1.0 Title Page

Clinical Study Protocol M16-043

A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax Co-Administered with Low Dose Cytarabine Versus Low Dose Cytarabine in Treatment Naïve Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

Incorporating Administrative Change 1, 2, and 3 and Amendments 1, 1.01 (China Only), 1.02 (UK Only), 2, 3, 4, 5, 6, 7 and 8

AbbVie Investigational Product:	Venetoclax (ABT-199/GDC-0199)
Date:	01 March 2022
Development Phase:	3
Study Design:	This is a randomized, double-blind, placebo controlled, multicenter trial evaluating efficacy and safety of venetoclax co-administered with low dose cytarabine versus low dose cytarabine co-administered with placebo in treatment naïve patients with Acute Myeloid Leukemia who are ineligible for intensive chemotherapy.
EudraCT Number:	2016-003900-30
Investigator:	Investigator information on file at AbbVie
Sponsor:	AbbVie Inc.
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* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

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

Confidential Information
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	10 November 2016
Amendment 1	17 February 2017
Amendment 1.01 (China Only)	29 March 2017
Amendment 1.02 (UK Only)	02 August 2017
Amendment 2	06 October 2017
Administrative Change 1	09 October 2017
Administrative Change 2	10 November 2017
Amendment 3	22 June 2018
Administrative Change 3	11 September 2018
Amendment 4	29 November 2018
Amendment 5	29 May 2019
Amendment 6	07 January 2020
Amendment 7	29 July 2020

The purpose of this amendment is to:

- Update Section 5.1.4, Post Treatment Follow-Up, update post treatment follow up language.

  Rationale: *To allow Post Treatment and Survival collection every 4 months until the end of the study*
- Update Appendix C, Study Activities, with multiple footnote section language updates.

  Rationale: *To clarify post treatment follow up visit data collection timeframe.*
- Update Appendix B, List of Protocol Signatories, to update and add signatories.

  Rationale: *To add and replace signatories.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-043
Name of Study Drug: Venetoclax (ABT-199/GDC-0199)	**Phase of Development:** 3
Name of Active Ingredient: ABT-199 (GDC-0199)	**Date of Protocol Synopsis:** 01 March 2022
Protocol Title: A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax Co-Administered with Low Dose Cytarabine Versus Low Dose Cytarabine in Treatment Naïve Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy	

Objectives:

Primary Objective:

- To evaluate if venetoclax when co-administered with low dose cytarabine (LDAC) improves overall survival (OS) versus LDAC and placebo, in treatment naïve subjects with acute myeloid leukemia (AML).

Secondary Objectives:

- To evaluate if venetoclax when co-administered with LDAC improves composite complete remission rate (complete remission + complete remission with incomplete blood count recovery, CR + CRi).
- To evaluate if venetoclax when co-administered with LDAC improves complete remission and complete remission with partial hematologic recovery rate (CR + CRh).
- To evaluate if venetoclax when co-administered with LDAC improves the proportion of subjects achieving a composite CR (CR + CRi) by the initiation of Cycle 2.
- To evaluate if venetoclax when co-administered with LDAC improves complete remission rate (CR).
- To evaluate if venetoclax when co-administered with LDAC reduces fatigue based on patient reported outcome (PRO) assessment of the Patient Reported Outcomes Measurement Information System (PROMIS), and Fatigue Short Form (SF) 7a.
- To evaluate if venetoclax when co-administered with LDAC improves subjects Global Health Status/Quality of Life (GHS/QoL) based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30).
- To evaluate if venetoclax when co-administered with LDAC improves event-free survival (EFS).
- To evaluate if venetoclax when co-administered with LDAC improves the transfusion independence rates.
- To evaluate if venetoclax when co-administered with LDAC improves the proportion of subjects achieving complete remission and complete remission with partial hematologic recovery (CR + CRh) by the initiation of Cycle 2.
- To evaluate if venetoclax when co-administered with LDAC improves the minimal residual disease (MRD) response rate.

Objectives (Continued):

- To evaluate if venetoclax when co-administered with LDAC improves the response rates and overall survival in molecular subgroups (e.g., IDH1/2, FLT3).

Exploratory Objectives:

- Exploration of biomarkers predictive of venetoclax activity and duration of response may be performed. These analyses may be part of a multi-study assessment to compare responses to the therapies and/or disease state. Potential analysis may include, but will not be limited to:
  - To evaluate BCL-2 expression and outcome measures of overall survival and complete remission rate
- To evaluate the impact of venetoclax based on remaining subscales/items from the EORTC QLQ-C30 and EQ-5D-5L.

Investigators: Investigator information on file at AbbVie.

Study Sites: Approximately 125 sites

Study Population: Patients with treatment-naïve AML who are ineligible for intensive induction chemotherapy due to comorbidities.

Number of Subjects to be Enrolled: Approximately 210 subjects

Methodology:

This is a randomized, double-blind, placebo controlled, multicenter trial.

Screening

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

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

Study Treatment

All subjects in Arm A will receive venetoclax orally once daily (QD) plus LDAC (QD) beginning on Cycle 1 Day 1. Venetoclax should be taken within 30 minutes of food intake, preferably breakfast. Subjects will receive LDAC on Days 1 – 10 of each cycle.

