Below are the minimum requirements for TLS prophylaxis and management for all subjects enrolled into the study. All other prophylaxis and monitoring procedures for TLS will be implemented as per regional guidelines/institutional standards:

- All subjects will be hospitalized on or before Day 1 of Cycle 1 prior to administration of the initial dose of study treatment and remain in the hospital for at least for 24 hours after reaching the final dose of venetoclax/placebo.
- All subjects must receive uric acid reducing agent, adequate oral and intravenous hydration as tolerated while monitoring the fluid status of the subject prior to and during the ramp up of venetoclax/placebo. The uric acid reducing agent, type of fluids and the rate of infusion will be determined by the investigator based on regional standards or institutional guidelines.
- TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax/placebo dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose.
- Additional laboratory assessments may be performed, per investigator discretion, post-dose during ramp up and up to 48 hours after reaching final dose if clinically indicated.

- Abnormal chemistry tests during ramp up should be corrected promptly. If a subject meets criteria for clinically significant laboratory or clinical TLS please follow institutional guidelines or recommendations in Appendix G, no additional venetoclax/placebo dose should be administered until resolution.[41] For continued dosing of venetoclax/placebo, monitor for evidence of TLS during study treatment, and manage abnormalities of serum creatinine, and electrolytes promptly.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:
[redacted]
Study Management Associate III
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office:
Email:

AbbVie TA MD:
[redacted], MD, FACP
Senior Medical Director
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Office:
Cell:
Fax:
Email:

Alternate Contact:
[redacted]
Study Project Manager II
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
Office:
Cell:
Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Definition for Analysis Populations

The safety analysis set consists of all subjects who take at least one dose of study drug (the combination of venetoclax/placebo and azacitidine). The safety analysis set will be

used for safety analyses. The full analysis set consists of all randomized subjects. The full analysis set will be used for efficacy analyses.

8.1.2 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics prior to the initiation of any component of study drug (or randomization for non-treated subjects). 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.

Continuous demographic data (e.g., age, height, and weight) will be summarized with means, standard deviation, minimum, maximum, and range. Frequencies and percentages will be computed for categorical data (e.g., sex, race, number of prior therapies, geography, and baseline ECOG performance status).

8.1.3 Pharmacokinetics

Plasma concentrations of venetoclax and/or azacitidine will be listed for each subject by arm and scheduled visit. Summary statistics will be computed for each arm and dose level by scheduled visit. Samples with significant sampling time deviations will be excluded from summary statistics calculations.

8.1.4 Efficacy Endpoints

8.1.4.1 Primary Efficacy Endpoint

8.1.4.1.1 Primary Efficacy Endpoint in US and US Reference Countries

For US and US reference countries, this study has single primary efficacy endpoint of overall survival (OS), with significance level of 0.05 (two-sided).

Overall survival will be defined as the number of days from the date of randomization to the date of death. Subjects that have not died will be censored at the last known date to be alive. The distribution of overall survival will be estimated for each treatment arm using

Kaplan-Meier methodology and compared between treatment arms using the log-rank test stratified by age (18 – < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk).

8.1.4.1.2 Primary Efficacy Endpoints in EU and EU Reference Countries

For Japan, EU and EU reference countries, this study has dual primary endpoints of CR + CRi rate (as assessed by investigator) and overall survival (OS). The significance level of 0.05 (two sided) will be split between the dual primary endpoints to give a 0.01 significance level to the CR + CRi rate analysis (based on the investigator assessment) and an overall 0.04 significance level to the OS analysis.

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRi) will be calculated based on the modified IWG criteria for AML. Subjects who are randomized but have no IWG disease assessment will be considered as non-responders for CR + CRi rate. CR + CRi rate will be compared between treatment arms using CMH test stratified by age (18 – < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk). In addition, 95% confidence interval will be constructed for CR + CRi rate.

8.1.4.2 Secondary Efficacy Endpoints

Fixed sequence testing procedure will be used for analyses of the primary and key secondary efficacy endpoints. If statistical test is not significant for the primary efficacy endpoint(s), then statistical significance will not be declared for any of the secondary efficacy endpoints.

For US and US reference countries, the key secondary efficacy endpoints are CR + CRi rate, CR + CRh rate, CR + CRi at initiation of Cycle 2, CR rate, post-baseline transfusion independence rates for RBC and/or platelets, the rates of conversion from baseline transfusion dependence to post-baseline transfusion independence post-baseline.

For Japan, EU and EU reference countries, the key secondary efficacy endpoints are CR + CRh rate, CR + CRi at initiation of Cycle 2, CR rate, post-baseline transfusion

independence rates for RBC and/or platelets, the rates of conversion from baseline transfusion dependence to post-baseline transfusion independence post-baseline.

Additional secondary efficacy endpoints are: MRD response rate among subjects with CR + CRi and subjects with CR + CRh: CR + CRi rate in biomarker subgroups (e.g., FLT3, IDH1, IDH2), CR + CRh rate in biomarker subgroup (e.g., FLT3, IDH1, IDH2), OS in biomarker subgroup (e.g., FLT3, IDH1, IDH2), change from baseline in PROMIS Cancer Fatigue SF 7a global fatigue score, change from baseline in GHS/QoL scale from the EORTC QLQ-C30, and event free survival (EFS).

To adjust for multiple testing of the key secondary efficacy endpoints, a fixed sequence testing procedure will be used. The key secondary efficacy endpoints and corresponding ranking will be specified in the statistical analysis plan (SAP) prior to the primary analysis of CR + CRi. Unless otherwise specified, all response/progression related endpoints (e,g., CR/CRi and EFS) will be based on the investigator assessment.

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

- Bone marrow with < 5% blasts
- peripheral blood neutrophil count of > $0.5 \times 10^3/\mu L$*
- peripheral blood platelet count of > $0.5 \times 10^5/\mu L$*

* 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.

* platelet transfusion independence for ≥ 7 days prior to the hematology lab results

The same analysis planned for CR + CRi rate will be performed for CR + CRh rate.

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRi) by the initiation of Cycle 2 will be calculated

based on the modified IWG criteria for AML. Subjects who are randomized but have no IWG disease assessment will be considered as non-responders for CR + CRi rate by the initiation of Cycle 2. CR + CRi rate by the initiation of Cycle 2 will be compared between treatment arms using CMH test stratified by age (18 – < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk). In addition, 95% confidence interval will be constructed for CR + CRi rate by the initiation of Cycle 2.

Post baseline transfusion independence rate will be calculated as the portion of subjects who achieved transfusion independence post baseline. Transfusion independence is defined as a period of at least 56 days with no transfusion between the first dose of study drug and the last dose of study drug + 30 days. In addition, the rate of conversion will be calculated as proportion of subjects being post-baseline transfusion independent from baseline transfusion dependence. The transfusion independence rate will be evaluated for 1) RBC 2) platelet. All randomized subjects will be included to estimate the post-baseline transfusion independence rate. The post-baseline transfusion independence rates will be compared between two arms using CMH test stratified by age (18 – < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk). In addition, 95% confidence interval will be constructed for the post-baseline transfusion independence rates. The rates of conversion from baseline transfusion dependence to post-baseline transfusion independence will be estimated. The conversion rate will be evaluated for 1) RBC 2) platelet.

EFS will be defined as the number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi or MLFS after at least 6 cycles of study treatment, or death from any cause. If a specified event does not occur, subjects will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after randomization will be censored at the date of randomization. The distribution of EFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using the log-rank test stratified by age (18 – < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk).

The proportion of subjects (CR + CRi, or CR + CRh) achieving an MRD response will be calculated and 95% confidence interval will be constructed. MRD response will be defined using a threshold of less than 0.1% of residual blasts per leukocytes as measured in bone marrow. Additional thresholds may also be explored and correlated with efficacy outcomes. The response rates (CR + CRi, or CR + CRh, or CR) and overall survival in molecular subgroups may be evaluated.

