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Protocol for Study M19-072

Acute Myeloid Leukemia: Venetoclax and Azacitidine or Decitabine for AML Patients

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SPONSOR:	AbbVie Inc.	PLANNED NUMBER OF SITES:	Approximately 20 sites in the United States
ABBVIE INVESTIGATIONAL PRODUCT:	Venetoclax (ABT-199)		

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

Incorporating Versions 1.0, 2.0, and 3.0.

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Additional study contact information can be found in the Operations Manual (Appendix J).

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1 SYNOPSIS

Title: A Phase 3b, Single-Arm, Multicenter Open-Label Study of Venetoclax in Combination with Azacitidine or Decitabine in an Outpatient Setting in AML Patients Ineligible for Intensive Chemotherapy	
Background and Rationale:	Acute myeloid leukemia (AML) is an aggressive hematologic malignancy defined by the World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow. Of all types of leukemia, AML has the lowest survival rate and accounts for the largest number of deaths, as patients are often elderly and ineligible to receive intensive therapy. Patients ineligible to receive intensive chemotherapy are treated with less intensive therapies such as azacitidine or decitabine. In combination with azacitidine or decitabine, venetoclax (a BCL-2 inhibitor) has shown, in an ongoing study, remission rates of 70 - 74% when subjects were being hospitalized during treatment initiation. However, in community practices, patients with AML are often treated in an outpatient setting. This study evaluates whether venetoclax, in combination with azacitidine or decitabine, can be safely initiated in an outpatient setting and to assess clinical effectiveness in community centers.
Objective(s) and Endpoint(s):	The primary objective of this study is to determine composite complete remission (CR + CRi) rate, during the initial 6 cycles of treatment, as determined by the modified International Working Group (IWG) criteria, of venetoclax in combination with azacitidine or decitabine given appropriately in an outpatient setting to treatment-naïve subjects with AML who are ineligible for intensive chemotherapy. The primary effectiveness endpoint is the Composite Complete Remission Rate (CR + CRi): complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi) as described by the modified IWG criteria.
Investigator(s):	Multicenter.
Study Site(s):	Approximately 20 sites in the United States.
Study Population and Number of Subjects to be Enrolled:	Subjects who have histological confirmation of AML, who are treatment naïve, ≥ 12 years of age, and who are not eligible to receive intensive chemotherapy due to co-morbidity or other factors will be selected to participate in this study. This study will enroll approximately 60 subjects.
Investigational Plan:	This is a Phase 3b, open label, single-arm, multicenter study evaluating the composite complete remission rate and safety of venetoclax, in combination with azacitidine or decitabine, in an outpatient setting for treatment-naïve subjects with AML who are ineligible for intensive chemotherapy. Enrolled subjects will undergo a venetoclax dose ramp-up over 3 days in an outpatient, community setting, to the targeted dose of 400 mg of venetoclax. The choice of azacitidine or decitabine will be determined by the investigator. All subjects will be treated with venetoclax and azacitidine or decitabine for a maximum of six 28-day cycles. All subjects will undergo a final visit when treatment is discontinued or at the end of the sixth cycle. A 30-day safety

	follow-up visit will be conducted for all subjects. After the study period ends, subjects may continue receiving AML-directed therapy including commercially-acquired standard-of-care treatments for venetoclax and azacitidine or decitabine.
Key Eligibility Criteria:	Male or female subjects, at least 12 years old, with a diagnosis of AML, and a projected life expectancy of at least 12 weeks are eligible to enroll in this study. Subjects must have a confirmation of their AML diagnosis by WHO criteria and, as determined by the investigator, must be ineligible for treatment with standard cytarabine and anthracycline induction regimens. Additionally, the subject needs to be deemed by the investigator as an appropriate candidate for outpatient ramp-up of venetoclax. These subjects must also meet the following disease criteria: • Subject must not have received any prior treatment for AML with the exception of hydroxyurea. • Subject has no evidence of spontaneous tumor lysis syndrome (TLS) at Screening. • Subject can have progressed from myelodysplastic syndrome (MDS) or be considered to have secondary AML and could have been treated with growth factors or other agents with the exception of HMAs. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 3. Subjects must also have no history of other malignancies within 2 years prior to study entry, with 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, or previous malignancy confined and surgically resected (or treated with other modalities) with curative intent. Subjects must have no conditions that could interfere with drug absorption, no history of allergic reactions or sensitivities, no clinically relevant cardiac abnormalities, and no history of clinically significant medical conditions which would interfere with the subject's participation in this study. Subjects enrolling in this study must not have been treated with any investigational drug within 30 days of the first dose of study treatment and must not use known strong cytochrome P450 (CYP) 3A inducers for the duration of the study. Female subjects of childbearing potential must not be pregnant or breastfeeding, at the time of study enrollment. Both male subjects and female subjects of childbearing potential must agree to use at least 1 protocol-specified methods of birth control.
Study Drug and Duration of Treatment:	**Venetoclax:** 400 mg administered orally, once daily, for each 28-day cycle for a total of 6 cycles. Initiation of venetoclax dosing in Cycle 1 will be administered in a 3-step ramp-up over 3 days to the target dose of 400 mg/day. Each dose should be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in clinic and administered prior to these agents.

	Azacitidine: 75 mg/m^2 administered subcutaneously (SC) or intravenously (IV) for 7 days beginning on Day 1 of each 28-day cycle (as per institutional practice). **Decitabine:** 20 mg/m^2 administered intravenously (IV) for 5 days, beginning on Day 1 of each 28-day cycle (as per institutional practice). Depending on investigator's choice, azacitidine or decitabine will be administered to each subject beginning on Cycle 1 Day 1. The subject is to remain on their assigned therapy for the duration of the study.
Date of Protocol Synopsis:	29 October 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy defined by the World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow.[1] In AML, the clonal expansion of myeloid blasts in bone marrow, peripheral blood, and occasionally extramedullary tissues leads to disruption of normal hematopoiesis.[2,3] It is the most common form of acute leukemia in adults, with a projected estimate of 19,520 new cases and 10,670 deaths in the United States (US) in 2018.[4] Of all types of leukemia, AML has the lowest survival rate and accounts for the largest number of deaths, as patients are often elderly and ineligible to receive intensive therapy.[3]

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 account 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.[5] 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 (HMAs, such as azacitidine or decitabine), 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 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.[6,7]

In Europe, azacitidine and decitabine are approved as single agents for patients with treatment naïve AML. However, the reported overall response rate (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) in a randomized trial was 25.6% and a with median overall survival of 7.7 months with decitabine compared with 7.8% and 5.0 months in treatment arms consisting of either subcutaneous (SC) cytarabine (88.5% of patients) or supportive care (11.5% of patients).[7] In another study of azacitidine, 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.[8] Both of these trials in AML patients who were ≥ 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.

B-cell lymphoma (BCL)-2 overexpression has 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 AML.[9,10]

AbbVie is developing a potent, selective, and orally bioavailable small molecule inhibitor of BCL-2, venetoclax (also referred to as ABT-199, A-1195425.0, GDC-0199, RO5537382, Venclexta®, and Venclyxto®), that may address some of the needs for patients with AML. In addition, venetoclax is being evaluated for the treatment of patients with Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia, and multiple myeloma (MM).

Venetoclax binds with high affinity (inhibition rate constant [K_i] < 0.010 nM) to anti-apoptotic protein BCL-2 and with lower affinity to other anti-apoptotic BCL-2 family proteins, like B-cell lymphoma extra-large (BCL-X_L) and B-cell lymphoma-Walter and Eliza Hall Institute (BCL-w) (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to BCL-2, respectively). The anticipated and observed venetoclax-associated toxicities are also mechanism based; in particular, BCL-2-mediated effects on lymphocytes.[9,11] Venetoclax, as a BCL-2-selective (BCL-X_L-sparing) inhibitor, is projected to yield an improved therapeutic profile compared to dual BCL-2/BCL-X_L inhibitors. Because survival of platelets depends on BCL-X_L,[12] thrombocytopenia, a major dose-limiting toxicity (DLT) caused by inhibition of BCL-X_L in the clinic,[13] is not expected to be dose-limiting for venetoclax.

Based on the mechanism of action, as well as the 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. Tumor lysis syndrome (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 subjects treated with venetoclax.

Venetoclax has been evaluated as a single agent (Study M14-212)[14] in patients with relapsed/refractory AML or frontline in patients with AML who were unfit to receive intensive chemotherapy and in combination with azacitidine or decitabine (Study M14-358)[15] or low-dose cytarabine (Study M14-387)[16] for treatment naïve patients ineligible for intensive chemotherapy.

In Study M14-212, a total of 32 subjects were dosed with venetoclax.[14] The most common adverse events observed in ≥ 30% of the subjects 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%). 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 relapsed/refractory AML and a few (2 subjects, 6%) were deemed unfit for intensive therapy. The objective response rate (ORR) was 19% (6 of 32 subjects), with CR in 2 subjects (6%) and CRi in 4 subjects (13%). Anti-leukemic activity was observed in an additional 7 subjects (22%), with ≥ 50% bone marrow reduction with hematologic recovery in 4 of these subjects.

In Study M14-358, venetoclax was administered daily in a three day ramp-up from 100 to 200 to 400 mg and coadministered with either azacitidine 75 mg/m^2 IV or SC on Days 1 - 7 or decitabine 20 mg/m^2 IV on Days 1 - 5 within each 28 day cycle.[15] Dose adjustments for venetoclax were implemented for

concomitant medications routinely used for prophylaxis with known drug-drug interactions. Safety and efficacy were evaluated. Of 115 subjects treated with the 400 mg dose of venetoclax, 84 subjects were treated with venetoclax and azacitidine, and 31 subjects received venetoclax and decitabine. The median age for subjects treated with azacitidine or decitabine were 75 (range: 61 – 90) and 72 (range: 65 – 86), respectively. Key adverse events of Grade ≥ 3, across all subjects, were febrile neutropenia (44%), anemia (28%), pneumonia (25%), thrombocytopenia (22%), and neutropenia (18%). For subjects treated with azacitidine or decitabine, 70% and 74% of subjects achieved CR/CRi, respectively, and the median time to first response was 1.2 and 1.9 months, respectively. The median overall survival was 14.9 months for subjects treated with azacitidine and 16.2 months for subjects treated with decitabine. Subjects who received venetoclax dose reduction for cytochrome (CYP) P450 3A inhibitors had similar responses compared to those without dose reduction.