All subjects in Arm B will receive placebo orally (QD) plus LDAC (QD) beginning on Cycle 1 Day 1. Placebo should be taken within 30 minutes of food intake. Subjects will receive LDAC on Days 1 – 10 of each cycle.

Cycle Length – 28 Days

- Venetoclax 600 milligram (mg) or Placebo Daily on Days 1 – 28
- LDAC 20 mg/m^2 Subcutaneous (SC) Daily on Days 1 – 10

The end of study is defined as the date of the last subject's last visit (LSLV) worldwide (Section 13.0 Completion of Study).

Methodology (Continued):

Subjects will continue their treatment assignment until documented disease progression per Investigator Assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). Accordingly, subjects may, in rare occasions, continue treatment after documented disease progression if the investigator believes it is in the best interest of the patient. All subjects will have a Final Visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. Baseline laboratory assessments will be obtained at Cycle 1 Day 1 prior to first dose of study treatment. PRO measures should generally be completed prior to other procedures, clinical assessments, and the administration of study treatment; however, they may be administered following confirmation that the subject is able to receive study treatment at the visit. Disease assessments by IWG criteria will be performed at end of Cycle 1 (± 3 days). Subjects with resistant disease at the end of Cycle 1 will repeat assessment at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to confirm a suspected response, and every 3 cycles thereafter starting at the end of Cycle 4 and continuing until disease progression per the modified IWG criteria until 2 successive disease assessments result in CR or CRi, or the subject withdraws consent. For subjects achieving 2 successive disease assessments that result in CR or CRi, disease assessments consist of laboratory and physical examination, bone marrow evaluation required upon concern for relapse. For subjects with a response of CRi a repeat bone marrow aspirate must be performed to confirm a CR once peripheral blood count recovery is noted. Disease assessments should also occur at the Final Visit and any other time the patient features suggest relapse or progressive disease. For subjects who are unblinded following the final analysis results, bone marrow collection every 3 cycles starting at the end of Cycle 4 and bone marrow collection after CRi to confirm CR are not required. Bone marrow collection until 2 successive disease assessments resulting in CR or CRi is not required. Bone marrow collection can be completed as per institutional standard of care. In addition to being reviewed by the Investigator and local hematopathologists, all disease assessment information will be sent to an Independent Review Committee (IRC) to provide response assessment. Interpretations from the IRC will not be shared with sites.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets the following criteria within 21 days prior to randomization (bone marrow samples and peripheral blasts used for AML diagnosis can be collected within 30 days prior to randomization).

1. Subject must have histological confirmation of AML by WHO criteria, be ineligible for intensive induction chemotherapy and either be:
   - ≥ 75 years of age

   OR

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

Main Inclusion (Continued):

- ≥ 18 to 74 years of age and fulfill at least one criteria associated with lack of fitness for intensive induction chemotherapy:
  - Eastern Cooperative Oncology Group (ECOG) Performance status of 2 – 3
  - Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina
  - DLCO ≤ 65% or FEV1 ≤ 65%
  - Creatinine clearance ≥ 30 mL/min to < 45 ml/min
  - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN
  - Other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy which must be reviewed and approved by the study medical monitor before study enrollment

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

   OR
   - of 0 to 3 for subjects between 18 to 74 years of age
3. Subject must have a projected life expectancy of at least 12 weeks.
4. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hours urine collection.
5. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 3.0 × ULN*
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN*
   - bilirubin ≤ 1.5 × ULN*
     - Subjects who are < 75 years of age may have bilirubin of ≤ 3.0 × ULN

   * Unless considered to be due to leukemic organ involvement.
6. Female subjects must be either postmenopausal defined as:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

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

     OR
   - A Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control starting at Study Day 1 through at least 180 days after the last dose of study drug.
7. Male subjects who are sexually active, must agree, from Study Day 1 through at least 180 days after the last dose of study drug, to practice protocol-specified methods of contraception (Section 5.2.4). Male subjects must agree to refrain from sperm donation from initial study drug administration through at least 180 days after the last dose of study drug.

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

Main Inclusion (Continued):

8. Females of childbearing potential must have negative results for pregnancy test performed:
   - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
   - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.
   - Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
9 Subject must voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Main Exclusion:

1. Subject has received any prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment. **Note**: Prior treatment for Myelodysplastic Syndrome is allowed except for use of cytarabine.
2. Subject had an antecedent myeloproliferative neoplasm (MPN) including myelofibrosis, essential thrombocytosis, polycythemia vera, or chronic myelogenous leukemia (CML) with or without BCR-ABL1 translocation and AML with BCR-ABL1 translocation.
3. Subjects that have acute promyelocytic leukemia (APL).
4. Subject has known CNS involvement with AML.
5. Subject has known HIV infection (due to potential drug-drug interactions between antiretroviral medications and venetoclax). HIV testing will be performed at Screening, if required per local guidelines or institutional standards.
6. Subject is known to be positive for hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals (non-exclusionary medications) are not excluded.
7. Subject has received strong or moderate CYP3A inducers 7 days prior to the initiation of study treatment.
   - Chinese subjects are excluded from receiving strong and/or moderate CYP3A inhibitors 7 days prior to the initiation of study treatment through the end of intensive PK collection (24 hours post dose on Cycle 1 Day 10).
8. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within 3 days prior to the initiation of study treatment
9. Subject has cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease which subjects are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain.
10. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, any other medical condition or known hypersensitivity to any of the study medications including excipients of LDAC that in the opinion of the investigator would adversely affect his/her participating in this study.