Fatigue will be assessed using the PROMIS Cancer Fatigue SF 7a global fatigue score. Scores will be computed according to the procedures outlined in the PROMIS Fatigue scoring manual, available at https://www.assessmentcenter.net/Manuals.aspx. A linear mixed effects regression model with a variable covariance structure will be fitted to the longitudinal data to test for differences between the two treatment arms.

Quality of life will be assessed using the GHS/QoL scale from the EORTC QLQ-C30. Scores will be computed according to procedures outlined in the EORTC QLQ-C30 scoring manual, available at http://groups.eortc.be/qol/manuals. A linear mixed effects regression model with a variable covariance structure will be fitted to the longitudinal data to test for differences between the two treatment arms.

8.1.4.3 Exploratory Efficacy Endpoint

Exploratory analyses comparing the effects of venetoclax + azacitidine versus placebo + azacitidine will be performed on the following PRO measures: EQ-5D-5L, and the subscales/items from the EORTC QLQ-C30 and PROMIS Cancer Fatigue SF 7a. Descriptive statistics will be calculated as per the scoring manuals for all scales/items of the EORTC QLQ-C30, PROMIS Cancer Fatigue SF 7a, the EQ-5D-5L utility score, and the EQ-5D VAS score at each assessment. Linear mixed effects regression models will be used to test for differences between treatment arms, and mean change in values at each assessment will be calculated to identify any statistically significant differences versus baseline. Within-group changes from baseline at each assessment will also be assessed. Additional analyses will include an assessment of time to deterioration and time to improvement.

8.1.5 Efficacy Endpoints per Independent Review Committee

An Independent Review Committee (IRC) will evaluate response and disease progression. The following efficacy endpoints, described in Section 8.1.4.2, will also be summarized based on this IRC review in addition to the investigators' assessments: CR + CRi rate, event-free survival, and CR + CRi rate by the initiation of Cycle 2.

8.1.6 Timing of Efficacy Analyses

The primary analysis for CR + CRi will occur 6 months after the first 225 subjects are randomized. A significance level of 0.01 will be allocated for this analysis.

There will be three planned analyses for the primary endpoint of overall survival.

- At the same time as the CR + CRi analysis. An administrate spending of 0.0001 significance level will be allocated to this analysis.
- An interim analysis at the time of approximately 270 OS events (75% of the total 360 events).
- Final analysis at the time of approximately 360 OS events.

A formal interim analysis for safety will be performed and reviewed by the Independent Data Monitoring Committee (IDMC) after approximately 20 subjects have been dosed and followed by 3 months. In addition, IDMC will review safety data every 3 months after the formal interim analysis for safety.

For Japan, EU and EU reference countries, two interim analyses for efficacy will be performed. The first interim analysis will be performed when 225 subjects have been randomized and followed up for 6 months. Only the CR + CRi endpoint will be analyzed and reviewed by IDMC. This is the Final Analysis for CR + CRi and will be based on investigator's assessment. The second interim analysis will be performed when approximately 270 death events (75% information time for OS) occur.

For US and US reference countries, only one interim analysis for efficacy will be performed at the 75% information time for OS (same timing as the second interim analysis for Japan, EU and EU reference countries).

The details of primary endpoint efficacy boundaries will be described in SAP.

8.1.7 Safety

The safety of venetoclax in combination with azacitidine will be assessed by evaluation of study drug exposure, adverse events, serious adverse events, deaths, and changes in laboratory determinations and vital sign parameters.

8.1.7.1 Study Drug Exposure

The number of days and/or cycles that subjects were exposed to study drug will be summarized.

8.1.7.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug. Treatment-emergent adverse events will be summarized by preferred terms within a System Organ Class according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.[42] In addition, the percentage of subjects experiencing an adverse event at a given NCI CTCAE Version 4.03[43] toxicity grade and relationship to study drug will be provided.

8.1.7.3 Serious Adverse Events

Serious adverse events will be summarized as described for Adverse Events above.

8.1.7.4 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of randomization, (2) for deaths occurring within 60 days of randomization, (3) for deaths occurring within 30 days of the last dose of study drug, (4) for deaths occurring more than 30 days of the last dose of study drug, and (5) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.1.7.5 Laboratory Tests and Vital Signs

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

Where applicable, blood chemistry and hematology laboratory determinations will be categorized according to NCI CTCAE (version 4.03) grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post baseline grades of 3 to 4 will be summarized.

8.1.7.6 Special Safety Evaluation of Venetoclax Among Chinese Subjects

When there are nine evaluable Chinese AML subjects enrolled to receive open-label venetoclax plus azacitidine combination treatment the enrollment into this safety cohort of

Chinese subjects will be temporarily suspended until the safety evaluation is performed on these nine Chinese subjects. Assessment of Dose Limiting Toxicities in these subjects is described in Appendix K. Once the safety is deemed acceptable, Chinese sites will be fully open to enrollment for the double blind, randomized portion of the study. Open-label Chinese subjects will also be included in the safety analyses only.

8.2 Determination of Sample Size

For US and countries using the US as the reference country, the study includes single primary endpoint of overall survival. For Japan, EU and countries using EU as reference for obtaining approval, the study includes dual-primary endpoints of overall survival (OS) and CR + CRi rate.

The sample size calculation is based on the following assumptions:

- The significance level (two-sided 0.05) will be split to give a 0.01 significance level to the CR + CRi rate analysis and an overall 0.04 significance level to the OS analysis.
- Median OS of 10.4 months for placebo plus azacitidine arm
- Median OS of 14.9 months for venetoclax plus azacitidine arm (hazard ratio of 0.7)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary
- 2:1 randomization ratio to venetoclax plus azacitidine, and placebo plus azacitidine arm

With the above assumptions, a total of 360 death events will provide 86.7% power to detect statistically significant difference in OS between treatment arms at alpha level of 0.04. A total of approximately 400 subjects (267 in venetoclax in combination with azacitidine arm, and 133 in placebo with azacitidine arm) will be randomized into the study to obtain the 360 death events. The subject randomization will be stratified by age ($18 - < 75, \geq 75$), cytogenetics based on NCCN guidelines for AML Version 2.2016 (intermediate risk, poor risk) and region (US, EU, China, Japan Rest of world). With twelve subjects in the open label Chinese safety cohort required per the CFDA, the overall

sample size will be approximately 412, as described in Appendix K. The subjects from China who participate in the open label safety cohort described in Appendix K will not be included in the efficacy analysis and will not count towards the 360 death events.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing

clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to Section 5.3.1.1, Study Procedures and Appendix C, Study Activities, for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker and exploratory research samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker and exploratory research samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

A separate informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for the **optional exploratory research**. The nature of the testing should be explained and the subject given an opportunity to ask questions. This separate informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the **optional exploratory research**, it will not impact their participation in the study.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRFs) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 Code of Federal Regulations (CFR) Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person

performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

Patient-reported data must be completed for each subject enrolled in this study. These data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor Signant Health of Blue Bell, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device, except in cases where completion by interview is necessary due to COVID-19 restrictions; the data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived

on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected electronically via a tablet device into which the patient will directly enter the required pieces of information, except in cases where completion by interview is necessary due to COVID-19 restrictions. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients to complete more than one of the same assessments at any one visit. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by CRF Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive. If the PRO data is collected by phone interview, the delegated staff will enter the subject's responses into TrialMax. Completion of PROs by phone interview should be approved by the site's IRB/EC.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the Investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

The AbbVie monitor will monitor the study site throughout the study. Source document review will be made against entries on the case report forms and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after the case report forms are retrieved, a review of the data will be conducted by a physician or representative at AbbVie.

All data hand-entered in the database will be verified at AbbVie. Any discrepancies will be reviewed against the hard-copy case report form and corrected on-line. After completion of the entry process, computer logic and manual checks will be created to identify such items as inconsistent study dates. Any necessary corrections will be made to the database via the appropriate change form/electronic CRF.

Routine hematology, serum chemistry and serology, and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study and updated as necessary throughout the course of the study. A review of all laboratory results will be conducted by the AbbVie monitor, the Investigator and other appropriate personnel from AbbVie.