Study M14-387 evaluated the safety and efficacy of venetoclax in combination with low-dose cytarabine in patients with previously untreated AML who were ineligible for intensive chemotherapy due to comorbidities or age.[16] Venetoclax was initiated at 50 or 100 mg daily and dose escalated over 4 - 5 days to reach 600 mg. In subsequent 28-day cycles, venetoclax was administered at 600 mg on all days. Low-dose cytarabine (20 mg/m^2 daily) was administered SC on Days 1 – 10 of each cycle. At the beginning of the study, concomitant strong and moderate cytochrome P450 3A isoform subfamily (CYP3A) inhibitor use was prohibited; however, as additional safety and pharmacokinetic data became available, their use was allowed with appropriate venetoclax dose adjustments. The most common adverse events of Grade ≥ 3 across all subjects were febrile neutropenia (43%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%). Laboratory evidence of Grade 3 TLS was observed in 2 subjects; both subjects achieved the target dose of venetoclax. Forty seven percent of subjects received moderate (40%) or strong (7%) CYP3A inhibitors for at least 7 days (predominantly azole antifungals); no relevant differences in serious adverse event rates were observed. Median time to first response was 1.4 months, and 54% and 46% of subjects achieved CR/CRi and CR/complete remission with partial hematologic recovery (CRh), respectively. The rates of CR/CRi for subjects with secondary and de novo AML were 35% and 71%, respectively; median duration of response for those with secondary and de novo AML was 8.1 and 11.6 months, respectively.

Supported by these results, 2 randomized trials (Studies M15-656 and M16-043) have been initiated evaluating venetoclax in combination with the common frontline treatments of azacitidine or low-dose cytarabine in subjects with treatment-naïve AML who are ineligible for intensive chemotherapy.

With the general improvement seen in AML treatment over the last decades, an interest to move AML treatment towards outpatient care has emerged. Potential benefits with outpatient care that have been cited include reduction of healthcare costs, improvement in quality of life, and decreased risk of hospital-acquired infections.[17] Given the severity of the disease, there are potential safety issues related to outpatient management that need to be addressed: one of these issues is the introduction of new treatment options and how they can be safely and effectively administered in an outpatient setting.

In Studies M14-358 and M14-387, hospitalization was a requirement during treatment initiation and drug ramp-up. There is a need to confirm the safety and effectiveness of the administration and ramp-up of venetoclax in patients treated in an outpatient setting.

The clinical trial described in this Protocol is designed to ascertain whether venetoclax, in combination with azacitidine or decitabine, can be safely initiated in an outpatient setting and to assess clinical effectiveness in a community setting.

The clinical hypothesis for this study is that venetoclax, in combination with azacitidine or decitabine, can safely be given in an outpatient setting during the ramp-up phase for AML patients who are ineligible to receive intensive chemotherapy as demonstrated by a composite complete remission rate (CR + CRi) of approximately 60% in a community setting and consistent with Phase 1/2 results conducted in a controlled scenario.

2.2 Benefits and Risks to Subjects

As described above, data from previous clinical trials with venetoclax demonstrate favorable safety profiles and promising clinical activity in subjects with untreated AML, including subjects who are unfit to receive intensive chemotherapy.

Benefits for subjects participating in this study include receiving outpatient care which could have quality of life implications, as well as making the treatment accessible to larger numbers of patients. Furthermore, treatment in an outpatient setting would reduce the risk of infections acquired due to hospitalization.

Rapid tumor lysis of AML may occur upon initiation of venetoclax dosing in combination with azacitidine or decitabine. 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 schedules of azacitidine or decitabine to optimize the opportunity for achieving a response and enable close subject monitoring. The dosing regimen will also enable interruptions and extensions at dose levels if rapid tumor lysis is observed.

For further details, please see findings from completed and ongoing studies, including safety data in the current Venetoclax Investigator's Brochure.[18]

Considering the coronavirus disease - 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving venetoclax, azacitidine, or decitabine may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for AML, no change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

This study will evaluate the safety and effectiveness of venetoclax in combination with azacitidine or decitabine for those AML subjects appropriately treated in the outpatient setting and ineligible to receive intensive chemotherapy.

Primary

The primary objective of this study is:

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

Secondary

The secondary objectives of this study are:

- To determine the incidence and severity of adverse events including, but not limited to, rates of TLS and neutropenia
- To assess the rate of red blood cell (RBC) and platelet independence upon treatment with venetoclax and azacitidine or decitabine

3.2 Primary Endpoint

The primary endpoint is the Composite Complete Remission Rate (CR + CRi): complete remission (CR) plus complete remission with incomplete hematologic recovery (CRi) as described by the modified IWG criteria.

3.3 Secondary Endpoints

The secondary endpoints are:

- Overall Response Rates (CR, CRi): complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as described by the modified IWG criteria.
- Transfusion Independence: evaluate the rate of RBC and platelet transfusion dependence (defined as having received ≥ 2 units of RBCs and/or platelets within 56 days prior to study) at baseline and assess transfusion independence, defined as at least 56 consecutive days without a RBC or platelet transfusion during the treatment period.

3.4 Safety Endpoints

Safety evaluations include adverse event monitoring, physical examinations, vital sign measurements, clinical laboratory testing (chemistry, hematology, and coagulation), and rate of hospitalizations observed as measures of safety and tolerability for the entire study duration.

3.5 Exploratory Research and Validation Endpoints

The exploratory endpoints are to:

- Evaluate the time to blood count improvements and duration of blood count improvements for subjects who experience cytopenias and anemia.
- Evaluate effectiveness (CR/CRi) in molecular subtypes identified per institutional practices.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

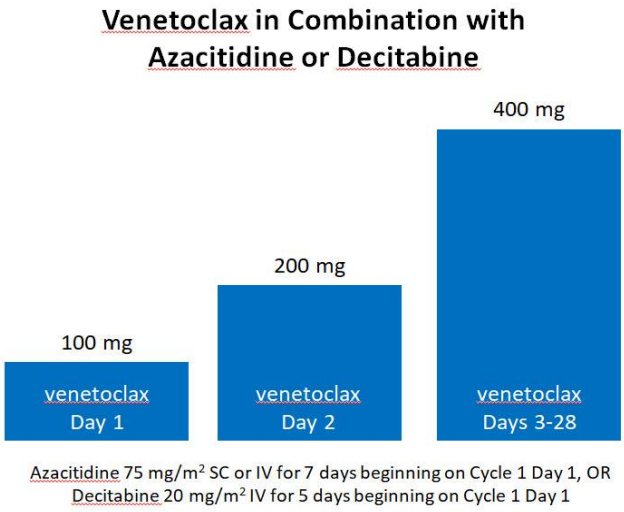
This is a Phase 3b, open label, single-arm, multicenter study evaluating the composite complete remission rate and safety of venetoclax in combination with azacitidine or decitabine in an outpatient setting for treatment-naïve subjects with AML who are ineligible for intensive chemotherapy.

The study will enroll approximately 60 subjects with a venetoclax dose ramp-up over 3 days and adjusted as appropriate with concomitant use of CYP3A inhibitors. Ramp-up activities for subjects, in this study, will be performed in an outpatient, community setting. The choice of azacitidine or decitabine for each subject will be determined by the investigator, and the subject is to remain on their assigned therapy for the duration of the study.

The schematic for the venetoclax dosing ramp-up is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Cycle 1 Dosing Ramp-Up Schematic



IV = intravenous; SC = subcutaneous

Screening

Screening procedures must be performed within 21 days prior to first dose of study drug administration. Longer intervals require discussion with the Medical Monitor. Once screening procedures are complete and eligibility is confirmed, subjects will be enrolled.

Study Treatment

All subjects will receive venetoclax (daily for 28 days), in combination with azacitidine or decitabine, beginning on Cycle 1 Day 1. Depending on investigator's choice, subjects will receive either azacitidine for 7 days beginning on Day 1 of each 28-day cycle or decitabine for 5 days beginning on Day 1 of each 28-day cycle, as per institutional practice. The subject is to remain on their assigned therapy for the duration of the study. All subjects will receive a maximum of 6 cycles of venetoclax during the study period. After the study period ends, subjects may continue receiving AML-directed therapy including commercially-acquired standard-of-care treatments for venetoclax and azacitidine or decitabine.

Cycle Length – (28 Days)

- Venetoclax orally daily: 100 mg on Cycle 1 Day 1, 200 mg on Cycle 1 Day 2, and 400 mg on Cycle 1 Days 3 – 28; 400 mg daily for each 28-day cycle thereafter.
- Azacitidine 75 mg/m^2 subcutaneous (SC) or intravenous (IV) for 7 days beginning on Day 1 of each cycle, as per institutional practice.
- Decitabine 20 mg/m^2 intravenous (IV) for 5 days beginning on Day 1 of each cycle, as per institutional practice.

Subjects with progressive disease for whom the treating physician feels are still deriving clinical benefit can be continued on treatment after discussion with the medical monitor or until no longer achieving

clinical benefit per investigator assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). All subjects will have a Final Visit performed when treatment is discontinued or when the end of the 6th cycle has been achieved 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 drug administration. Disease assessments by modified IWG criteria (Operations Manual, Section 3.16) will be performed at the timepoints described in Section 3.14 of the Operations Manual.

4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All effectiveness measurements in this study are standard for assessing disease activity in subjects with AML. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Subjects who have histological confirmation of AML, who are treatment naïve, greater than or equal to 12 years of age, and who are not eligible to receive intensive chemotherapy due to co-morbidity or other factors will be selected to participate in this study.