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

Main Exclusion (Continued):

11. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
12. Subject exhibits evidence of other clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial or fungal).
13. Subject has a history of other malignancies 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.
14. Subject has a white blood cell count > 25×10^9/L. (Note: Hydroxyurea administration or leukapheresis is permitted to meet this criterion).
15. Previous treatment with venetoclax and/or current participation in any other research study with investigational products.

Investigational Product:	Venetoclax, 100 mg/50 mg/10 mg tablet
Dose:	600 mg QD
Mode of Administration:	Oral
Reference Therapy:	Placebo (to match venetoclax 100 mg/50 mg/10 mg tablet)
Dose:	Not Applicable
Mode of Administration:	Oral
Reference Therapy:	LDAC
Dose:	20 mg/m^2; Days 1 – 10 of all cycles, Cycle = 28 days QD
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

Subjects will receive venetoclax/placebo/LDAC until documented disease progression per Investigator assessment, unacceptable toxicity or intolerance, withdrawal of consent, or the subject meets other criteria for discontinuation per study protocol (whichever occurs first).

Criteria for Evaluation:

Efficacy:

Bone marrow biopsies and aspirates must be performed at screening for all subjects. Cytogenetic assessment will be done at a local lab during screening. Samples for molecular markers and baseline disease assessment for potential MRD evaluation must be collected at screening. Bone marrow aspirate and biopsy must be performed at the end of Cycle 1. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) thereafter, however, these collections are not required for subjects who are unblinded following the final analysis results. Bone marrow collection can be completed as per institutional standard of care. Bone marrow aspirate and biopsy should also be performed upon concern for relapse or progressive disease and at the Final Visit (if no bone marrow was collected within the last 6 – 8 weeks, or if relapse or progression of disease has already been confirmed). Bone marrow will be obtained until two successive samples indicate CR or CRi, however, these collections are not required for subjects who are unblinded following the final analysis results. For subjects achieving 2 successive disease assessments that result in CR or CRi, disease assessments consist of laboratory and physical examination, bone marrow evaluation required upon concern for relapse. For subjects with a response of CRi on two successive bone marrow samples an additional bone marrow aspirate and biopsy must be performed to confirm a CR once peripheral blood count recovery is noted, however, these collections are not required for subjects who are unblinded following the final analysis results. Subjects will be assessed for response rate according to modified IWG criteria for AML (Cheson et al J Clin Oncol 2003). Progressive disease is defined per European LeukemiaNet (ELN) recommendations. If additional treatments are needed to optimize subjects' medical care, they can be performed following institutional standards and procedures. Subject's disease assessment is based on the most recent physical examination, bone marrow results and recent hematology values. For subjects who require a delay in the next cycle of study treatment for blood count recovery after a bone marrow evaluation, hematology values up to pre-dose labs from Day 1 of the next cycle or 2 weeks from the bone marrow if there is no additional dosing can be used to determine the IWG response.

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

Criteria for Evaluation (Continued):

Efficacy (Continued):

CR:	No morphologic evidence of AML and absolute neutrophil count ≥ 10^3/μL, platelets ≥ 10^5/μL, red cell transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRi:	All criteria as CR except for residual neutropenia < 10^3/μL (1,000/μL) or thrombocytopenia < 10^5/μL (100,000/μL). If all criteria for CR are met except for RBC transfusion independence, this also fulfills CRi criteria.
PR:	All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
MLFS:	Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of circulating leukemia cells, absence of extramedullary disease, and absolute neutrophils < 10^3/μL (1,000/μL) and thrombocytopenia < 10^5/μL (100,000/μL).
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.
MR:	Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
PD*:	• 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 10^9/L [500/μL], and/or platelet count to > 50 × 10^9/L [50000/μL] non-transfused); or • 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L (> 25000/μL); or • New extramedullary disease

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

* PD = Progressive disease as defined by ELN criteria.

In addition to investigator's assessment using the modified IWG response criteria, complete remission with partial hematologic recovery (CRh) will be derived by the sponsor for each subject's assessments.

Pharmacokinetic:

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

Criteria for Evaluation (Continued):

Safety:

Adverse event (AE) monitoring, vital signs, physical examination, and laboratory values will be assessed. Any additional clinically significant cardiac, pulmonary, or radiographic testing will be assessed and recorded. Note: All subjects will be hospitalized during the venetoclax ramp-up period during Cycle 1 (i.e., Day 1 through Day 5). Subjects will remain in the hospital for at least for 24 hours after reaching the final dose of venetoclax or longer as needed for bone marrow recovery and management of disease complications during the escalation of venetoclax dose from 100 to 600 mg.

Patient-Reported Outcomes:

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

Statistical Methods:

Efficacy:

Primary Efficacy Endpoints:

Overall Survival (OS):

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

Secondary Efficacy Endpoints:

Composite Complete Remission Rate:

The proportion of subjects with complete remission or complete remission with incomplete blood count recovery (CR + CRi) will be calculated based on the modified IWG criteria for AML.