12.0 Use of Information

All information concerning venetoclax processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of venetoclax. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Data from research may be provided to investigators, used in scientific publications, or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator (Director of the Site in Japan) will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory coordinating Investigator from the Investigators who participate in each multi-center study. Selection criteria for this signatory Investigator will be based on level of participation, and significant knowledge of the clinical research, investigational drug, and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for venetoclax and the product labeling for azacitidine.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy
Protocol Date:	01 July 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19(2):202-8.
2. Konopleva M, Contractor R, Tsao T, et al. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. Cancer Cell. 2006;10(5):375-88.
3. Tsao T, Shi Y, Kornblau S, et al. Concomitant inhibition of DNA methyltransferase and BCL-2 protein function synergistically induce mitochondrial apoptosis in acute myelogenous leukemia cells. Ann Hematol. 2012;91(12):1861-70.
4. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov. 2014;4(3):362-75.
5. van Delft MF, Wei AH, Mason KD, et al. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. Cancer Cell. 2006;10(5):389-99.
6. Tahir SK, Yang X, Anderson MG, et al. Influence of Bcl-2 family members on the cellular response of small-cell lung cancer cell lines to ABT-737. Cancer Res. 2007;67(3):1176-83.
7. Touzeau C, Dousset C, Bodet L, et al. ABT-737 induces apoptosis in mantle cell lymphoma cells with a Bcl-2high/Mcl-1 low profile and synergizes with other antineoplastic agents. Clin Cancer Res. 2011;17(18):5973-81.
8. Wei G, Margolin AA, Haery L, et al. Chemical genomics identifies small-molecule MCL1 repressors and BCL-xL as a predictor of MCL1 sensitivity. Cancer Cell. 2012;21(4):547-62.
9. Marsden VS, Strasser A. Control of apoptosis in the immune system: Bl-2, BH3-only proteins and more. Annu Rebv Immunol. 2003;21:71-105.

10. Sugiyama N, Obinata M, Matsui Y. Bcl-2 inhibits apoptosis of spermatogonia and growth of spermatogonial stem cells in a cell-intrinsic manner. Mol Reprod Dev. 2001;58(1):30-8.
11. Oldereid NB, Angelis PD, Wiger R, et al. Expression of Bcl-2 proteins and spontaneous apoptosis in normal human testis. Mol Hum Reprod. 2001;7(5):403-8.
12. Yamamura K, Kamada S, Ito S, et al. Accelerated disappearance of melanocytes in bcl-2-deficient mice. Cancer Res. 1996;56(15):3546-50.
13. Gregoli PA, Bondurant MC. The roles of Bcl-X(L) and apopain in the control of erythropoiesis by erythropoietin. Blood. 1997;90(2):630-40.
14. AbbVie. Venetoclax (ABT-199) Investigator's Brochure Edition 9. 08 March 2018.
15. Cheson BD, Bennett JM, Kopecky KJ, et al; International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-9.
16. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.
17. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405.
18. SEER Stat Fact Sheets: Acute Myeloid Leukemia (AML). Available from: http://seer.cancer.gov/statfacts/html/amyl.html. Accessed on: 30 April 2016.

19. Thein MS, Ershler WB, Jemal A, et al. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. Cancer. 2013;119(15):2720-7.

20. Foon K, Zighelboim J, Yale C, et al. Intensive chemotherapy is the treatment of choice for elderly patients with acute myelogenous leukemia. Blood. 1981;58(3):467-70.

21. Konopleva M, Pollyea DA, Potluri J, et al. A phase 2 study of ABT-199 (GDC-0199) in patients with acute myelogenous leukemia (AML). Presented at: 56th Annual Meeting of the American Society of Hematology; December 6-9, 2014; San Francisco, CA. Abstract 118.

22. DiNardo C, Pollyea DA, Pratz K, et al. A phase 1b study of venetoclax (ABT-199/GDC-0199) in combination with decitabine or azacitidine in treatment-naive patients with acute myelogenous leukemia who are ≥ 65 years and not eligible for standard induction therapy. Presented at: 57th Annual Meeting of the American Society of Hematology; December 5-8, 2015; Orlando, FL. Abstract 327.

23. 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.

24. 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.

25. Cella D, Yount S, Rothrock N, et al. The patient-reported outcomes measurement information system (PROMIS): progress of an NIH roadmap cooperative group during its first 2 years. Med Care. 2007;45 (5 Suppl 1):S3-11.

26. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol. 2007;25(32):5106-12.

27. Cella D, Riley W, Stone A, et al. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-94.

28. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six PROMIS Cancer scales in advanced-stage cancer patients. J Clin Epidemiol. 2011;64(4):507-16.

29. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

30. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

31. Oppe M, Devlin NJ, van Hout B, et al. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014;17(4):445-53.

32. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial. Eur J Cancer. 2012;48(3):311-23.

33. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70-8

34. Alibhai SMH, Leach M, Kermalli H, et al. Fatigue in older adults with acute myeloid leukemia: predictors and associations with quality of life and functional status. Leukemia. 2007;21(4):845.

35. Sekeres MA, Stone RM, Zahrieh D, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. Leukemia. 2004;18(4):809-16.

36. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348-59.

37. Agarwal SK, Salem AH, Danilov AV, et al. Effect of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of venetoclax, a BCL-2 inhibitor, in patients with non-hodgkin lymphoma. Br J Clin Pharmacol. 2016. doi: 10.1111/bcp.13175. [Epub ahead of print].

38. Agarwal SK, DiNardo C, Potluri J, R et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther. 2017. In press.

39. Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors. Haematologica. 2008;93(1):67-74.

40. Mato AR, Riccio BE, Qin L, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. Leuk Lymphoma. 2006;47(5):877-83.

41. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

42. AbbVie. Coding Guidelines for MedDRA Term Selection, AbbVie Global Pharmaceutical Research and Development (GPRD), Global Pharmacovigilance and Clinical Project Team. Current version on file at AbbVie.

43. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), v4.03, NCI, NIH, DHHS. May 28 June 14, 2010 [cited 2010 September 10]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Director	Statistics
[redacted]	Director	Statistics
[redacted]	Head of Statistics, Late Oncology	Statistics
[redacted]	Study Project Manager II	Clinical
[redacted]	Executive Medical Director	Therapeutic Area
[redacted]	Principal Bioanalytical Investigator	Bioanalysis
[redacted]	Senior Medical Director	Therapeutic Area
[redacted]	Director	Clinical Pharmacology and Pharmacometrics

Appendix C. Study Activities

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
Informed Consent	X[d]															
Medical/Oncology History Assessment	X		X[e]													
AE/Concomitant Medication Assessment[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytogenetic Testing[f]	X															
Tumor Lysis Syndrome Prophylaxis[g]		X	X	X	X	X	X									
Physical Exam (including weight)[h,u]	X[i]		X						X[j]		X			X	X	
Vital Signs[h,u]	X		X								X			X	X	
Pregnancy Test[u]	X		X[s]								X					
ECOG Performance Status[h,u]	X		X								X			X	X	
Hematology/Chemistry[k,u]	X		X	X	X	X	X[t]			X	X			X	X	
Coagulation[h]	X		X											X		
Urinalysis[h]	X		X											X		
12-lead ECG	X													X[l]		
Pulmonary Function Test[m]	X															
MUGA (preferred)/2D Echocardiogram w/Doppler[m]	X															

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
Disease Assessments	X												X	X		X
Bone Marrow Aspirate and Biopsy for Local Disease Assessment	X[n]												X[n,o,p]	X		
PROMIS Cancer Fatigue SF 7a[q,v]			X									X		X		
EORTC QLQ-C30[q,v]			X									X		X		
EQ-5D-5L[q,v]			X									X		X		
Dispense Venetoclax/Placebo[w]											X					
Dispense Subject Calendar/Diary									X[r]		X					
Collect venetoclax and Subject Calendar/Diary											X			X		
Administer Azacitidine[u,*]			X	X	X	X	X	X	X							
Survival Assessments																X