Preliminary studies have demonstrated that venetoclax in combination with azacitidine or decitabine can induce responses for patients with AML and be dosed safely. Additionally, these clinical studies indicate that the combination may be more efficacious than either agent alone (Study M14-358). Therefore, given the prognosis, current limited effective options, safety of venetoclax and HMAs to date, and the preclinical signals of efficacy, the subject population is suitable.

Selection of Doses in the Study

The currently approved venetoclax dose is 400 mg in combination with either azacitidine or decitabine and 600 mg in combination with low-dose cytarabine. This study will adhere to the US label in terms of dosing and, thus, the target venetoclax dose is 400 mg in combination with either azacitidine or decitabine. The regimen is designed to ramp up the dose of venetoclax rapidly with azacitidine or decitabine thereby optimizing the opportunity for achieving a response and enabling close subject monitoring. The dosing regimen will also enable interruptions and extensions at dose levels if rapid tumor lysis is observed. To date, this strategy has been effective at minimizing the risk of clinical TLS with a rate across the AML program at < 1%.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Subjects must be at least 12 years old.
- 3. Subjects must have a projected life expectancy of at least 12 weeks.
- 4. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN)*
  - Serum aspartate aminotransferase (AST) ≤ 3 × ULN*
  - Bilirubin ≤ 1.5 × ULN*

    ** Unless considered to be due to leukemic organ involvement or if a patient has confirmed Gilbert's disease.*
  - Creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection

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

Or, if serum creatinine is in µmol/L:

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

  - White blood cell (WBC) count < 25×10^9/L (hydroxyurea is permitted to meet this criterion)
- 5. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 3.
- 6. Are willing or able to comply with procedures required in this Protocol.

Disease Activity

- 7. Subject must have confirmation of AML by WHO criteria and, as determined by the investigator, must be ineligible for treatment with a standard cytarabine and anthracycline induction regimen and deemed by the investigator as an appropriate candidate for outpatient ramp-up of venetoclax.
- 8. Subject meets the following disease activity criteria:
  - Subject must not have received any prior treatment for AML with the exception of hydroxyurea.
  - Subject has no evidence of spontaneous TLS at Screening.
  - Subject can have progressed from myelodysplastic syndrome (MDS) or be considered to have secondary AML and could have been treated with growth factors or other agents with the exception of HMAs.

Subject History

- 9. Subject has no history of the following conditions:
  - Acute promyelocytic leukemia.
  - Known active central nervous system (CNS) involvement with AML.
  - Positive for HIV (HIV testing is not required).
  - Positive for hepatitis B or C infection, with the exception of those with an undetectable viral load within 3 months (Hepatitis B or C testing is not required). Subjects with serologic evidence of prior vaccination to hepatitis B virus [i.e., HBs Ag–, and anti-HBs+] may participate.
  - 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.
  - Chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the investigator would adversely affect his/her participating in this study.
  - Malabsorption syndrome or other condition that precludes enteral route of administration.
- 10. No 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.
- 11. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.

- 12. No conditions that could **interfere with drug absorption** including but not limited to short bowel syndrome.
- 13. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 14. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 15. No clinically relevant or **significant electrocardiogram (ECG) abnormalities**, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females) at Screening.

Contraception

- 16. Female subjects must be either postmenopausal defined per one of the following criteria:
  - 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 a follicle-stimulating hormone (FSH) level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

OR,

- 17. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** that is effective from Cycle 1 Day 1 through at least 90 days after the last dose of study drug.
- 18. For all female subjects of childbearing potential, negative results should be obtained for pregnancy tests performed:
  - At Screening, with a serum sample obtained within 14 days prior to the first dose of study drug administration, and
  - Prior to dosing obtained on Cycle 1 Day 1, with urine sample if it has been > 7 days since obtaining serum pregnancy test results.
- 19. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study, from Screening through at least 90 days after the last dose of study drug.
- 20. Male who is not considering **fathering a child or donating sperm** during the study from Cycle 1 Day 1 through at least 90 days after the last dose of study drug. For subjects receiving azacitidine, this period is 6 months following the last dose of azacitidine.
- 21. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Cycle 1 Day 1 through at least 90 days after the last dose of study drug, to practice the protocol-specified contraception. For subjects receiving azacitidine, this period is 6 months following the last dose of azacitidine.

Concomitant Medications

- 22. Subject has not received treatment with the following:
  - CAR-T cell therapy
  - Prior therapy or experimental therapies for AML
- 23. Subject has not consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the initiation of study treatment.
- 24. Subject must not have received **any investigational drug** within the 30 days prior to the first dose of study drug or must not be currently enrolled in another clinical study.
- 25. Subject must not have systemically used known strong or moderate CYP3A inducers within 7 days prior to the initiation of study treatment.
- 26. Subject must not have received **any live vaccine** within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)
  - Females who have not experienced menarche (at least one menstrual period)
- Females, of Childbearing Potential
  - Females of childbearing potential must give consent to abide by contraception requirements
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 90 days after the last dose of study drug
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to Cycle 1 Day 1

- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Cycle 1 Day 1
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
- Intrauterine device (IUD)
- Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicide AND a condom)
- Intrauterine hormone-releasing system (IUS)
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject)
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the usual and preferred lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use condoms, even if the male subject has undergone a successful vasectomy**, from Cycle 1 Day 1 through at least 90 days after the last dose of study drug. For subjects receiving azacitidine, this period is 6 months following the last dose of azacitidine.

- His female partner(s) must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to Cycle 1 Day 1
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to Cycle 1 Day 1
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
  - Intrauterine device (IUD)
  - Contraceptive sponge, diaphragm or cervical cap with spermicide
  - Intrauterine hormone-releasing system (IUS)

5.3 Prohibited Medications and Therapy

In addition to the medications and therapy listed in the eligibility criteria (Section 5.1, concomitant medications), the following is not allowed during the study (refer to the Operations Manual, Appendix J):

- Grapefruit, grapefruit products, Seville oranges, or star fruits are not allowed during the study
- Strong or moderate CYP3A inducers are prohibited 7 days prior to the first dose of study drug
- Strong CYP3A inducers are prohibited through the end of the study

Subjects must be consented for the study before discontinuing any prohibited medications for the purpose of meeting study eligibility.

A sample list of excluded and cautionary medications, with additional guidance noted, is provided in Appendix D.

5.4 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins, and/or herbal supplements, or if administration of any medication becomes necessary, beginning with the screening visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded. Although cautionary, use of strong or moderate CYP3A inhibitors or moderate inducers, or P-gp substrates or inhibitors are allowed if no appropriate therapeutic alternative exists (refer to the Operations Manual, Section 3.3). Concomitant use of a moderate CYP3A inducer should be avoided. Alternative treatments with less CYP3A induction or inhibition should be considered. Concomitant use of a P-gp substrate should be avoided. Alternative treatments should be considered. If use of P-gp substrate is unavoidable, P-gp substrate should be separately dosed at least 6 hours before venetoclax. Herbal supplements known to inhibit or induce CYP3A or P-glycoprotein (P-gp) should be excluded and use of other supplements should be discouraged. Transfusion of blood and blood products, antibiotics, anti-fungals, anti-emetics, granulocyte-colony stimulating factor (G-CSF), and other standard supportive care medications are permitted as needed, per institutional practices. Anti-uric acid agents (such as hydroxyurea or allopurinol) or leukapheresis are also permitted per institutional guidelines and to decrease WBC counts to $< 25 \times 10^9$/L at the time of study entry or during the study, as needed. Filgrastrim may be administered, per clinical practice.

Venetoclax dose modifications for co-administration with strong or moderate CYP3A inhibitors and P-gp inhibitors during Cycle 1 and after ramp-up are noted below and in Table 1. Two to three days post the removal of the strong or moderate CYP3A inhibitor or P-gp inhibitor, venetoclax treatment will be given at the target dose of 400 mg without the need to ramp-up.

- For subjects who are on a strong CYP3A inhibitor, at the time of initiation, the dose of venetoclax will be reduced (Table 1) for the duration of treatment with the strong CYP3A inhibitor.

- For subjects who are on posaconazole, at the time of initiation, the dose of venetoclax will be reduced (Table 1) for the duration of treatment with posaconazole.
- For subjects who are on a moderate CYP3A inhibitor (such as ciprofloxacin, fluconazole or isavuconazole) or a P-gp inhibitor (such as amiodarone or captopril), the venetoclax dose will be reduced by 50% (Table 1) for the duration of treatment with the moderate CYP3A inhibitor or P-gp inhibitor.

Table 1. Dose Modification for Venetoclax When Co-administered with P-gp Inhibitors or Moderate or Strong CYP3A Inhibitors

Venetoclax Dose (mg)[a]	Venetoclax Dose if Co-Administered with 1 or more Strong CYP3A Inhibitor	Venetoclax Dose if Co-Administered with posaconazole	Venetoclax Dose if Co-Administered with 1 or more Moderate CYP3A Inhibitor or P-gp Inhibitor
100 mg (Cycle 1 Day 1 only)	10 mg	10 mg	50 mg
200 mg (Cycle 1 Day 2 only)	20 mg	20 mg	100 mg
400 mg (Cycle 1 Day 3)	50 mg	50 mg	200 mg
400 mg (Cycle 1 Day 4 and daily thereafter)	100 mg	70 mg	200 mg
400 mg (Target Dose after Ramp-up)	100 mg	70 mg	200 mg

CYP3A = Cytochrome P450 3A; P-gp = P glycoprotein

a. If a subject requires co-administration of venetoclax with both a strong and a moderate CYP3A inhibitor or a P-gp inhibitor, venetoclax dose modification recommended for strong CYP3A inhibitors should be followed.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with venetoclax (ABT-199) can be located in the Venetoclax Investigator's Brochure.[18] A sample list of excluded and cautionary medications is provided in Appendix D.

If a CYP3A inhibitor or P-gp inhibitor is discontinued, resume the venetoclax target dose 2 to 3 days after discontinuation of the inhibitor.