Complete Remission and Complete Remission With Partial Hematologic Recovery:

The proportion of subjects with complete remission or complete remission with partial hematologic recovery (CR + CRh) will be calculated.

Composite Complete Remission Rate by Initiation of Cycle 2:

The proportion of subjects with complete remission or complete remission with incomplete blood count recovery (CR + CRi) by the initiation of Cycle 2 will be calculated based on the modified IWG criteria for AML.

Complete Remission Rate:

The proportion of subjects with complete remission (CR) will be calculated based on the modified IWG criteria for AML.

Patient-Reported Outcomes:

Fatigue as assessed by the PROMIS Fatigue SF 7a and GHS/QoL as assessed by the EORTC QLQ-C30 will be evaluated using a linear mixed effects regression model to test for differences between the two treatment arms.

Statistical Methods (Continued):

Event-Free Survival (EFS):

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

Post Baseline RBC Transfusion Independence:

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

Post Baseline Platelets Transfusion Independence:

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

The Rate of Conversion (RBC):

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

The Rate of Conversion (Platelets):

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

Complete Remission and Complete Remission With Partial Hematologic Recovery by Initiation of Cycle 2:

The proportion of subjects with complete remission or complete remission with partial hematologic recovery (CR + CRh) by the initiation of Cycle 2 will be calculated.

Minimal Residual Disease (MRD) Response Rate:

The proportion of subjects achieving CR + CRi and MRD or CR + CRh and MRD response status may be calculated.

CR + CRi Rate, CR + CRh rate, and OS in molecular subgroups:

CR + CRi rate, CR + CRh rate, and OS will be evaluated for molecular subgroups (e.g., FLT3, IDH1/2 etc.).

Pharmacokinetic:

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

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

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

Statistical Methods (Continued):

Safety:

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

Exploratory Endpoints:

Patient-Reported Outcomes:

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

Sample Size:

The primary endpoint of the study is overall survival. The sample size calculation is based on the following assumptions:

- Median OS of 6 months for placebo plus LDAC arm
- Median OS of 11 months for venetoclax plus LDAC arm (hazard ratio of 0.545)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary
- 2:1 randomization ratio to venetoclax plus LDAC, and placebo plus LDAC

With the above assumptions, a total of 133 death events will provide 90% power to detect a statistically significant difference between treatment arms at an alpha level of 0.05. A total of approximately 210 subjects (140 in the venetoclax plus LDAC arm and 70 in the placebo plus LDAC arm) will be randomized into the study to obtain the 133 death events.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALL	Acute Lymphocytic Leukemia
ALT	Alanine Aminotransferase (also called SGPT)
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
ASD	Amorphous solid dispersion
AST	Aspartate aminotransferase (also called SGOT)
BCL-2	B-Cell Lymphoma 2
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CLL	Chronic Lymphocytic Leukemia
CMH	Cochran Mantel Haenszel
CML	Chronic Myelogenous Leukemia
Cm	Centimeter
CNS	Central Nervous System
COVID-19	Coronavirus Disease – 2019
CR	Complete Remission
CRh	Complete Remission with Partial Hematologic Recovery
CRi	Complete Remission with Incomplete Blood Count Recovery
CS	Clinically Significant
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19

CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DLBCL	Diffuse Large B-cell Lymphoma
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event Free Survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core
EQ-5D-5L	EuroQol EQ-5D-5L
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GHS/QoL	Global Health Status/Quality of Life
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HNSTD	Highest Non-severely Toxic Dose
HR	Hematologic Response
Hr	Hour
HRQoL	Health-related quality of life
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
IWG	International Working Group
Kg	Kilogram
LDAC	Low Dose Cytarabine
LDH	Lactate Dehydrogenase
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
Mg	Milligram
mL	Milliliter
µM	Micromolar
MLFS	Morphologic Leukemia Free State
MM	Multiple Myeloma
MPN	Myeloproliferative Neoplasm
MPV	Mean Platelet Volume
MR	Morphologic Relapse
MRD	Minimal Residual Disease
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NCCN	National Cooperative Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
ORR	Overall Response Rate

OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PHI	Protected Health Information
PK	Pharmacokinetic
PO	Per Os Orally
PR	Partial Remission
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Prothrombin Time
QD	Once Daily
QTcF	QT interval measurement corrected by Fridericia's formula
RBC	Red Blood Cell
RD	Resistant Disease
RNA	Ribonucleic Acid
RPTD	Recommended Phase 2 Dose
R/R	Relapse/Refractory
RS	Richter's Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGOT	Serum Glutamic-oxaloacetic Transaminase (also called AST)
SGPT	Serum Glutamic-pyruvic Transaminase (also called ALT)
SLE	Systemic Lupus Erythematosus
SLL	Small Lymphocytic Lymphoma
SmPC	Summary of Product Characteristics
STD	Severely Toxic Dose
TEAE	Treatment Emergent Adverse Event
TLS	Tumor Lysis Syndrome
TTP	Time to Progression
ULN	Upper Limit of Normal
USPI	United States Prescribing Information
VAS	Visual Analog Scale
WBC	White Blood Cell

WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

Pharmacokinetic and Statistical Abbreviations

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

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3.0 Introduction

Venetoclax Activity and Preclinical Pharmacokinetic Profile

Hematologic malignancies are highly dependent upon the anti-apoptotic protein BCL-2 for survival. Over-expression of BCL-2 is associated with tumor initiation, disease progression, and drug resistance, and is thus a compelling target for anti-tumor therapy. Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (K_i < 0.010 nM) than for BCL-X_L (K_i = 48 nm) or MCL-1 (K_i > 444 nM).[1] In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines, including acute myelogenous leukemia (AML).[1]

BCL-2 over-expression has also been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. In addition, high levels of BCL-2 were associated with poor survival in a subset of patients with this disease.[2,3] The BCL-2/BCL-X_L inhibitor ABT-737 has been shown to kill AML cells, including leukemic stem/progenitor cells, as both a single agent and in combination with cytarabine[2] or 5-azacitidine.[3] To further define the role of BCL-2 in this disease, panels of AML cell lines and primary patient samples were cultured in the presence of venetoclax. Twelve of 24 AML cell lines tested were sensitive to venetoclax, with cell killing IC_{50} values of < 1.0 μM (Appendix H). The sensitivity of primary AML subject samples was comparable to that observed for primary CLL samples, with a median IC_{50} = 0.010 μM (n = 57) for AML[4] (Appendix H) versus a median IC_{50} = 0.003 μM (n = 35) for CLL (AbbVie R&D/10/1025, AbbVie R&D/12/538). Venetoclax has also demonstrated killing of AML leukemic stem/progenitor cells ex vivo and antitumor efficacy in vivo, inhibiting the growth of AML cell lines or AML patient-derived primary cells systemically engrafted into immunocompromised mice.[4] Single agent venetoclax has been studied in relapsed/refractory (R/R) AML and was found to induce rapid reduction in blast counts in some patients indicating activity in subject with this disease. However, not all AML cell lines, primary patient samples, or subjects treated with single

agent venetoclax were found to be sensitive, and there is biologic rationale for combining venetoclax with certain chemotherapeutic agents in the treatment of AML. The MCL-1 protein can act as a resistance factor for Bcl-2 family inhibitors[5,6] including in AML.[2] Therapeutic agents such as the DNA methyltransferase inhibitor azacitidine,[3] the DNA synthesis inhibitor cytarabine[7] and the anthracycline doxorubicin[8] have shown an ability to down-regulate MCL-1, indicating that they might combine well with BCL-2 inhibitors. In support of this, ABT-737 has demonstrated synergistic killing of AML cell lines when combined with cytarabine or doxorubicin.[2] Likewise, the combination of ABT-737 and azacitidine demonstrated synergistic killing of 7 of 8 primary AML patient samples and completely inhibited the engraftment of human CD45 + AML cells into immunocompromised mice.[3] Combinations of venetoclax and chemotherapeutic agents commonly used in the treatment of AML were recently tested against a panel of 20 AML cell lines. While most combinations resulted in additive cell killing, venetoclax combined with cytarabine or azacitidine showed synergistic effects on several AML cell lines (Appendix H). These data suggest that BCL-2 inhibition alone may be sufficient for the synergistic effects that have been observed between ABT-737 and cytarabine or azacitidine, and thus provides a rationale for testing these combinations with venetoclax in subjects with AML.

Venetoclax and M27 metabolite are predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Venetoclax is also substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. No active uptake of venetoclax was observed in cells overexpressing organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3. Based on in vitro results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (IC_{50} > 30 µM); and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 µM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Venetoclax Preclinical Toxicology

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current Investigator's Brochure.[9]

Acute Myeloid Leukemia

Acute myeloid leukemia is characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood and extramedullary tissues which disrupts normal haematopoiesis. It is a heterogeneous disease, encompassing a large number of distinctly different subtypes that may have different clinical presentations and differing responses to treatment. AML is defined by the World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow.[10] It is the most common form of acute leukemia in adults with an estimated 19,950 new cases and 10,430 deaths in 2016 in the United States.[11] The incidence is approximately 36,000 in the US alone. The median age of diagnosis is 67 years, with 55% of the patients diagnosed at 65 years or older, and approximately a third of them are diagnosed over the age of 75.

For many patients with AML, initial treatment recommendations are a function of the patient's ability to receive and benefit from anthracycline-containing induction chemotherapy. Most younger adults diagnosed with AML are considered fit enough to receive an anthracycline-containing induction chemotherapy regimen. For fit patents, standard treatment for newly diagnosed AML consists of remission induction therapy with cytarabine and an anthracycline, usually daunorubicin or idarubicin (7 + 3), followed by consolidation therapy.

Though some older patients receive anthracycline-containing induction chemotherapy, most older patients do not receive intensive induction chemotherapy but rather receive less-intensive therapy such as LDAC or a hypomethylating therapy. Indeed, AML in older patients is often a biologically and clinically distinct disease with a diminished response to chemotherapy, low remission rates, and short disease-free/overall survival. In older patients higher proportions of unfavorable cytogenetics, higher frequency of

antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype contribute to 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 often associated with AML therapy. Though less common than for older patients, some younger patients may also be unfit to receive anthracycline-containing chemotherapy for reasons such as severe cardiac, pulmonary, renal, or other comorbidities. Several studies have also demonstrated the benefits of active therapy over supportive care only, with respect to survival and quality of life, suggesting that treatment should be offered to nearly all patients diagnosed with AML.