F/U = Follow-Up; PT = Post Treatment

a. Screening procedures must be performed within 21 days prior to initial study drug administration.

b. Final Visit procedures should be performed when a subject discontinues from the study.

c. Post Treatment and survival visits will be performed every 2 months after the last study visit or as needed until end of study, defined as last subject last visit.

d. Obtain informed consent prior to performing any screening or study-specific procedures.

e. On Cycle 1 Day 1, additional medical history that is observed after signing of the informed consent but prior to initial venetoclax or azacitidine administration and not considered related to study-required procedures will be recorded in the subject's medical history.

f. Cytogenetic testing should be performed if not completed within 1 month prior to Screening.

g. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to refer to Section 6.1.7.1, Management of Tumor Lysis Syndrome and Appendix I – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

h. For all study visits after Cycle 3, physical examination, vital signs, ECOG performance status, coagulation and urinalysis may be performed within 3 days before the scheduled visit. Under certain circumstances, these assessments may be performed within 3 days after the scheduled visit with discussion and approval by the AbbVie medical monitor TA MD. PROs can be completed within 3 days prior to Cycle 1 Day 1 Visit.

i. Height will be measured only at Screening.

j. All subjects must have Physical exam prior to discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated venetoclax dose.

k. Only hematology required for disease assessment. TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax/placebo dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose (see Section 6.1.7.1).

l. Final visit ECG may be obtained within ± 2 days of visit.

m. Only required if ECHO or MUGA, DLCO or FEV1 is being used to confirm eligibility for subjects ≥ 18 to 74 years of age.

n. Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis could be used as baseline assessment to satisfy eligibility criteria as long as the samples were taken within 30 days prior to randomization. A bone marrow aspirate and biopsy must be performed for all subjects during screening to collect mandatory samples for biomarker assessments. Bone marrow aspirate and biopsy samples must be collected for all subjects for each of the disease assessments. Bone marrow core biopsy sample collection is considered an optional procedure only for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects if the aspirate sample is inadequate or unevaluable for disease assessment, repeat bone marrow aspirate and biopsy must be performed within 7 days. The corresponding local laboratory pathology report should be sent to the central laboratory for IRC review for each local disease assessment. Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

o. End of Cycle 1 bone marrow aspirate and biopsy must be performed within ± 3 days of Cycle 1 Day 28. Assessments should be performed and resulted by Day 31 prior to the administration of study drugs for Cycle 2. Cycle 1 venetoclax/placebo dosing should continue until bone marrow aspirate result is available. For subjects who require a delay in study treatment for blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks can be used to determine the IWG response. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) and upon concern for relapse. The corresponding local laboratory pathology/bone marrow report will be sent to the central laboratory for IRC review Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

p. For subjects with resistant disease at end of Cycle 1 a repeat bone marrow must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to confirm response.

q. PRO assessments should be completed after a blood sample is taken to confirm the subject is able to receive study treatment at the study visit, but prior to any other procedures or clinical assessments and prior to dosing. PROs can be completed within 3 days prior to Cycle 1 Day 1 dosing.

r. Diaries will be dispensed upon discharge from the hospital.

s. Urine pregnancy test must be obtained at Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at screening. Pregnancy test should be repeated on Day 1 of each cycle and evaluated prior to dosing.

t. Additional laboratory assessments may be performed, per investigator discretion, up to 48 hours after reaching final dose if clinically indicated.

u. Procedure may be performed in the subject's home or local hospital/clinic by adequately trained personnel if required due to COVID-19 restrictions.

v. ePROs may be performed virtually/phone interview by delegated personnel only if required due to COVID-19 restrictions.

w. Venetoclax/placebo may be shipped directly to a subject's home only if required due to COVID-19 restrictions.

* AZA is administered for 7 days for each cycle starting with Day 1.

Appendix D. Schedule of Biomarker/Pharmacodynamic/Pharmacogenetic Sample Collection (Not Applicable for China)

Sample Collections	Screening	Cycle 1 Day 1	End of Cycle 1[a] and Every 3 Cycles	Cycle 3 Day 1	Final Visit/ Time of Relapse[a]	Comments
Plasma	X		X		X	4 mL blood at screening and 20 mL at all other plasma collection time points
Disease Assessment/MRD by Flow	X		X		X	1 – 2 mL bone marrow aspirate
AML Mutational Profiling	X				X	1 mL bone marrow aspirate
Translational Research	X		X		X	4 mL bone marrow aspirate at Screening, and Final Visit. 1 mL at all other collection assessments.
Bone Marrow Biopsy Core for BCL 2 Family Protein Analysis	X				X	FFPE Block or 6 – 10 FFPE slides
Pharmacogenetics (DNA and RNA)[b]		X		X	X	6.5 mL Blood

a. Sample should be split from the bone marrow aspirate for disease assessment. In subjects, that have two successive samples which indicate CR or CRi, bone marrow aspirates are no longer required for response assessments, therefore, the bone marrow aspirate biomarker samples will also not be collected for those subjects. Plasma will still be collected at those visits.

b. Sample is optional and collected only if patient has signed the optional informed consent.

Appendix E. Schedule of Blood Collection for Venetoclax and Azacitidine Assay (Pharmacokinetic Sampling)

Procedures	Cycle 1 Days 1 – 5	Cycle 2, 4, 6, and 8 Day 5
Venetoclax	8 hours post-dose[a]	0 hour (pre-dose)
Azacitidine	End of Infusion[b,c]	End of Infusion[c]

a. The 8-hour post-dose PK sample on Days 1 – 5 of Cycle 1 will be collected if venetoclax is initiated or escalated to a new dose level. If there is a delay in the escalation step, the 8-hour post-dose PK sample will be delayed accordingly. The PK collection performed 8 hours post-dose after each dose escalation may be taken up to 1 hour prior or up to 20 minutes after the scheduled time to allow for processing, if necessary.

b. Cycle 1 Day 5 only.

c. For azacitidine given subcutaneously, PK samples should be drawn 30 minutes post end of injection.

- All "pre-dose" samples in venetoclax PK sampling are relative to venetoclax/placebo administration.
- The date and time (start and end times to the nearest minute) of each azacitidine infusion/injection taken, will be recorded on the eCRF.
- The date and time (to the nearest minute) of each venetoclax/placebo dose taken will be recorded on the eCRF for every scheduled venetoclax PK day and for the 2 doses prior to every scheduled venetoclax PK day.

Appendix F. NCCN Risk Categorization: Guidelines for AML Version 2.2016

Risk Category	Cytogenetics
Favorable Risk	Core binding factor: inv(16) or t(16;16) or t(8;21) t(15;17)
Intermediate Risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor Risk	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5,5q-,-7,7q- 11q23-non t(9;11) inv(3),t(3;3) t(6;9) t(9;22)

Appendix G. Tumor Lysis Syndrome Classification

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome*	Criteria for Classification of Clinical Tumor Lysis Syndrome**
Hyperuricemia	Uric acid > 8 mg/dL (475.8 µmol/liter)	N/A
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter)	N/A
Hyperkalemia	Potassium > 6 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 mg/dL (0.3 mmol/liter)[#]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute Kidney Injury[!]	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) or the presence of oliguria (average urine output of < 0.5 mL/kg/hr over a 6-hour period)

* Laboratory TLS requires two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.

** Clinical TLS requires the presence of Laboratory TLS plus one or more findings from the Clinical TLS column.

Corrected calcium = measured calcium level in mg/dL + 0.8 × (4 – albumin in gm/dL).

! Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; ≥ 12 to < 16 years, both male and female, 88 µmol/L; ≥ 16 years, female 105.6 µmol/L, male 114.4 µmol/L.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Cross reference: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Appendix H. Sample List of Excluded and Cautionary Medication

Excluded
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Cautionary, Consider Alternative Medications, Additional Guidance Noted:
Moderate CYP3A inducers** – bosentan, efavirenz, etravirine, modafinil, nafcillin **Strong CYP3A inhibitors**† – Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole **Moderate CYP3A inhibitors**‡ – Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem[1], dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil **P-gp inhibitors**‡ – Amiodarone, captopril, carvedilol, felodipine, propafenone, quercetin, quinidine, ranolazine, ticagrelor
Cautionary
Warfarin and Coumarin derivatives^ **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate,* mitoxantrone,* irrinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Asunaprevir, atrasentan, atorvastatin, certivastatin, docetaxel, ezetimibe, fluvastatin, glyburide, nateglinide, paclitaxel, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **BCRP inhibitors** Geftinib,* curcumin

* These are anticancer agents; that must not be used during study participation.

** If subject requires use of these medications, use with caution and contact AbbVie Primary TA MD or designee (refer to Section 6.1.5) for guidance.

† If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 8-fold. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the target dose per Table 2.

‡ If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 2-fold. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the target dose per Table 2.

^ Closely monitor International Normalized Ratio (INR).

Note: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Appendix I. Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS)

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Creatinine	
Increase ≥ 25% from baseline	Start or increase rate of IV fluids. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 – 2 hours STAT.

Appendix J. Japan Specific Information

1.0 Clinical Expense and Compensation

1.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses of screening test, etc. will be paid based on the contract concluded with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

1.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and take other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might occur between the investigative site and the subject, the investigative site will report it to the sponsor immediately, and resolve it. The sponsor will cooperate with the investigative site in resolving the problem.
3. When the investigative site must compensate to the subject's health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by investigative site.

4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

1.3 Pharmacogenetic Testing

Pharmacogenetic testing on samples collected in Japan will be restricted to the subject's response to study treatment in terms of pharmacokinetics, efficacy, tolerability, and safety.

Appendix K. Safety Cohort for Evaluation of Venetoclax in AML Chinese Subjects

1.0 Objectives

The objective of the Chinese (enrolled at sites in mainland China) AML safety cohort is to evaluate the safety and PK profile of venetoclax at 400 mg daily dose in combination with azacitidine in a subset of up to 12 Chinese AML prior to allowing China to be fully open to enrollment into the double blind, randomized portion of the study.

2.0 Safety Cohort Procedures

Chinese subjects with AML will be enrolled to receive venetoclax plus azacitidine combination treatment at mainland China sites according to the eligibility criteria and procedures described in Section 5.2. Per Exclusion Criteria Section 5.2.2 strong and moderate CYP3A inhibitors/inducers will be excluded from 7 days prior to the initiation of study treatment through the entire dose limiting toxicity (DLT)/safety evaluation period. The first 9 evaluable Chinese AML subjects for DLT will be treated in an open-label manner. When the first 9 evaluable subjects are enrolled, consenting and enrollment of Chinese AML subjects will be temporarily suspended until the safety and PK evaluation is performed on these subjects.

- A subject who has interrupted venetoclax dosing during the DLT evaluation period due to an adverse event that is believed to be possibly or probably related to venetoclax will be included in the safety evaluation.
- If a subject discontinues the study for any reason other than an adverse event possibly or probably related to venetoclax before the DLT evaluation period of 28 days is complete, the subject will be replaced within the Chinese AML safety cohort.
- The discontinued subject(s) will not be replaced in the main study and will follow procedures in the main protocol as outlined in Appendix C for the Final Visit and Post-Treatment Follow-Up assessments.

Chinese AML safety cohort will receive the same venetoclax plus azacitidine treatment as the subjects in Arm A of the Phase 3 study as described in Section 5.1. The blood samples for venetoclax PK evaluation in the safety cohort will be collected according to the below schedule. All other study procedures should be conducted as outlined in Appendix C.

- Cycle 2 Day 4: PK samples will be collected at 0 (pre-dose), 2, 4, 6, 8 hours after venetoclax dosing.

The date and time of the venetoclax doses on Cycle 2 Day 4 will be captured on the eCRF.

PK samples should be collected and processed according to the instructions provided in the current Study M15-656 laboratory manual.

3.0 Safety Cohort DLT Evaluation

The Chinese AML safety cohort will be monitored for a DLT evaluation period, defined as 4 weeks (during Cycle 1, for 28 days) beginning the first day of venetoclax dosing, to assess the safety of the 400 mg QD dose in combination with azacitidine.

Safety data collected during the DLT evaluation period will be reviewed and the incidence of DLTs will be assessed based on the following definitions:

Definition of DLT:

- Subjects who entered the study with Grade 3 or 4 anemia, neutropenia, or thrombocytopenia will be un-evaluable for hematology related DLT.
- Any of the following events, which are considered possibly or probably related to the administration of venetoclax, will be considered a dose limiting toxicity (DLT):
  - Grade 3, 4, or 5 anemia, neutropenia or thrombocytopenia with a hypocellular bone marrow and no greater than or equal to 5% marrow blasts lasting for 42 days or more.

- NCI CTCAE Grade ≥ 3 non-hematological toxicity with the exception of nausea, vomiting, anorexia, diarrhea, constipation and electrolyte abnormality which are controlled with an intervention and which the investigator judges not to be a DLT.

Any DLT will require an interruption and possible discontinuation of venetoclax or azacitidine. Venetoclax may be reintroduced at a reduced dose, if the toxicity grade returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. If the subject is considered to be acceptable for resumption of venetoclax dosing at the same dose or reduced dose on seventh day of the dose interruption, the event should not be designated as a DLT.

If DLTs occur in < 50% of the Chinese AML safety cohort subjects (e.g., DLT incidence ≤ 4 out of 9 subjects), venetoclax dosing can be considered to be tolerable in Chinese AML subjects and the enrollment of Chinese AML subjects will resume into the study. If the same DLTs occur in ≥ 50% of the Chinese AML safety cohort subjects (e.g., DLT incidence ≥ 5 out of 9 subjects), enrollment of Chinese AML subjects will NOT resume and the study will not continue with enrollment in mainland China. If different DLTs occur in ≥ 50% of the Chinese AML safety cohort subjects (e.g., DLT incidence ≥ 5 out of 9 subjects), the data will be reviewed by AbbVie and the investigator(s) to determine if additional subjects should be enrolled into the Chinese AML safety cohort or if the study should not continue with enrollment in mainland China.

- If the same DLT occurs in 4 subjects before 9 Chinese AML subjects have been enrolled, additional Chinese AML subjects will NOT be enrolled and the study will not continue with enrollment in mainland China.
- If 2 or 3 different DLTs occur in 4 subjects before 9 Chinese AML subjects have been enrolled, or in the opinion of AbbVie and/or the investigator(s) the event is considered clinically significant, the following actions may be taken by AbbVie (in consultation with the investigator[s]):
    - Enrollment of Chinese AML subjects will be suspended and the data will be reviewed by AbbVie and the investigator(s) to determine if additional subjects should be enrolled into the AML safety cohort or if the study should not continue with enrollment in mainland China.

- If the DLT is considered an unmanageable and lethal event, enrollment of Chinese AML subjects will not be continued in mainland China. If the DLT is not considered an unmanageable and lethal event, enrollment of Chinese AML subjects should be continued until 9 subjects are enrolled in the cohort.

For subjects who experience a DLT, the toxicity should be managed according to Section 6.1.7 and the subjects should continue on study until discontinuation criteria, as outlined in Section 5.4.1, are met. Post-treatment assessments will be collected via eCRF at monthly intervals (or as requested by sponsor to support data analysis) for all Chinese AML safety cohort subjects after the last study visit until the endpoint of death or until the subject has become lost-to follow-up or until study termination by AbbVie.

4.0 Planned PK Analysis

Values for the pharmacokinetic parameters of venetoclax including maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) will be determined using noncompartmental methods if the data warrants. Additional parameters may be calculated if useful in the interpretation of the data. Additional analyses may be performed if useful in the interpretation of the data.