Subjects must be able to safely discontinue any prohibited medications 4 weeks prior to first dose of study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study

Subjects will continue their treatment assignment until documented disease progression, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). All subjects will have a Final Visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. A 30-day safety follow-up visit will also be conducted after the last dose of study drug. After the study period ends, subjects may continue

receiving AML-directed therapy including commercially acquired standard-of-care treatments for venetoclax and azacitidine or decitabine.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or adverse events, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- The investigator believes discontinuation is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The occurrence of an adverse event that precludes further azacitidine or decitabine drug administration.
- The subject experiences toxicities related to study drug requiring more than a 4-week (1 cycle) dose interruption of venetoclax, azacitidine, or decitabine, in the absence of clinical benefit.
- The subject requires radiotherapy or alternate anti-neoplastic agents for a new primary cancer diagnosis or AML during the study period (with the exception of hydroxyurea for AML during Cycle 1 only)
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix J.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix J for details on how to handle study activities/procedures.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for effectiveness and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation, the procedures outlined for the Final Visit should be completed as soon as possible, preferably within 2 weeks. In addition, if a subject is willing, a 30-day follow-up visit after the last dose of study drug should be completed to capture all treatment-emergent adverse events/serious adverse events have been resolved to ≤ Grade 1, baseline level, or initiation of a new treatment, whichever is earlier, or, in the opinion of the investigator, the event is unlikely to resolve.

5.7 Study Drug

Venetoclax, manufactured by AbbVie, will be taken orally daily beginning on Cycle 1 Day 1, through Cycle 6 Day 28, and should be taken at approximately the same time every day for each 28-day cycle. Each dose of venetoclax should be administered with approximately 240 mL of water and within 30 minutes after the completion of breakfast or the subject's first meal of the day. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in clinic and administered prior to these agents.

All subjects will receive a maximum of 6 cycles of venetoclax during the study period. After the study period ends, the subject may continue receiving AML-directed therapy including commercially-acquired standard-of-care treatments for venetoclax and azacitidine or decitabine.

Depending on investigator's choice, subjects will receive azacitidine or decitabine on Cycle 1 Day 1. The subject is to remain on their assigned therapy for the duration of this study. Azacitidine (75 mg/m^2) infusions or injections and decitabine (20 mg/m^2) infusions should be prepared and administered per the respective package inserts. Azacitidine will be administered SC or IV beginning on Day 1 for 7 days of each 28-day cycle, as per institutional practice. Decitabine will be administered IV beginning on Day 1 for 5 days of each 28-day cycle, as per institutional practice.

Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If a subject should forget to take his/her venetoclax dose at his/her regularly scheduled dosing time, the subject should take the forgotten dose as soon as he/she remembers, provided that the dose will be taken within 8 hours of the missed dose. Otherwise, the subject should take the next dose at the next scheduled dosing time. If the subject vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Subject dosing will be recorded on a subject dosing diary (as described in the Operations Manual, Section 3.13). The subject will be instructed to return all study drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will provide venetoclax. AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. The site will be responsible for obtaining azacitidine or decitabine.

Venetoclax will be packaged in blisters or bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Study drug information is presented in Table 2.

Table 2. Study Drug Information

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Venetoclax (ABT-199)	AbbVie	Oral	Film-coated tablet	10, 50, and 100 mg

5.8 Randomization/Drug Assignment

This is an open-label study. There is no randomization for this study.

All subjects will be assigned a unique identification number by the IRT at the screening visit (refer to the Operations Manual, Section 6.3). For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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 (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject 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 "special situations," which must be reported whether associated with an adverse event or not.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

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/or 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.

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or CRO (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

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.

All adverse events reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Worsening of disease or underlying cancer (serious or nonserious events) will be collected as an adverse event due to disease progression on the electronic case report form (eCRF). For serious adverse events with the outcome of death, the date and cause of death will be recorded in the appropriate case report

form (CRF). Deaths due to disease progression that occur within the adverse event reporting period will be collected as an adverse event on the eCRF.

Adverse Events of Special Interest

The following adverse events of special interest will be monitored during the study:

- Cytopenias
- TLS

Subjects will be monitored for blood counts through resolution of cytopenias. 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 for associated adverse events. Additional details are provided in Section 6.2.

If additional dose reductions are thought to be necessary by the investigator, a discussion with the AbbVie medical monitor 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 Primary TA MD or a designee.

Anti-infective prophylaxis should be implemented per regional guidelines or institutional standards including appropriate prophylaxis for bacterial, viral, and fungal infections. Potential for drug-drug interactions should be considered and appropriate dose adjustments made if required.

Subjects with resistant disease, based on modified IWG criteria (as described in the Operations Manual, Section 3.16), after End of Cycle 1 will need a bone marrow aspirate to evaluate response after End of Cycle 2. Subjects with resistant disease after end of Cycle 2, based on modified IWG criteria (as described in the Operations Manual, Section 3.16) will need a bone marrow aspirate to evaluate response after end of Cycle 4. Subjects who have not recovered absolute neutrophil count (ANC) ≥ 500/µL within 14 days of drug interruption or require longer duration of interruption between treatment cycles, bone marrow aspirate may be performed, as determined by the investigator, to assess disease status before resuming treatment with next cycle.

Guidelines for TLS management are provided in Section 6.2. Chemistry labs (including creatinine, potassium, calcium, inorganic phosphorus, lactate dehydrogenase, and uric acid) will be performed real-time pre-dose, 4 - 6 hours post-dose, and 24 hours post-dose for each venetoclax dose escalation, and also as deemed necessary per investigator to monitor TLS.

Adverse Event Severity and Relationship to Study Drug

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 5.0). 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. The dates on the adverse events 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 and requires urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

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.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5).

All subjects should be informed of the contraceptive measure requirements. 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 for release of medical information from the partner must be obtained prior to collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug or at least 90 days after the last dose of the selected combination.

The pregnancy outcome, for either mother or infant, of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

The management of specific adverse events and laboratory parameters is described below. This includes adverse events of TLS and neutropenia for venetoclax. Subjects will be monitored for these events throughout the study and treatment may be discontinued or adjusted as appropriate.

Prophylaxis and Management of Tumor Lysis Syndrome

There is a potential risk for TLS in subjects with AML, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment LDH levels, dehydration, or renal dysfunction.

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of treatment (Appendix F). Definitions of laboratory TLS and clinical TLS are provided in Appendix E (Howard grading classification). If a subject experiences blood chemistry changes suggestive of TLS, the dose of venetoclax may be withheld and/or reductions may be required.

Tumor lysis syndrome prophylaxis must be initiated in all subjects before the first dose of study drug or first new escalated dose. For subjects who had dose delay or interruptions TLS prophylactic measures may need to be implemented based on the disease status prior to resuming treatment. Below are the minimum requirements for TLS prophylaxis and management. Additional prophylaxis and monitoring procedures for TLS should be implemented as per institutional/regional standards.

- An oral agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 28 days based on the ongoing risk of TLS development. Subjects allergic to or otherwise unable to receive allopurinol must use another uric acid reducer starting at least 72 hours prior to dosing or rasburicase on the day of treatment (prior to venetoclax dosing).
- Adequate hydration per day starting from at least 24 hours prior to first dose or any dose escalation.
- TLS Chemistry panel (creatinine, potassium, calcium, inorganic phosphorus, lactate dehydrogenase, and uric acid) will be performed real-time pre-dose, 4 - 6 hours post-dose and 24-hours post-dose for each venetoclax dose escalation, and as deemed necessary per investigator to monitor TLS.
- TLS Chemistry panel results (creatinine, potassium, calcium, inorganic phosphorus, lactate dehydrogenase, and uric acid) must be reviewed by the investigator in real time and prior to the subject's next dose to ensure appropriate subject management.
- If any clinically significant laboratory changes are observed within the first 24 hours after initiation of dosing or after a dose escalation, see Appendix F for management guidelines. Refer to table in Appendix E for definitions of laboratory and clinical TLS.
- If subjects develop TLS and the treatment is withheld, they should be admitted and managed as inpatient until the ramp-up is complete and TLS labs have normalized.

Subjects with reduced renal function (CLcr < 80 mL/min, Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with venetoclax. For subjects with a higher risk for TLS and lower creatinine clearance, additional measures with more intensive lab monitoring and intervention should be implemented (Appendix F).

If a subject meets criteria for clinically significant laboratory or clinical TLS please follow institutional guidelines or recommendations in Appendix G; no additional venetoclax dose should be administered until resolution.

For continued dosing of venetoclax, monitor for evidence of TLS during study treatment, and manage abnormalities of serum creatinine, and electrolytes promptly. After resolution of electrolyte imbalances (Appendix F), venetoclax may be continued at the original dose after discussion between the investigator and the AbbVie TA MD.

Management of Cytopenias

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in both treated and untreated patients with AML. Subjects with baseline neutropenia or those who have significant bone marrow involvement may be particularly at high risk.

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 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 or decitabine will also be delayed until ANC ≥ 500/µL. Both venetoclax and azacitidine or decitabine 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, dosing with venetoclax and azacitidine or decitabine may 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 should be administered for 21 days out of 28 days during each of the subsequent cycles. The treatment cycle should also be delayed to allow for count recovery until ANC ≥ 500/µL, platelet count ≥ 50×10^3/µL, or for up to 14 days, whichever occurs earlier.

Subjects with resistant disease, based on modified IWG criteria (as described in the Operations Manual, Section 3.16) 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. Transfuse blood products, administer prophylactics, and administer treatment anti-infectives as clinically indicated and as per institutional practice. Once CRi or MLFS 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 (where the CRi or MLFS is demonstrated), the duration of venetoclax is reduced to 21 days of the subsequent 28-day cycle.

Azacitidine

During subsequent cycles, if hematologic recovery with > 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 per Table 3, or according to institutional standards.

Table 3. 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%

Decitabine

If a dose reduction for decitabine is believed to be necessary, a discussion with the AbbVie medical monitor is required.

Management of Non-TLS Serum Electrolytes and Renal Impairment

If unexplained reductions in serum bicarbonate levels to < 20 mEq/L occur, azacitidine dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of blood urea nitrogen (BUN) or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course.

Management of Decrease in Spermatogenesis

Venetoclax may cause a decrease in spermatogenesis. Male subjects considering preservation of fertility should bank sperm before initiating treatment with venetoclax.