Venetoclax Clinical Data

As of 28 November 2021, based on the data available in the AbbVie and Genentech/Roche clinical databases, a total of 4796 subjects have been exposed to at least one dose of venetoclax in the oncology development program. Of these, 1108 had AML, 1694 subjects had CLL/SLL, 205 subjects had MDS, 586 subjects had NHL/MCL, 57 subjects had ALL/LL, 12 subject has solid tumor and 526 subjects had MM. An additional 299 subjects were healthy volunteers who participated in the drug-drug interaction (DDI) studies. Based on the available data, a total of 1208 oncology subjects received the drug as monotherapy and 2934 subjects received the drug in combination with other therapies.

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

Clinical Data in AML

As of 09 March 2016 a total of 102 subjects with AML have been treated in the venetoclax oncology clinical program: 32 subjects with R/R and in unfit AML received venetoclax as a single agent (Study M14-212) and 70 subjects received venetoclax in combination with other therapeutic agents including 45 subjects with HMAs (Study M14-358) and 25 subjects with low-dose cytarabine (LDAC) (Study M14-387). To date, the adverse events observed occurred at an incidence that appeared to be consistent with what would be expected in the AML patients both in monotherapy and combination studies. Neutropenia is being closely monitored.

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

This is a completed study with single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study.[12] The most common adverse events observed in ≥ 30% of the subjects in Study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., one event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment.

Efficacy data for Study M14-212 are available for all 32 subjects, the majority (30, 94%) of the subjects had R/R AML and a few (2, 6%) were deemed unfit for intensive therapy. The ORR was 19% (6 of 32 subjects), with complete remission (CR) in 2 (6%) and complete remission with incomplete blood count recovery (CRi) in 4 (13%) subjects.

Anti-leukemic activity was observed in and additional 7 (22%) subjects, with ≥ 50% bone marrow reduction with hematologic recovery in 4 of these subjects.

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

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

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

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

reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

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

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

As of 28 November 2015, a total of 25 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled; 18 subjects were enrolled into the Phase 1 portion of the study and a RPTD of 600 mg has been identified. Enrollment into the subsequent Phase 2 portion with approximately 50 subjects is ongoing to evaluate the RPTD for efficacy and safety. Preliminary efficacy data for Study M14-387 are available for 18 subjects with AML without a prior MPN treated with a 600 mg venentoclax target dose and LDAC as of 31 March 2016 (ASH abstract 2016). The CR + CRi rate was 78%.

Of the 25 subjects enrolled across all doses at the 28 November 2015 data cut, the most common adverse events were nausea (68.0%), anemia (52.0%), and febrile neutropenia (36.0%). Events grade 3 and above were reported for all but one subject (96.0%); the most common event was anemia (48.0%). Serious adverse events were reported for 19 (76.0%) subjects, including febrile neutropenia (7 subjects), pyrexia, hyponatremia, and malignant neoplasm progression (2 subjects each). All other events occurred in one subject each. Fatal adverse events occurred in 5 (20.0%) subjects: 2 events of malignant neoplasm progression and one event each of acute hepatic failure, Candida pneumonia, and lung infection.

Additional safety and efficacy data are described in more detail in the current version of the Investigator's Brochure.[9]

3.1 Differences Statement

This is the first randomized study comparing venetoclax in combination with LDAC versus placebo in combination with LDAC in subjects with AML who are treatment naïve and are considered ineligible for treatment with an anthracycline-containing induction regimen due to age, co-morbidity or other risk factors.

3.2 Benefits and Risks

Initial studies from the Acute Leukemia Group B, over 40 years ago, reported that 15% – 20% of patients with AML receiving LDAC at dose of 10 – 30 mg/m^2 achieved a CR.[13] Subsequently, a meta-analysis including 293 previously untreated patients with newly diagnosed acute non-lymphocytic leukemia reported a CR rate of 32% with LDAC.[14] More recently, a large, international trial for newly diagnosed patients using modern and more sensitive methods to determine the depth of clinical response reported a CR + CRi rate of approximately 11% for the patients randomized to LDAC.[15]

There are currently no therapies approved by the US FDA specifically for elderly patients with AML who are ineligible to receive intensive chemotherapy, though low-intensity therapies including LDAC, azacitdine, or decitabine are relatively common treatment approaches worldwide.

As detailed in Section 3.0, preliminary efficacy and safety results of venetoclax in combination with LDAC are favorable and support further evaluation in treatment naive AML patients who are not eligible to receive intensive induction chemotherapy.

Rapid AML cell death in patients can result in risk of tumor lysis syndrome (TLS) during initial dosing. Because of the known background risk of TLS in AML patients, venetoclax dose will be gradually increased to the final dose during initiation of study treatment in Cycle 1 combined with of LDAC to optimize disease control and enable close subject monitoring.

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

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

4.0 Study Objectives

4.1 Primary Objective

The primary objective is:

- To evaluate if venetoclax when co-administered with LDAC improves overall survival (OS) versus LDAC and placebo, in treatment naïve subjects with acute myeloid leukemia (AML).