Appendix L. Venetoclax and Azacitidine Dose Modifications

Treatment Cycle	Efficacy Assessments	Hematology Results	Action	Modifications
After Cycle 1[a]	CRi MLFS	Incomplete count recovery	Delay upcoming cycle	Venetoclax/placebo should be interrupted to allow for ANC recovery from Day 29 until ANC ≥ 500/µL OR up to 14 days (until Day 42), whichever is earlier. If there is no recovery by Day 42, discussion between the PI and the TA MD is required Cycle 2 administration of azacitidine will also be delayed until ANC ≥ 500/µL OR up to 14 days (venetoclax/placebo and azacitidine will resume on the same day after the interruption)
After Cycle 2	CR, CRi MLFS at end of Cycle 1 or subsequent cycles	New Grade 4 Neutropenia after recovery lasting for more than 1 week (unless due to the underlying disease e.g., relapse)	Delay upcoming cycle	Venetoclax/placebo dosing should be interrupted once cycle is completed until ANC is ≥ 500/µL OR up to 14 days (unless medically necessary to study drug interrupt within cycle)
After Cycle 3	CR CRi MLFS at end of Cycle 1 or subsequent cycles	Subjects requiring interruption or delay of study drug administration for cytopenias (neutropenia/thrombocytopenia)	Reduce venetoclax/ placebo duration	Venetoclax/placebo should be administered for 21 days out of 28 days during each of the subsequent cycles and the treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/µL and/or platelet count ≥ 50×10^3/µL or for up to 14 days.

Treatment Cycle	Efficacy Assessments	Hematology Results	Action	Modifications
After Cycle 4 (azacitidine dose reduction) Applicable after reduced venetoclax/placebo duration	CR CRi MLFS at end of Cycle 1 or subsequent cycles	Hematologic recovery (ANC ≥ 1,000/µL OR PLT ≥ 100,000/µL) is achieved within 14 days after completion of the cycle	No azacitidine reduction	The duration of venetoclax/placebo is reduced to 21 days of the cycle.
		Hematologic recovery (ANC OR PLT) with more than 25% increase above the nadir (mid-cycle) is not seen by Day 28.	Monitor counts and reassess	Reassess counts every 7 days or as often as needed. Refer to the line below.
		If a 25% increase in nadir (mid-cycle) has not been achieved within 14 days after the completion of a cycle	Reduce azacitidine dose	If recovery is not achieved within 21 Days, azacitidine dose adjustment on next cycle can be made as follows: • Bone Marrow Cellularity* (15 – 50%): 50% • Bone Marrow Cellularity* (< 15%): 33% * For Bone Marrow Cellularity, use the most recent value.

a. RD or PR: there is no delay of next cycle. Once these subjects achieve CRi/MLFS, follow steps above in the sequence listed. CRi (ANC < 1,000/µL or PLT < 100,000/µL); MLFS (ANC < 1,000/µL & PLT < 100,000/µL).

Appendix M. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Number of Subjects to be Enrolled:
Previously read:

Approximately 400 to 412 subjects

Has been changed to read:

Approximately 400 to 412 subjects (Enrollment completed with 443 subjects)

Section 1.2 Synopsis
Subsection Methodology:
Heading "Cycle Length – 28 Days"
Add: new second sentence

Subjects will continue to receive the assigned study treatment without cross over until treatment discontinuation.

Section 1.2 Synopsis
Subsection Methodology:
Heading "Cycle Length – 28 Days"
Add: new last sentence

Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

Section 3.2 Benefits and Risks
Add: new fourth paragraph

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. No additional risk to study subjects is

anticipated with the use of venetoclax/placebo in this population with limited treatment options for their underlying AML.

Section 5.1 Overall Study Design and Plan: Description
Second paragraph previously read:

Approximately 400 subjects will be randomized to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Has been changed to read:

443 subjects were randomized to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1.3 Treatment Period
Subsection Cycle Length – 28 Days
First paragraph
Add: new second sentence

Subjects will continue to receive the assigned study treatment without cross over until treatment discontinuation.

Section 5.1.3 Treatment Period
Subsection Cycle Length – 28 Days
Last paragraph
Add: new fourth sentence

Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

Section 5.1.4 Post Treatment Follow-Up
First and second paragraph previously read:

Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of

initiation and completion, etc.) will be collected (e.g., via telephone calls and/or clinical visits) every 2 months after the last study visit for a period of 2 years after the last subject has been enrolled into the study.

Post treatment follow up for subjects who discontinue study drugs for reasons other than disease progression, hematology and disease assessments data will be collected every 2 months for 1 year after the last subject has been enrolled into the study.

Has been changed to read:

Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected (e.g., via telephone calls and/or clinical visits) every 2 months after the last study visit or as needed to allow for more frequent survival analyses until end of study, defined as last subject last visit.

Post treatment follow up for subjects who discontinue study drugs for reasons other than disease progression, hematology and disease assessments data will be collected every 2 months or as needed to allow for more frequent survival analyses until end of study, defined as last subject last visit.

Section 5.3.1.1 Study Procedures
Add: new second paragraph

Study visits may be impacted by changes in local regulations due to the COVID-19 pandemic. Every effort should be made to ensure the safety of subjects, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the details in this section and Appendix C on how to proceed.

Section 5.3.1.1 Study Procedures
Subsection Informed Consent

Due to the COVID-19 pandemic, modifications to the protocol procedures may be necessary. Subjects should be informed of the changes to the conduct of the study relevant to their participation (e.g., cancellation of visits, change in laboratory testing site, drug delivery method, etc.). Documentation of this notification and verbal consent should be maintained at the site. A signed and dated informed consent form should be obtained from the subject afterwards as soon as possible.

Section 5.3.1.1 Study Procedures
Subsection Patient-Reported Outcome (PRO) Variables
Add: new last paragraph

Due to the COVID-19 pandemic and any local restrictions, sites may administer PRO instruments over the phone as needed. Delegated site staff may read the PRO questions and response options to the subject and record the subject's responses. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information. Subject responses will be entered into Trialmax, the Electronic Patient Reported Outcome (ePRO) system, instead of the electronic tablet, by the site staff. IRB/EC approval should be obtained prior to completing PROs by phone interview.

Section 5.3.1.1 Study Procedures
Subsection Bone Marrow Aspirate and Biopsy For Disease Assessment
Last paragraph, fourth sentence previously read:

The corresponding local laboratory pathology/bone marrow report should be sent to the central laboratory for each local disease assessment which is conducted.

Has been changed to read:

The corresponding local laboratory pathology/bone marrow report should be sent to the central laboratory for each local disease assessment.

Section 5.3.1.1 Study Procedures
Subsection Bone Marrow Aspirate and Biopsy For Disease Assessment
Last paragraph
Add: new last sentence

Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Add: new second and third paragraph

Due to travel restrictions and other changes in local regulations in light of the COVID-19 pandemic, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible for subject safety and to determine the next cycle of study treatment.

If laboratory samples cannot be obtained, study drug administration cannot be continued unless the investigator has reviewed all prior laboratory results as close to the planned new cycle of study treatment, confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within approximately 3 days from the scheduled visit.

Section 5.4.1 Discontinuation of Individual Subjects from Treatment
First paragraph, last sentence previously read:

In addition, the investigator will discontinue a subject from the study at any time if the investigator considers it necessary for any reason including:

Has been changed to read:

In addition, the investigator will discontinue a subject from the study treatment at any time if the investigator considers it necessary for any reason including:

Section 5.4.1 Discontinuation of Individual Subjects from Treatment
Add: new fifth paragraph

Due to the COVID-19 pandemic, temporary study drug interruption may occur. Refer to the Section 5.3.1.1, Study Procedures and Appendix C for details on how to handle study activities/procedures accordingly. Study drug interruptions due to COVID-19 restrictions should be captured in EDC.

Section 5.5.5.1 Blinding of Investigational Product
First paragraph previously read:

All AbbVie personnel with direct oversight conduct and management of the trial (with the exception of AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team), the Investigator, the study site personnel, and the subject will remain blinded to each subject's treatment with venetoclax/placebo throughout the course of the study.