Management of Other Toxicities

If other events occur that are related to venetoclax, azacitidine, or decitabine, the investigator, in consultation with the AbbVie medical monitor, may interrupt or reduce the dose of venetoclax and/or azacitidine or decitabine, as appropriate. Grade 3 or greater nonhematologic toxicity (e.g., nausea, vomiting, and diarrhea when additional supportive care fails or neurotoxicity, AST, ALT, or bilirubin increased), that is related to venetoclax, azacitidine, or decitabine will require interruption and possible discontinuation of dosing. Venetoclax, azacitidine, or decitabine may be reintroduced, but only at a reduced dose, (in consultation with the AbbVie medical monitor) if the toxicity returns to ≤ Grade 1 or to baseline if Grade 2 at study entry.

Management of Infections

Anti-infective prophylaxis should be implemented per regional guidelines or institutional standards including appropriate prophylaxis for bacterial, viral and fungal infections. Potential for drug-drug interactions should be considered.

All subjects should be monitored for new onset hematologic toxicity and renal toxicities, with dose delay or reduction as appropriate. Please follow local, approved product label or applicable Summary of Product Characteristics (SmPC) for monitoring guidelines.

Dose Modifications Based on Toxicities

Subjects who discontinue 1 study drug because of study drug-related toxicities may continue to receive the other study drug for up to a maximum of 21 days, as determined by the investigator.

Dose Modifications for Venetoclax

See Appendix G for dose modifications for toxicities related to venetoclax. Venetoclax dose modifications for possible drug-drug interactions are provided in the Section 5.4.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

Effectiveness and safety analyses will be performed on all subjects who receive at least one dose of venetoclax and azacitidine or decitabine. Subjects in the trial will have AML, will be treatment-naïve, and will be ineligible for intensive chemotherapy.

7.3 Statistical Analyses for Effectiveness

Endpoints

The primary objective for the study is to determine the composite complete remission rate (CR + CRi), during the initial 6 cycles of treatment, in AML subjects treated with venetoclax and either azacitidine or decitabine in an outpatient setting. The composite complete remission rate will be achieved if IWG criteria for complete remission or complete remission with incomplete hematologic recovery (CR + CRi) have been met.

Secondary effectiveness endpoints include:

- Overall Response (CR, CRi).
- RBC and platelet transfusion independence.

Exploratory effectiveness endpoints include:

- Time to blood count improvements and duration of blood count improvements
- Remissions (CR/CRi) in molecular subtypes.

Details on the primary and other effectiveness analyses are provided in the SAP.

Sample Size Estimation

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

7.4 Statistical Analyses for Safety

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

Safety and tolerability will be assessed for all treated subjects and for azacitidine or decitabine separately.

Details on the statistical analyses for safety will be provided in the SAP.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The Protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the Protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the Protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may 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. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved Protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the Protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or date of the last follow-up contact, whichever is later.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCL	B cell lymphoma
BCL-w	B-cell lymphoma - Walter and Eliza Hall Institute
CL/F	Apparent clearance
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus Disease – 2019
CR	complete remission
CRF	Case Report Form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete blood count recovery
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A isoform subfamily
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FSH	follicle-stimulating hormone
GCP	Good clinical practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
IWG	International Working Group

MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia free bone marrow
NCI	National Cancer Institute
NCS	not clinically significant
P-gp	P-glycoprotein
PT	Preferred term
QD	once daily
RBC	red blood cell
RSI	Reference Safety Information
SAP	Statistical analysis plan
SC	subcutaneous(ly)
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-072: A Phase 3b, Single-Arm, Multicenter Open-Label Study of Venetoclax in Combination with Azacitidine or Decitabine in an Outpatient Setting in AML Patients Ineligible for Intensive Chemotherapy

Protocol Date: 29 October 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Therapeutic Area Medical Director	Medical Affairs
[redacted]	Group Medical Director	Clinical Development
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Associate Director	Statistics
[redacted]	Director	Clinical Pharmacology and Pharmacometrics
[redacted]	Director	Medical Writing

APPENDIX D. SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS, WITH ADDITIONAL GUIDANCE NOTED

Excluded
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort
Cautionary, 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, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole **Moderate CYP3A inhibitors** – amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil **P-gp substrates** – aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan* **P-gp inhibitors** – amiodarone, captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor
Cautionary
Warfarin and Courmarin Derivatives (e.g., phenprocoumon)** **BCRP substrates** – methotrexate,* mitoxantrone,* irinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** – atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, pitavastatin, pravastatin, repaglinide, simvastatin acid, telmisartan, valsartan, olmesartan **BCRP inhibitors** – geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.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.

^ Avoid concomitant use with venetoclax. Alternative treatments should be considered. Refer to Protocol Section 5.3 and Section 5.4.

* These are anticancer agents; consult contact the AbbVie medical monitor before use.

** Closely monitor the international normalized ratio (INR).

APPENDIX E. DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L) in adults	
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)[a]	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[b]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value > 1.5 × the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

a. The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 × (4-albumin in g/dL).

b. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 µmol/L) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome.

Note: In laboratory tumor lysis syndrome, 2 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 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

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

APPENDIX F. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES AND PREVENTION OF TUMOR LYSIS SYNDROME

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. • As determined by the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the decision 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 to 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.

Abnormality	Management Recommendations
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 to 2 mEq IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 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.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on local guidelines and/or institutional standards). • 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 predose level	• Administer rasburicase (dose based on local guidelines and/or institutional standards). ◦ When 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.

Abnormality	Management Recommendations
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 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.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

ECG = electrocardiogram; IV = intravenous; ULN = upper limit of normal; WNL = within normal limit

APPENDIX G. RECOMMENDED DOSE REDUCTIONS RELATED TO DRUG TOXICITIES IN AML

Recommended Venetoclax Dose Modifications for Toxicities

Event	Occurrence	Action
Hematologic Toxicities		
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia (see Warnings and Precautions in Management of Cytopenias, Section 6.2)	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, venetoclax and azacitidine or decitabine cycles should not be interrupted due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent treatment cycle of venetoclax and azacitidine or decitabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose in combination with azacitidine or decitabine or low-dose cytarabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine or decitabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and the duration reduced by 7 days for each subsequent cycle.

AML = acute myeloid leukemia; G-CSF = granulocyte-colony stimulating factor.

APPENDIX H. ACTIVITY SCHEDULE

The following table shows the required activities across the subject encounters, as well as the period of continued venetoclax supply. The individual activities are described in detail in the **Operations Manual**.

Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Activities Table

Activity	Screening	Cycle 1						Cycle 2 Day 1, and Day 1 of every cycle thereafter	Cycles 2 to 6 Days 2 to 7	Cycle 2 Day 28 (only if CR/CRi not achieved at end of Cycle 1)	Cycle 4 Day 28 (only if CR/CRi not achieved at end of Cycle 2)	Final Visit/Cycle 6 Day 28	30-Day Safety Follow-up
		Cycle 1 Day 1 (Baseline Visit)	Cycle 1 Day 2	Cycle 1 Day 3	Cycle 1 Day 4 (24 hrs post Day 3)	Cycle 1 Days 5 to 7	Cycle 1 Day 28						
Screening visit to occur within 21 days prior to first study drug administration. Cycle 1 Day 1 visit acts as the baseline visit													
INTERVIEWS & QUESTIONNAIRES													
Subject information and Informed Consent	✓												
Eligibility criteria	✓												
Medical/oncological history	✓												
ECOG Performance Status	✓	✓						✓				✓	✓
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LABS & EXAMS													
Height and Weight (Height at Screening only)	✓	✓						✓				✓	
Physical examination	✓	✓						✓				✓	✓
A complete physical examination will be performed at Screening. A targeted physical examination will be performed at all other specified visits. A symptom-directed physical examination may be performed, as needed.													
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
12-lead electrocardiogram	✓												
Serum pregnancy test	✓												
Urine pregnancy test, if applicable		✓											

Activity	Screening	Cycle 1						Cycle 2 Day 1, and Day 1 of every cycle thereafter	Cycles 2 to 6 Days 2 to 7	Cycle 2 Day 28 (only if CR/CRi not achieved at end of Cycle 1)	Cycle 4 Day 28 (only if CR/CRi not achieved at end of Cycle 2)	Final Visit/Cycle 6 Day 28	30-Day Safety Follow-up
		Cycle 1 Day 1 (Baseline Visit)	Cycle 1 Day 2	Cycle 1 Day 3	Cycle 1 Day 4 (24 hrs post Day 3)	Cycle 1 Days 5 to 7	Cycle 1 Day 28						
Cytogenetic Assessment	✓												
Molecular subtypes testing	✓												
Bone marrow aspirate	✓						✓			✓	✓	✓	
Clinical chemistry, hematology, and coagulation	✓	✓					✓	✓		✓	✓	✓	✓
TLS risk assessment	✓	✓	✓	✓	✓	✓							
Laboratory monitoring for TLS		✓	✓	✓	✓	✓							
Laboratory monitoring for TLS to occur at pre-dose, 4 - 6 hrs post-dose, and 24 hrs post-dose after each dose escalation.													
Post-treatment safety follow-up													✓
℞ TREATMENT													
TLS Prophylaxis		✓	✓	✓	✓								
Dispense venetoclax and subject diary		✓						✓					
Dosing with venetoclax		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Collect venetoclax and subject diary								✓				✓	
Dosing with azacitidine or decitabine (assigned at Cycle 1 Day 1)		✓	✓	✓	✓	✓		✓	✓				
Dispense venetoclax in a 3-step ramp-up in 3 days to target dose of 400 mg/day: Day 1 – 100 mg, Day 2 – 200 mg, Day 3 – 400 mg, and then continuous throughout. If on concomitant: strong CYP3A inhibitor (Day 1 – 10 mg, Day 2 – 20 mg, Day 3 – 50 mg, Day 4 – 100 mg [70 mg, if on posaconazole]); moderate CYP3A inhibitor or P-gp inhibitor (Day 1 – 50 mg, Day 2 – 100 mg, Day 3 – 200 mg).													