4.2 Secondary Objectives

The secondary objectives are:

- To evaluate if venetoclax when co-administered with LDAC improves composite complete remission rate (complete remission + complete remission with incomplete blood count recovery, CR + CRi).
- To evaluate if venetoclax when co-administered with LDAC improves complete remission and complete remission with partial hematologic recovery rate (CR + CRh).
- To evaluate if venetoclax when co-administered with LDAC improves the proportion of subjects achieving composite CR (CR + CRi) by the initiation of Cycle 2.
- To evaluate if venetoclax when co-administered with LDAC improves complete remission rate (CR).
- To evaluate if venetoclax when co-administered with LDAC reduces fatigue based on patient reported outcome (PRO) assessments (Patient Reported

Outcomes Measurement Information System (PROMIS), and Fatigue Short Form (SF) 7a).

- To evaluate if venetoclax when co-administered with LDAC improves subjects Global Health Status/Quality of Life (GHS/QoL) based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30).
- To evaluate if venetoclax when co-administered with LDAC improves event-free survival (EFS).
- To evaluate if venetoclax when co-administered with LDAC improves the transfusion independence rates.
- To evaluate if venetoclax when co-administered with LDAC improves the proportion of subjects achieving complete remission and complete remission with partial hematologic recovery (CR + CRh) by the initiation of Cycle 2.
- To evaluate if venetoclax when co-administered with LDAC improves the MRD response rate.
- To evaluate if venetoclax when co-administered with LDAC improves the response rates and overall survival in molecular subgroups (e.g., IDH1/2, FLT3).

4.3 Exploratory Objectives

The exploratory objectives are:

- Exploration of biomarkers predictive of venetoclax activity and duration of response may be performed. These analyses may be part of a multi-study assessment to compare responses to the therapies and/or disease state. Potential analyses may include, but will not be limited to:
  - To evaluate BCL-2 expression and outcome measures of overall survival and complete remission rate.
- To evaluate the impact of venetoclax based on the remaining subscales/items from the EORTC QLQ-C30 and EQ-5D-5L.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo controlled, multicenter study of venetoclax co-administered with LDAC versus LDAC in treatment naïve patients with acute myeloid leukemia who are ineligible for intensive induction chemotherapy sponsored by AbbVie. Subjects will be randomized to one of the two treatment arms in a 2:1 ratio, both of which will have treatment cycles of 28 days.

- Arm A: Venetoclax 600 mg orally QD on Days 1 – 28 plus LDAC 20 mg/m^2 SC QD on Days 1 – 10
- Arm B: Placebo 600 mg orally QD on Days 1 – 28 plus LDAC 20 mg/m^2 SC QD on Days 1 – 10

Approximately 210 subjects will be randomized to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures will receive a unique subject number via the Interactive Response Technology (IRT) system. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit up to dosing on Cycle 1 Day 1, and will record the results of this assessment and the details of the informed consent process in the subject's medical records.

Eligible subjects have up to 21 days to complete screening procedures, with the exception of bone marrow samples and peripheral blasts used for AML diagnosis which can be collected within 30 days prior to randomization. Once screening procedures are completed and eligibility is confirmed, subjects will be randomized. After being

randomized, subjects will have up to 5 days to initiate Cycle 1 Day 1; however, this window cannot exceed the allotted 21-day Screening period.

5.1.2 Rescreening

Rescreening may be performed upon investigator discussion with the AbbVie Medical Monitor and subsequent agreement.

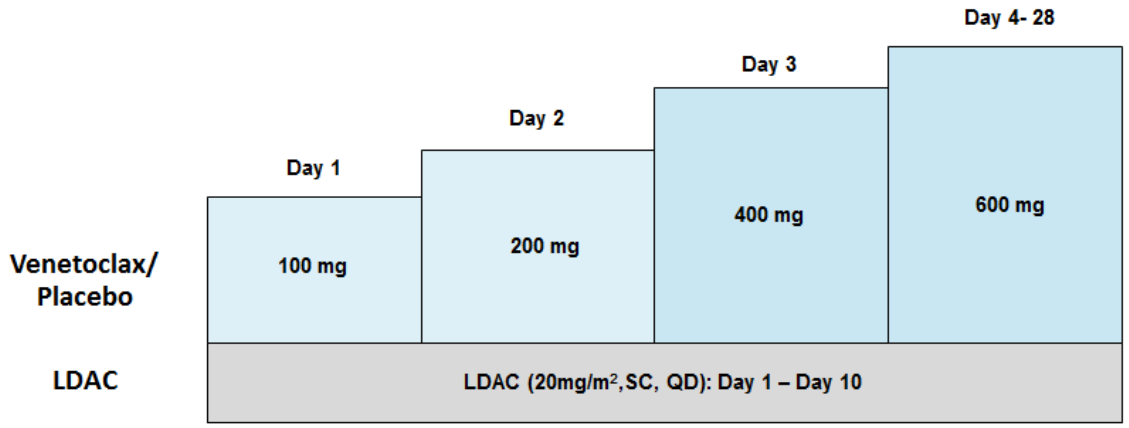
5.1.3 Treatment Period

After meeting the eligibility criteria, subjects will be enrolled via IRT into a treatment arm. All subjects will begin study drugs (venetoclax/placebo and LDAC) on Cycle 1 Day 1. Subjects in Arm A will receive venetoclax orally QD plus LDAC SC QD beginning on Cycle 1 Day 1. Venetoclax should be taken within 30 minutes after completion of a meal (preferably breakfast). Subjects in Arm B will receive placebo orally QD plus LDAC SC QD beginning on Cycle 1 Day 1. Placebo should be taken within 30 minutes after completion of a meal (preferably breakfast). Subjects will receive LDAC on Days 1 – 10 of each cycle beginning on Cycle 1.