Has been changed to read:

The Investigator, the study site personnel, AbbVie site monitoring team and the subject will remain blinded to each subject's treatment with venetoclax/placebo throughout the course of the study. Limited AbbVie personnel have been unblinded following the planned second interim analysis, including AbbVie Clinical Drug Supply Management and AbbVie Pharmacovigilance Team.

Section 5.5.5.1 Blinding of Investigational Product
Add: new last paragraph

If the blind is broken for a subject currently on study treatment by the investigator, that subject would need to be discontinued from study treatment and post treatment or survival follow-up would commence.

Section 5.5.6 Treatment Compliance
Add: new third and fourth paragraph

Depending on local regulations due to the COVID-19 pandemic, provision of study drug for direct-to-patient (DTP) and direct-from□patient (DFP) transfer will be available upon

request. AbbVie has contracted with a third party vendor, Marken, for sites to ship study drug DTP and DFP. Sites will be able to use Marken and/or another local courier for drug shipment, as needed. If necessary, notify AbbVie if DTP and/or DFP shipping will be used.

Sites will be responsible to:

- Meet IRB/IEC reporting requirements and submit the booking form (which will be provided) to the local IRB/IEC, as applicable.
- Submit the booking form at least 72 business hours before the drug needs to be picked up.
- Discuss the DTP and DFP process with the subject including:
  - Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
  - Obtain results of required safety procedures (e.g., urine pregnancy testing) before registering subject dispensation of study drug in IRT.
  - Confirm the subject will be available to accept delivery.
  - Confirm the subject will maintain the drug containers, as well as any unused drug for return to site.
- Follow up with the subject after shipment is received.
- Retain documentation of the shipment for IP accountability and monitoring.

Section 6.1 Medical Complaints
First paragraph, third sentence previously read:

For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event.

Has been changed to read:

For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other cause of the event."

Section 6.1.1.1 Adverse Events
Add: new last paragraph

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol.

Section 6.1.5 Adverse Event Reporting
Add: new last paragraph

Due to the COVID-19 pandemic and evolving local regulations, urgent safety measures may need to be employed in order to protect participating subjects from any immediate hazard. Such events and measures should be reported to the sponsor emergency medical contact listed above immediately.

Section 6.1.7 Toxicity Management
Subsection <u>Management of Cytopenias and Infections</u>
Third paragraph, last sentence previously read:

Treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/μL or platelet count ≥ 50 × 10^3/μL or for up to 14 days whichever occurs earlier.

Has been changed to read:

Treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/μL and/or platelet count ≥ 50 × 10^3/μL or for up to 14 days whichever occurs earlier.

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

[redacted]
Study Project Manager II
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Email:

Has been changed to read:

[redacted]
Study Project Manager II
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Email:

Section 9.2 Ethical Conduct of the Study
Add: new last paragraph

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to Section 5.3.1.1, Study Procedures and Appendix C, Study Activities, for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators

should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Section 10.2 Case Report Forms
Fifth paragraph, second sentence previously read:

These data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA.

Has been changed to read:

These data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor Signant Health of Blue Bell, PA, USA.

Section 10.2 Case Report Forms
Sixth paragraph, first sentence previously read:

The subject will be entering the data on an electronic device; the data will be uploaded to a server.

Has been changed to read:

The subject will be entering the data on an electronic device, except in cases where completion by interview is necessary due to COVID-19 restrictions; the data will be uploaded to a server.

Section 10.2 Case Report Forms
Last paragraph, first sentence previously read:

The ePRO data will be collected electronically via a tablet device into which the patient will directly enter the required pieces of information.

Has been changed to read:

The ePRO data will be collected electronically via a tablet device into which the patient will directly enter the required pieces of information, except in cases where completion by interview is necessary due to COVID-19 restrictions.

Section 10.2 Case Report Forms
Last paragraph
Add: new fifth and sixth sentence

If the PRO data is collected by phone interview, the delegated staff will enter the subject's responses into TrialMax. Completion of PROs by phone interview should be approved by the site's IRB/EC.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	Director	Statistics
[redacted]	Study Project Manager II	Clinical
[redacted]	Group Medical Director	Therapeutic Area
[redacted]	Principal Bioanalytical Investigator	Bioanalysis
[redacted]	Senior Medical Director	Therapeutic Area
[redacted]	Director	Clinical Pharmacology and Pharmacometrics

Has been changed to read:

Name	Title	Functional Area
[redacted]	Director	Statistics
[redacted]	Director	Statistics
[redacted]	Head of Statistics, Late Oncology	Statistics
[redacted]	Study Project Manager II	Clinical
[redacted]	Executive Medical Director	Therapeutic Area
[redacted]	Principal Bioanalytical Investigator	Bioanalysis
[redacted]	Senior Medical Director	Therapeutic Area
[redacted]	Director	Clinical Pharmacology and Pharmacometrics

Appendix C. Study Activities
Previously read:

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
Informed Consent	X[d]															
Medical/Oncology History Assessment	X		X[e]													
AE/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytogenetic Testing[f]	X															
Tumor Lysis Syndrome Prophylaxis[g]		X	X	X	X	X	X									
Physical Exam (including weight)[h]	X[i]		X						X[j]		X			X	X	
Vital Signs[h]	X		X								X			X	X	
Pregnancy Test	X		X[s]								X					
ECOG Performance Status[h]	X		X								X			X	X	
Hematology/Chemistry[k]	X		X	X	X	X	X[t]			X	X			X	X	
Coagulation[h]	X		X											X		
Urinalysis[h]	X		X											X		
12-lead ECG	X													X[l]		
Pulmonary Function Test[m]	X															

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
MUGA (preferred)/2D Echocardiogram w/Doppler[m]	X															
Disease Assessments	X												X	X		X
Bone Marrow Aspirate and Biopsy for Local Disease Assessment	X[n]												X[n,o,p]	X		
PROMIS Cancer Fatigue SF 7a[q]			X									X		X		
EORTC QLQ-C30[q]			X									X		X		
EQ-5D-5L[q]			X									X		X		
Dispense Venetoclax/Placebo											X					
Dispense Subject Calendar/Diary									X[r]		X					
Collect venetoclax and Subject Calendar/Diary											X			X		
Administer Azacitidine*			X	X	X	X	X	X	X							
Survival Assessments																X

F/U = Follow-Up; PT = Post Treatment

a. Screening procedures must be performed within 21 days prior to initial study drug administration.

b. Final Visit procedures should be performed when a subject discontinues from the study.

c. Post Treatment and survival visits will be performed every 2 months after the last study visit for a period of 2 years after the last subject has been enrolled into the study.

d. Obtain informed consent prior to performing any screening or study-specific procedures.

e. On Cycle 1 Day 1, additional medical history that is observed after signing of the informed consent but prior to initial venetoclax or azacitidine administration and not considered related to study-required procedures will be recorded in the subject's medical history.

f. Cytogenetic testing should be performed if not completed within 1 month prior to Screening.

g. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to refer to Section 6.1.7.1, Management of Tumor Lysis Syndrome and Appendix I – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

h. For all study visits after Cycle 3, physical examination, vital signs, ECOG performance status, coagulation and urinalysis may be performed within 3 days before the scheduled visit. Under certain circumstances, these assessments may be performed within 3 days after the scheduled visit with discussion and approval by the AbbVie medical monitor TA MD. PROs can be completed within 3 days prior to Cycle 1 Day 1 Visit.

i. Height will be measured only at Screening.

j. All subjects must have Physical exam prior to discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated venetoclax dose.

k. Only hematology required for disease assessment. TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax/placebo dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose (see Section 6.1.7.1).

l. Final visit ECG may be obtained within ± 2 days of visit.

m. Only required if ECHO or MUGA, DLCO or FEV1 is being used to confirm eligibility for subjects ≥ 18 to 74 years of age.

n. Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis could be used as baseline assessment to satisfy eligibility criteria as long as the samples were taken within 30 days of first dose. A bone marrow aspirate and biopsy must be performed for all subjects during screening to collect mandatory samples for biomarker assessments. Bone marrow aspirate and biopsy samples must be collected for all subjects for each of the disease assessments. Bone marrow core biopsy sample collection is considered an optional procedure only for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects if the aspirate sample is inadequate or unevaluable for disease assessment, repeat bone marrow aspirate and biopsy must be performed within 7 days. The corresponding local laboratory pathology report should be sent to the central laboratory for IRC review for each local disease assessment which is conducted.

o. End of Cycle 1 bone marrow aspirate and biopsy must be performed within ± 3 days of Cycle 1 Day 28. Assessments should be performed and resulted by Day 31 prior to the administration of study drugs for Cycle 2. Cycle 1 venetoclax/placebo dosing should continue until bone marrow aspirate result is available. For subjects who require a delay in study treatment for blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks can be used to determine the IWG response. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) and upon concern for relapse. The corresponding local laboratory pathology/bone marrow report will be sent to the central laboratory for IRC review.

p. For subjects with resistant disease at end of Cycle 1 a repeat bone marrow must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to confirm response.

q. PRO assessments should be completed after a blood sample is taken to confirm the subject is able to receive study treatment at the study visit, but prior to any other procedures or clinical assessments and prior to dosing. PROs can be completed within 3 days prior to Cycle 1 Day 1 dosing.

r. Diaries will be dispensed upon discharge from the hospital.

s. Urine pregnancy test must be obtained at Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at screening. Pregnancy test should be repeated on Day 1 of each cycle and evaluated prior to dosing.

t. Additional laboratory assessments may be performed, per investigator discretion, up to 48 hours after reaching final dose if clinically indicated.

* AZA is administered for 7 days for each cycle starting with Day 1.

Has been changed to read:

			Cycle 1													
Procedures	**Screening[a]**	**Day –1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Days 8, 15, 22**	**Day 1 of Each Cycle**	**Day 1 of Every Other Cycle**	**End of Cycle 1 and Every 3 Cycles Thereafter**	**Final Visit[b]**	**30-Day Safety F/U**	**PT F/U[c]**
Informed Consent	X[d]															
Medical/Oncology History Assessment	X		X[e]													
AE/Concomitant Medication Assessment[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytogenetic Testing[f]	X															
Tumor Lysis Syndrome Prophylaxis[g]		X	X	X	X	X	X									
Physical Exam (including weight)[h,u]	X[i]		X						X[j]		X			X	X	
Vital Signs[h,u]	X		X								X			X	X	

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
Pregnancy Test[u]	X		X[s]								X					
ECOG Performance Status[h,u]	X		X								X			X	X	
Hematology/Chemistry[k,u]	X		X	X	X	X	X[t]			X	X			X	X	
Coagulation[h]	X		X											X		
Urinalysis[h]	X		X											X		
12-lead ECG	X													X[l]		
Pulmonary Function Test[m]	X															
MUGA (preferred)/2D Echocardiogram w/Doppler[m]	X															
Disease Assessments	X												X	X		X
Bone Marrow Aspirate and Biopsy for Local Disease Assessment	X[n]												X[n,o,p]	X		
PROMIS Cancer Fatigue SF 7a[q,v]			X									X		X		
EORTC QLQ-C30[q,v]			X									X		X		
EQ-5D-5L[q,v]			X									X		X		
Dispense Venetoclax/Placebo[w]											X					
Dispense Subject Calendar/Diary									X[r]		X					
Collect venetoclax and Subject Calendar/Diary											X			X		

Procedures	Screening[a]	Day –1	Cycle 1								Day 1 of Each Cycle	Day 1 of Every Other Cycle	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8, 15, 22						
Administer Azacitidine[u,*]			X	X	X	X	X	X	X							
Survival Assessments																X

F/U = Follow-Up; PT = Post Treatment

a. Screening procedures must be performed within 21 days prior to initial study drug administration.

b. Final Visit procedures should be performed when a subject discontinues from the study.

c. Post Treatment and survival visits will be performed every 2 months after the last study visit or as needed until end of study, defined as last subject last visit.

d. Obtain informed consent prior to performing any screening or study-specific procedures.

e. On Cycle 1 Day 1, additional medical history that is observed after signing of the informed consent but prior to initial venetoclax or azacitidine administration and not considered related to study-required procedures will be recorded in the subject's medical history.

f. Cytogenetic testing should be performed if not completed within 1 month prior to Screening.

g. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to refer to Section 6.1.7.1, Management of Tumor Lysis Syndrome and Appendix I – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

h. For all study visits after Cycle 3, physical examination, vital signs, ECOG performance status, coagulation and urinalysis may be performed within 3 days before the scheduled visit. Under certain circumstances, these assessments may be performed within 3 days after the scheduled visit with discussion and approval by the AbbVie medical monitor TA MD. PROs can be completed within 3 days prior to Cycle 1 Day 1 Visit.

i. Height will be measured only at Screening.

j. All subjects must have Physical exam prior to discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated venetoclax dose.

k. Only hematology required for disease assessment. TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax/placebo dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose (see Section 6.1.7.1).

l. Final visit ECG may be obtained within ± 2 days of visit.

m. Only required if ECHO or MUGA, DLCO or FEV1 is being used to confirm eligibility for subjects ≥ 18 to 74 years of age.

n. Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis could be used as baseline assessment to satisfy eligibility criteria as long as the samples were taken within 30 days prior to randomization. A bone marrow aspirate and biopsy must be performed for all subjects during screening to collect mandatory samples for biomarker assessments. Bone marrow aspirate and biopsy samples must be collected for all subjects for each of the disease assessments. Bone marrow core biopsy sample collection is considered an optional procedure only for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects if the aspirate sample is inadequate or unevaluable for disease assessment, repeat bone marrow aspirate and biopsy must be performed within 7 days. The corresponding local laboratory pathology report should be sent to the central laboratory for IRC review for each local disease assessment. Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

o. End of Cycle 1 bone marrow aspirate and biopsy must be performed within ± 3 days of Cycle 1 Day 28. Assessments should be performed and resulted by Day 31 prior to the administration of study drugs for Cycle 2. Cycle 1 venetoclax/placebo dosing should continue until bone marrow aspirate result is available. For subjects who require a delay in study treatment for blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks can be used to determine the IWG response. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) and upon concern for relapse. The corresponding local laboratory pathology/bone marrow report will be sent to the central laboratory for IRC review Upon unblinding at the 75% Overall Survival Interim Analysis, disease assessments will no longer be performed by the IRC.

p. For subjects with resistant disease at end of Cycle 1 a repeat bone marrow must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to confirm response.

q. PRO assessments should be completed after a blood sample is taken to confirm the subject is able to receive study treatment at the study visit, but prior to any other procedures or clinical assessments and prior to dosing. PROs can be completed within 3 days prior to Cycle 1 Day 1 dosing.

r. Diaries will be dispensed upon discharge from the hospital.

s. Urine pregnancy test must be obtained at Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at screening. Pregnancy test should be repeated on Day 1 of each cycle and evaluated prior to dosing.

t. Additional laboratory assessments may be performed, per investigator discretion, up to 48 hours after reaching final dose if clinically indicated.

u. Procedure may be performed in the subject's home or local hospital/clinic by adequately trained personnel if required due to COVID-19 restrictions.

v. ePROs may be performed virtually/phone interview by delegated personnel only if required due to COVID-19 restrictions.

w. Venetoclax/placebo may be shipped directly to a subject's home only if required due to COVID-19 restrictions.

* AZA is administered for 7 days for each cycle starting with Day 1.

Appendix L. Venetoclax and Azacitidine Dose Modifications
Treatment Cycle "After Cycle 3," column "Modifications" previously read:

Venetoclax/placebo should be administered for 21 days out of 28 days during each of the subsequent cycles and the treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/μL or platelet count ≥ 50 × 10^3/μL or for up to 14 days.

Has been changed to read:

Venetoclax/placebo should be administered for 21 days out of 28 days during each of the subsequent cycles and the treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/μL and/or platelet count ≥ 50 × 10^3/μL or for up to 14 days.