APPENDIX I. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	28 January 2019
Version 2.0	17 June 2019

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol and incorporate necessary protocol modifications due to the COVID-19 pandemic as follows:

- Section 2.2 - included information on the re-evaluation of the benefit and risk to subjects participating in the study. There is no additional risk to subjects or state what the additional risks are that may change the benefit-risk balance to participating subjects.
- Section 5.1 and Section 5.2 – added language that male subjects receiving azacitidine must practice protocol-specified contraception and must refrain from fathering children or donating sperm for 6 months following the last dose of azacitidine, as per updated safety risk language.
- Section 5.5 - added instructions to refer to Operations Manual for necessary changes to activities or procedures in the event of temporary study drug interruption/halt.
- Section 5.9 - clarified that protocol deviations may include modifications due to COVID-19.
- Section 8.2 - noted that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix J for additional details. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 9 - noted that remote monitoring may be employed as needed based on COVID-19.
- Appendix H - added reference to Operations Manual for allowed modification.
- Appendix J - Operations Manual updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.
- Appendix J - Operations Manual, Table 2, updated to capture the numerical corrections to the IWG disease assessment criteria of CR and CRi based on regulatory feedback.

APPENDIX J. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-072

Acute Myeloid Leukemia: Venetoclax and Azacitidine or Decitabine for AML Patients

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Venetoclax (ABT-199)

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

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] MBBS, MS AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: [redacted] Mobile: Fax: Email:
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SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 348-2303
Protocol Deviations and Product Complaints	[redacted] Study Project Manager AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Email:

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING:

INTERVIEW	• Informed consent • Eligibility criteria • Adverse event assessment	• ECOG Performance status • Medical/oncological history • Prior/concomitant therapy
EXAM	• Height and weight • Physical examination[a]	• Vital signs • 12-lead electrocardiogram
LAB	• Clinical chemistry, hematology, and coagulation • Bone marrow aspirate (disease assessment)[b]	• Serum pregnancy test • Cytogenetic assessment[c] • Molecular subtypes testing[d] • TLS risk assessment

NOTES: Screening visit to occur within 21 days prior to first study drug administration.

a. A complete physical examination will be performed at Screening. A targeted physical examination will be performed at all other specified visits. A symptom-directed physical examination may be performed, as needed.

b. Bone Marrow aspirate should be performed if not completed within 30 days prior to first study drug administration.

c. Cytogenetic testing should be performed if not completed within 3 months prior to first dose of study drug, as per institutional practice.

d. To be performed per institutional practices.

CYCLE 1 DAY 1:

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	• ECOG Performance status[a]
EXAM	• Vital signs[a] • Physical examination[a,b]	• Weight[a]
LAB	• Clinical chemistry, hematology, and coagulation[a] • Urine pregnancy test[a,c]	• TLS risk assessment • Laboratory monitoring for TLS[d]
TREATMENT	• TLS Prophylaxis[e] • Dispense venetoclax and subject diary	• Dosing with venetoclax[f,h] • Dosing with azacitidine or decitabine[g,h]

NOTES:

a. Assessments of ECOG Performance status, physical examination, vital signs, urine pregnancy test, clinical chemistry, hematology, coagulation, and measurement of weight are to be performed prior to first dose of study drug administration.

b. 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.

c. A urine pregnancy test is to be performed prior to the first dose of study drug on Cycle 1 Day 1, if it has been > 7 days since obtaining screening serum pregnancy test results.

d. Laboratory monitoring for TLS to occur at pre-dose, 4 - 6 hours post-dose, and 24 hours post-dose, for each venetoclax dose escalation.

e. TLS Prophylaxis will be done according to the guidelines in the Protocol, Section 6.2, and as per institutional guidelines.

f. Venetoclax will be administered orally in a 3-step ramp-up in 3 days to target dose of 400 mg/day: Day 1 – 100 mg, Day 2 – 200 mg, Day 3 – 400 mg, and then 400 mg daily thereafter. If on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1, for dose modifications.

g. Depending on Investigator's choice of azacitidine or decitabine at Cycle 1 Day 1 (as per institutional practice): Azacitidine (75 mg/m^2) subcutaneous (SC) or intravenous (IV) will be administered beginning at Cycle 1 Day 1 for 7 days of each 28-day cycle. Decitabine (20 mg/m^2) intravenous (IV) will be administered beginning at Cycle 1 Day 1 for 5 days of each 28-day cycle. The subject must remain on the assigned therapy for the duration of the study.

h. On the days subject is given either azacitidine or decitabine, venetoclax must be dosed in the clinic and administered prior to these agents.

CYCLE 1 DAYS 2 to 4

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy
EXAM	• Vital signs	
LAB	• TLS risk assessment	• Laboratory monitoring for TLS[a]
TREATMENT	• Dosing with venetoclax[b,e] • TLS Prophylaxis[c]	• Dosing with azacitidine or decitabine[d,e]

NOTES: Dose Day 4 is to occur 24 hours post-Day 3 dose.

a. Laboratory monitoring for TLS to occur at pre-dose, 4 - 6 hours post-dose, and 24 hours post-dose, for each venetoclax dose escalation.

b. Venetoclax will be administered orally in a 3-step ramp-up in 3 days to target dose of 400 mg/day: Day 1 – 100 mg, Day 2 – 200 mg, Day 3 – 400 mg, and then 400 mg daily thereafter. If on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1 for dose modifications.

c. TLS Prophylaxis will be done according to the Protocol, Section 6.2, and as per institutional guidelines.

d. Depending on Investigator's choice of azacitidine or decitabine at Cycle 1 Day 1 (as per institutional practice): Azacitidine (75 mg/m^2) SC or IV administered for 7 days beginning on Day 1 of each 28-day cycle. Decitabine (20 mg/m^2) IV administered for 5 days beginning on Day 1 of each 28-day cycle. The subject must remain on the assigned therapy for the duration of the study.

e. On the days subject is given either azacitidine or decitabine, venetoclax must be dosed in the clinic and administered prior to these agents.

CYCLE 1 DAYS 5 to 7

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy
EXAM	• Vital signs	
LAB	• TLS risk assessment[a]	• Laboratory monitoring for TLS[a]
TREATMENT	• Dosing with venetoclax[b]	• Dosing with azacitidine or decitabine[c]

NOTES: Administration Day 5 to 7 for subjects on azacitidine. Day 5 for subjects on decitabine (or dosed as per institutional practice).

a. For subjects on dose modification per Protocol, Table 1, where ramp-up occurs over 4 days, TLS risk assessment and laboratory monitoring would be performed on Day 5 (24 hours post-venetoclax dose escalation).

b. Venetoclax (400 mg) PO will be administered QD for each 28-day cycle except Cycle 1, due to 3-day ramp-up. If the subject is on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1, for dose modifications. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in the clinic and administered prior to these agents.

c. Depending on Investigator's choice of azacitidine or decitabine at Cycle 1 Day 1 (as per institutional practice): Azacitidine (75 mg/m^2) SC or IV administered for 7 days beginning on Day 1 of each 28-day cycle. Decitabine (20 mg/m^2) IV administered for 5 days beginning on Day 1 of each 28-day cycle. The subject must remain on the assigned therapy for the duration of the study.

CYCLE 1, 2*, and 4^; DAY 28

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy
EXAM	• Vital signs	
LAB	• Clinical chemistry, hematology, and coagulation	• Bone marrow aspirate[a]
TREATMENT	• Dosing with venetoclax[b]	

NOTES: * Cycle 2 Day 28: only if CR/CRi is not achieved at the end of Cycle 1.
^ Cycle 4 Day 28: only if CR/CRi is not achieved at the end of Cycle 2.

a. Bone marrow aspirate must be collected within ± 3 days of the Day 28 visit in Cycles 1, 2, and 4, and the samples must be assessed and resulted prior to study drug administration for the subsequent cycle.

b. Venetoclax (400 mg) PO will be administered QD for each 28-day cycle, except Cycle 1, due to 3-day ramp-up. If on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1, for dose modifications.

CYCLE 2 to 6; DAY 1

INTERVIEW	• Adverse event assessment • ECOG Performance status[a]	• Prior/concomitant therapy
EXAM	• Vital signs[a] • Physical examination[a,b]	• Weight[a]
LAB	• Clinical chemistry, hematology, and coagulation[a,c]	
TREATMENT	• Collect venetoclax and subject diary • Dispense venetoclax and subject diary	• Dosing with venetoclax[d] • Dosing with azacitidine or decitabine[e]

NOTES:

a. Assessments of ECOG Performance status, physical examination, vital signs, clinical chemistry, hematology, coagulation, and measurement of weight are to be performed prior to study drug administration.

b. Targeted physical examinations after screening may be performed within 72 hours before the scheduled visit.

c. If clinical chemistry, hematology, and coagulation are not collected at Cycle 2 Day 28 or Cycle 4 Day 28, then chemistry, hematology, and coagulation must be collected on Cycle 3 Day 1 and/or Cycle 5 Day 1. All Day 1 chemistry, hematology, and coagulation assessments should be collected pre-dose and results must be available prior to study drug administration.

d. Venetoclax (400 mg) PO will be administered QD for each 28-day cycle except Cycle 1, due to 3-day ramp-up. If on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1, for dose modifications. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in the clinic and administered prior to these agents.

e. Depending on Investigator's choice of azacitidine or decitabine at Cycle 1 Day 1 (as per institutional practice): Azacitidine (75 mg/m^2) SC or IV administered for 7 days beginning on Day 1 of each 28-day cycle. Decitabine (20 mg/m^2) IV administered for 5 days beginning on Day 1 of each 28-day cycle. The subject must remain on the assigned therapy for the duration of the study.

CYCLE 2 to 6 DAYS 2 to 7

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Dosing with venetoclax[a]	• Dosing with azacitidine or decitabine[b]

NOTES: Administration Days 2 to 7 for subjects on azacitidine or administration Days 2 to 5 for subjects on decitabine (or dosed as per institutional practice).

a. Venetoclax (400 mg) PO will be administered QD for each 28-day cycle except Cycle 1, due to 3-day ramp-up. If on concomitant posaconazole, strong or moderate CYP3A inhibitors, or P-gp inhibitors, refer to the Protocol, Table 1, for dose modifications. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in the clinic and administered prior to these agents.

b. Depending on Investigator's choice of azacitidine or decitabine at Cycle 1 Day 1 (as per institutional practice): Azacitidine (75 mg/m^2) SC or IV administered for 7 days beginning on Day 1 of each 28-day cycle. Decitabine (20 mg/m^2) IV administered for 5 days beginning on Day 1 of each 28-day cycle. The subject must remain on the assigned therapy for the duration of the study.

Final Visit/Cycle 6 Day 28:*

INTERVIEW	• Adverse event assessment • ECOG Performance status	• Prior/concomitant therapy
EXAM	• Vital signs • Physical examination[a]	• Weight
LAB	• Clinical chemistry, hematology, and coagulation	• Bone marrow aspirate
TREATMENT	• Collect venetoclax and subject diary	• Dosing with venetoclax[b]

NOTES: * Subjects prematurely discontinuing the study should have final visit procedures performed.

a. Targeted physical examinations after screening may be performed within 72 hours before the scheduled visit.

b. Subjects may take the Day 28 dose of venetoclax, but no additional study drug will be dispensed or administered.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

30-Day Safety Follow-Up:*

INTERVIEW	• Adverse event assessment • ECOG Performance status	• Prior/concomitant therapy
EXAM	• Vital signs • Post-treatment follow-up	• Physical examination
LAB	• Clinical chemistry, hematology, and coagulation	

NOTES: * This visit is to be performed for all subjects 30 days (± 2 days) after their last dose of study drug.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed 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 or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent 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.

In the event that the subject is rescreened for study participation or a protocol amendment alters the care of an ongoing subject, a new informed consent form must be signed.

Information regarding benefits 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.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical and Oncological History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at Screening. The subject's medical history will be updated before the first dose of study drug (Cycle 1, Day 1). This updated medical history will serve as the baseline for clinical assessment. A detailed oncology history will also be collected including: histology, date of diagnosis of acute myeloid leukemia (AML), any surgical procedures, transfusion of blood products within 8 weeks, and treatments administered (including dates and type of modality).

On Cycle 1 Day 1, any additional medical history observed after signing of the informed consent but prior to first dose of study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

3.3 Concomitant Medications

All reported concomitant medications, over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary beginning with the Screening visit through 30 days after last dose of study drug, the name of the medication, dosage information including dose, route, and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic Case Report Form (eCRF).

Subjects should receive full supportive care during study participation including transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

General guidelines regarding prohibited and cautionary concomitant medications and dietary restrictions are provided in Protocol Section 5.1, Section 5.3, and Section 5.4. Although cautionary, use of strong or moderate cytochrome P450 3A isoform subfamily (CYP3A) inhibitors or moderate inducers are allowed if no appropriate therapeutic alternative exists (refer to the Protocol Section 5.4). Dose reductions of venetoclax are required with concomitant administration of a P-gp inhibitor or strong or moderate CYP3A inhibitor (refer to the Protocol Section 5.4). Concomitant administration of a moderate CYP3A inducer should be avoided. Alternative treatments with less CYP3A induction or inhibition should be considered. If concomitant use of P-gp substrate is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

A sample list of prohibited medications and cautionary medications that may interact with study drug is provided in the Protocol, Appendix D. It is not possible to produce a complete list of medications that fall into these categories; if in question, please refer to the appropriate product label.

For guidance regarding medications for management of tumor lysis syndrome (TLS) and neutropenia, refer to the Protocol Section 6.2. The AbbVie Therapeutic Area Medical Director (TA MD) identified in Section 1 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

3.4 Adverse Event Assessment

Please refer to Section 4.2 and Section 4.3.

3.5 Eastern Cooperative Oncology Group

For all subjects, the Eastern Cooperative Oncology Group (ECOG) performance status will be performed as outlined in Section 2.1 and Section 2.2.

It is recommended, when possible, that a subject's performance status be assessed by the same person throughout the study. ECOG performance status will be assessed as follows:

Grade	Description
0	Fully active, able to carry on all predisease 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.
5	Dead

3.6 Height and Weight

Height will be measured at Screening only. Body weight will be measured for all subjects at scheduled visits as specified in the Activity Schedule and Section 2.1. The subject will wear lightweight clothing and no shoes during weighing.

3.7 Physical Examination

A physical examination (complete and targeted) will be performed at the designated study visits as specified in Section 2.1 and Section 2.2. The complete physical examination performed at Screening will serve as the baseline physical examination for the entire study. If the screening physical examination is performed within 7 days of Cycle 1 Day 1, it is not required to repeat the physical examination on Cycle 1 Day 1 unless clinically indicated. Targeted physical examinations will be performed at all other specified visits after Screening and may be performed within 72 hours before the scheduled visit.

Physical examination abnormalities noted at the Baseline Visit prior to the first dose of study drug should be recorded in the subject's medical history. Any significant physical examination findings after the first dose of study drug administration will be recorded as adverse events. All findings, whether related to an adverse event or part of each subject's medical history, will be captured on the appropriate eCRF page.

The targeted physical examination includes an assessment of heart, lungs, abdomen, as well as any system of the body, 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 or delegated to qualified medical staff (e.g., sub-investigator, nurse practitioner, etc.). At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

3.8 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1 and Section 2.2. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

3.9 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the Screening visit as specified in Section 2, and when clinically indicated per Investigator's determination.

ECGs 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 (no talking, laughing, deep breathing, sleeping, or swallowing) 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 electrical interference in the room.

Each ECG will be printed and evaluated by an appropriately qualified physician (preferably a cardiologist) 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 decision on whether a subject will be discontinued from the study.

The local reader will sign and date all safety ECGs and provide a global interpretation for each ECG 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 source documents, electronic case report forms (CRFs), or paper CRFs. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia).

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.

3.10 Cytogenetic Assessment

Local, certified laboratories will be utilized to process and provide results for cytogenetic assessment as per institutional practice. Cytogenetic testing should be performed at Screening, if it is not completed within 3 months prior to the first dose of study drug administration.

3.11 Molecular Subtypes Testing

Local, certified laboratories will be utilized to process and provide results for molecular subtype testing of bone marrow aspirates as per institutional practice. If done per institutional practice, then testing should be performed at Screening (if it is not completed within 3 months prior to the first dose of study drug) administration. This will be obtained at visits as specified in Section 2.1.

3.12 Dispense Study Drug

Venetoclax will be dispensed to subjects beginning at Cycle 1 Day 1 and as specified in Section 2.1. The first dose of study drug will be administered after all other Day 1 procedures are completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Each dose of venetoclax should be taken with approximately 240 mL of water and within 30 minutes after the completion of breakfast or the subject's first meal of the day. Venetoclax tablets should be taken together and swallowed whole (i.e., not chewed, crushed, or broken prior to swallowing). Azacitidine (75 mg/m^2) injections or infusions and decitabine (20 mg/m^2) infusions should be prepared and administered per the respective package inserts. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in clinic and administered prior to these agents.

3.13 Subject Diaries

Subject diaries will be dispensed at Cycle 1 Day 1 and at Day 1 of every cycle thereafter. Subjects will be instructed to bring their 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 venetoclax, (indicating if any doses are missed).

The diaries are to be reviewed at each visit. The completed diaries are to be collected and a new diary dispensed at Day 1 of every cycle. Diaries are to be appropriately filed with the subject's source documents for this study.

3.14 Clinical Laboratory Tests

Local, certified laboratories will be utilized to process and provide results for all the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. The blood samples for serum chemistry tests will be collected as specified in Section 2.

Chemistry, hematology, and coagulation will be analyzed by certified local laboratories. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study drug administration.

The baseline laboratory tests will be reviewed for eligibility before study drug administration. Beginning with Cycle 3 Day 1, chemistry, hematology, and coagulation may be performed within 72 hours prior to the scheduled visit. For cycles with bone marrow assessments, hematology laboratory tests should be performed on the same day as the bone marrow assessment. If the assessment occurs outside of the chemistry and hematology visit window, then the laboratory tests should be repeated prior to dosing. All Day 1 chemistry and hematology assessments should be performed pre-dose and the results should be available prior to the administration of treatment.

For chemistry labs performed for TLS prophylaxis and monitoring during the dose ramp-up period in Cycle 1, refer to the Protocol, Section 6.2 (Toxicity Management) and the Protocol, Appendix F (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome) for specific requirements.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator:

- may repeat the test to verify the out-of-range value;
- will follow the out-of-range value to a satisfactory clinical resolution; or
- may discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry[a]	Other Tests
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell count (WBC) Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Blast count	Blood urea nitrogen (BUN) Creatinine Calculated or measured creatinine clearance Total bilirubin Albumin Alanine transaminase (SGPT/ALT) Aspartate transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Total protein Glucose Bicarbonate/CO_2 Chloride Lactate dehydrogenase	Urine and serum - human chorionic gonadotropin[c,d,e] - Follicle-stimulating hormone[c,d,f] **TLS Chemistry Panel[a,g]** Creatinine Potassium Calcium Inorganic phosphorus Lactate dehydrogenase Uric acid[b] **Coagulation** Prothrombin time (PT) Activated partial thromboplastin time (aPTT)

TLS = tumor lysis syndrome

a. All chemistries should be performed at as specified in Section 2.1 and Section 2.2.

b. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation. Uric acid must be analyzed in plasma. Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath. Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

c. Performed only at Screening or Cycle 1 Day 1, as specified in the activity schedule and Section 2.1.

d. Females only.

e. Pregnancy testing is not required for females of non-childbearing potential.

f. If needed to determine postmenopausal status.

g. TLS chemistry samples for TLS monitoring will occur at pre-dose, 4 to 6 hours post-dose, and 24 hours post-dose for each venetoclax dose escalation.

Pregnancy Tests (Serum and Urine)

Pregnancy testing should not be performed for postmenopausal women.

A qualitative serum pregnancy test will be performed at Screening. A urine pregnancy test will be performed at Cycle 1 Day 1 if it has been > 7 days since obtaining the serum pregnancy test results for all female subjects of childbearing potential.

The serum pregnancy test will be sent to and performed by the local laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, and performed < 14 days prior to Cycle 1 Day 1, the subject can be enrolled into the trial;
- Still borderline, ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Urine pregnancy tests will be performed at Cycle 1 Day 1, as indicated in the Activity Schedule and Section 2.1.

- If the urine pregnancy test is negative, then dosing with study drug may begin.
- If the urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above).
- Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary.

Tumor Lysis Syndrome Monitoring

For chemistry laboratory tests performed for TLS prophylaxis and monitoring during ramp-up period, refer to Table 1.

3.15 Bone Marrow Aspirate and/or Biopsy

Bone marrow aspirate will be performed at time points described in Section 2.1. Bone marrow aspirates performed throughout the study should be captured on an eCRF, including those performed to confirm or rule out disease progression. Bone marrow will be assessed at:

- Screening
- the 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),
- the end of Cycle 2 (must be performed within ± 3 days of Cycle 2 Day 28 and resulted prior to administration of treatment for Cycle 3) [only if complete remission (CR)/complete remission with incomplete blood count recovery (CRi) not achieved at end of Cycle 1],
- the end of Cycle 4 (must be performed within ± 3 days of Cycle 4 Day 28 and resulted prior to administration of treatment for Cycle 5) [only if CR/CRi not achieved at end of Cycle 2], and
- upon concern for relapse, and

- the Final Visit/end of Cycle 6 (must be performed within ± 3 days of Cycle 6 Day 28).

Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis can be used as baseline assessments to satisfy eligibility criteria and for screening as long as the samples were taken 30 days prior to first study drug administration. Bone marrow aspirates and/or biopsies performed in addition to those required per protocol, as standard of care throughout the study as per institutional practice, should also be captured on an eCRF.

3.16 Disease Assessments

For all subjects, disease assessments at Screening will be performed as listed in Section 2.1. Disease response assessments while on treatment may be performed within approximately –3 days of the scheduled visit. All measurable disease must be documented at Screening for all subjects based on the analysis of bone marrow testing (AML), clinical laboratory tests (hematology), and physical examinations.

Disease assessments for AML will be evaluated based on the revised guidelines by the International Working Group (IWG) criteria.[1] Subject's response is based on most recent bone marrow results and recent hematology values. For subjects who require a delay in study treatment for peripheral blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks from the bone marrow analysis 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 will also be evaluated.

Each subject should receive only 1 response assessment at each time point where such data is being collected. This response assessment should represent the single best and most specific response achieved at that time. For example, any subject meeting CR criteria will also, by definition, meet criteria for CRi; such subjects should be categorized as CR. Response assessment categories are as follows in order of best response. The modified IWG criteria are presented in Table 2.

- CR
- CRi
- Partial Remission (PR)
- Morphologic Leukemia-Free State (MLFS)
- Resistant Disease (RD)
- Progressive Disease (PD)

Subjects with nonevaluable bone marrow will be reported as indeterminate and a repeat bone marrow should be completed within 1 week.

Table 2. Modified IWG Criteria

CR:	Absolute neutrophil count > 10^3/µL, platelets > 10^5/µL, red cell transfusion independence, and bone marrow with < 5% blasts.
CRi:	Bone marrow with less than 5% blasts, and absolute neutrophils of ≤ 10^3/µL (1000/µL) or platelets ≤ 10^5/µL (100,000/µL).
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.
RD:	Failure to achieve CR, CRi, PR; 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.
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/mL], and/or platelet count to > 50 × 10^9/L [50,000/mL] non-transfused); or • 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L (> 25,000/µL); or • New extramedullary disease

ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; IWG = International Working Group; PD = progressive disease, as defined by ELN criteria; PR = partial remission; MLFS = morphologically leukemia free state; RD = resistant disease; WBC = white blood cells

Note: Subjects should be classified at each response assessment based on BEST response to therapy using the assessments adapted from the IWG criteria in the table.

3.17 Post Treatment Follow-Up

Post-treatment follow-up (i.e., all cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected at the 30-day safety follow-up visit.

3.18 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. If a subject discontinues study participation, the procedures outlined for the Final Visit should be completed as soon as possible, preferably within 2 weeks. A 30-day safety follow-up visit will also be conducted after the last dose of study drug. If the subject refuses or is unable to attend the safety follow-up visit, this should be noted in the subject's source documentation.

However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the

study. Post-treatment follow-up (i.e., all cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected at the 30-day safety follow-up visit.

3.19 Unscheduled Visits

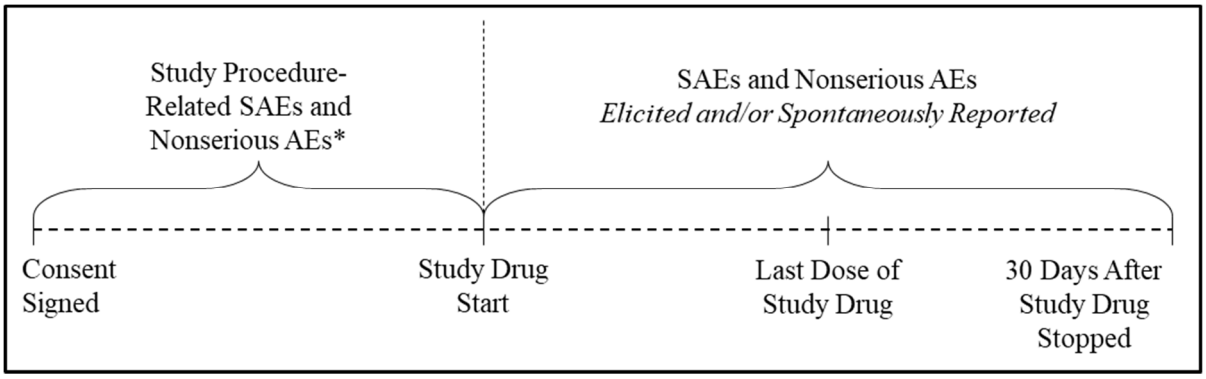
An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3, or for other tests, as determined by the investigator.

Visits for dispensing new study drug in case of temperature excursion, loss or damage are not considered an Unscheduled Visit. In addition, visits to only retest a lab will not be considered an Unscheduled Visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious adverse events which could be related to study procedures (e.g., infection at liver biopsy site, done during Screening), will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all adverse events and serious adverse events will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported serious adverse events will be collected (nonserious adverse events will not be collected), except for those subjects that are able to receive commercial venetoclax treatment after the end of study participation. Any new adverse events should be reported through the mechanism used for all post marketing adverse experiences.



AE = adverse event; SAE = serious adverse event

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

4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

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 serious adverse event nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 348-2303

For safety concerns, contact the Oncology Safety Team at:

Oncology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Office: +1 (833) 942-2226
Email: SafetyManagement_Oncology@abbvie.com

abbvie

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MBBS, MS**
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director 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 Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

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 and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the 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 a 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.

6 STUDY DRUG

6.1 Treatments Administered

Venetoclax will be dispensed in the form of 10-, 50-, and 100-mg film-coated tablets at the visits listed in Section 2.1 (refer to the Protocol Section 5.7). Each dose of venetoclax will be taken with approximately 240 mL of water. Subjects will be trained to self-administer venetoclax orally once daily (QD) **within 30 minutes after the completion of breakfast or the subject's first meal of the day**. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in clinic and administered prior to these agents.

Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If a subject should forget to take his/her venetoclax dose at his/her regularly scheduled dosing time, the subject should take the forgotten dose as soon as he/she remembers, provided that the dose will be taken within 8 hours of the missed dose. Otherwise, the subject should take the next dose at the next scheduled dosing time. If the subject vomits with 15 minutes of taking venetoclax, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Depending on the investigator's choice, subjects will receive azacitidine or decitabine on Cycle 1 Day 1. The subject is to remain on their assigned therapy for the duration of this study. Azacitidine (75 mg/m^2) infusions or injection and decitabine (20 mg/m^2) infusions should be prepared and administered per the respective package inserts. Azacitidine will be administered subcutaneously or intravenously beginning on Day 1 for 7 days of each 28-day cycle, as per institutional practice. Decitabine will be administered intravenously beginning on Day 1 for 5 days of each 28-day cycle, as per institutional practice.

AbbVie will provide venetoclax. AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Study drug must not be dispensed without contacting the Interactive Response Technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the final visit (Cycle 6 Day 28), the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

The venetoclax tablets will be packaged in high density polyethylene (HDPE) plastic bottles or blister cards to accommodate the study design. Each bottle or blister card will be labeled per local regulatory requirements. The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

The site will be responsible for obtaining azacitidine or decitabine.

Storage and Disposition of Study Drug

Venetoclax must be stored at controlled room temperature (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, destroyed on site, or returned to AbbVie, as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a non-randomized, open-label study. All eligible subjects will receive venetoclax QD in combination with azacitidine or decitabine as described in Section 2.1. The choice of azacitidine or decitabine will be as determined by the investigator. The subject is to remain on their assigned therapy for the duration of the study.

At the Screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in the study protocol, Section 4.2.

All tablets of venetoclax will be dosed together, QD for 28-day cycles. Azacitidine will be administered either SC or intravenously (IV), and decitabine will be administered IV. All subjects should take all doses of study drug with food around the same time each day, as described in Section 6.1. On the days the subject is given either azacitidine or decitabine, venetoclax must be dosed in clinic and administered prior to these agents.

All subjects will be treated with venetoclax and azacitidine or decitabine for a maximum of six cycles (28 days each). Subjects will undergo a final visit when treatment is discontinued or at the end of the sixth cycle. After the study period ends, subjects may continue receiving AML-directed therapy

including commercially-acquired standard-of-care treatments for venetoclax and azacitidine or decitabine.

7 REFERENCES

1. Cheson BD, Bennett JM, Kopecky KJ, et al. 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.