Dosing Schedule Overview – for Venetoclax/Placebo and LDAC

Venetoclax or placebo for venetoclax will be administered with a 4-day ramp up beginning with 100 mg dose on Day 1, 200 mg dose on Day 2, 400 mg dose on Day 3 and 600 mg dose on Day 4 of Cycle 1. Subjects will be hospitalized during the venetoclax ramp-up period during Cycle 1 (i.e., Day 1 through Day 5). Subjects will remain in the hospital for at least 24 hours after reaching the final dose of venetoclax on Day 4. Venetoclax or placebo for venetoclax will be continued at 600 mg daily thereafter. LDAC will be administered SC daily per protocol at 20 mg/m^2 daily on Days 1 – 10 of each cycle.

Figure 1. Dosing Schematic



Cycle = 28 days. For dosing delay and/or duration guidelines please refer to Section 6.1.7.

Cycle Length – 28 Days

- Venetoclax 600 mg or Placebo 600 mg QD on Days 1 – 28
- LDAC 20 mg/m^2 SC Daily on Days 1 – 10

Subjects will continue their study treatment until documented disease progression per Investigator assessment, unacceptable toxicity, withdrawal of consent, or the subject meets other protocol criteria for discontinuation (whichever occurs first). Study treatments may be administered in the hospital, clinic or in a non-hospital/clinic environment (home), as allowed per local regulations.

On cycles where LDAC is administered in a non-hospital/clinic environment (home), subjects will still visit the site within 3 days prior of Day 1 to have procedures completed so that subjects can be medically monitored for safety. All subjects will have a Final Visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. Baseline laboratory assessments will be obtained at Cycle 1 Day 1 prior to first dose of study treatment. PRO measures scheduled for administration should generally be completed prior to other procedures, clinical assessments, and the

administration of study treatment; however, they may be administered following confirmation that the subject is able to receive study treatment at the visit.

Disease assessments by the modified IWG criteria will be performed at end of Cycle 1 (± 3 days), subjects with resistant disease at end of Cycle 1 will repeat assessment at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to confirm a suspected response, and every 3 cycles starting at the end of Cycle 4 and continuing until disease progression as defined per ELN[16] criteria thereafter until 2 successive disease assessments result in CR or CRi, or the subject withdraws consent. For subjects achieving 2 successive disease assessments that result in CR or CRi, disease assessments consist of laboratory and physical examination, bone marrow evaluation required upon concern for relapse. For subjects who are unblinded following the final analysis results, bone marrow collections every 3 cycles starting at the end of Cycle 4 and bone marrow collection after CRi to confirm CR are not required. Bone marrow collection until 2 successive disease assessments resulting in CR or CRi is not required for these unblinded subjects. Bone marrow collection can be completed as per institutional standard of care. In addition to being reviewed by investigators, in conjunction with their hematopathologists, all pertinent information for disease assessment will be reviewed by an Independent Review Committee (IRC) to provide response assessment. Interpretations of the central hematopathologist from the IRC will not be shared with sites. A charter will outline the review process for the IRC's determination of response. An Independent Data Monitoring Committee (IDMC) will periodically review safety and efficacy data per the IDMC Charter. Details regarding the IDMC are provided in Section 5.5.5.2.

5.1.4 Post Treatment Follow-Up

After study treatment has ended and subjects have completed their Final Visit, subjects will be followed for overall survival, progressive disease and post-therapy disease status (if applicable). Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including transplantation, regimens, dates of initiation and completion, etc.) will be collected (e.g., via telephone calls and/or clinical visits) every 4 months until the end of the study. All subjects will be followed for

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

For subjects who had CR, CRi, MLFS, or PR at time of study drug discontinuation, hematology and disease assessments data will also be collected every 4 months (± 14 days) until the end of the study.

For subjects who had RD, MR or PD at time of study drug discontinuation, survival phone calls will be conducted every 4 months (± 14 days) until the end of the study.

The end of study is defined as the date of the last subject's last visit (LSLV) (Section 13.0 Completion of Study).

30 Day Safety Follow-Up Visit

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event is achieved.

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

5.2 Selection of Study Population

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

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria within 21 days prior to randomization (bone marrow samples and peripheral blasts used for AML diagnosis can be collected within 30 days prior to randomization):

1. Subject must have histological confirmation of AML by WHO criteria, is ineligible for intensive induction chemotherapy and either is:
   - ≥ 75 years of age

     OR
   - ≥ 18 to 74 years of age and fulfill at least one criteria associated with lack of fitness for intensive induction chemotherapy:
     - Eastern Cooperative Oncology Group (ECOG) Performance status of 2 – 3
     - Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina
     - DLCO ≤ 65% or FEV1 ≤ 65%
     - Creatinine clearance ≥ 30 mL/min to < 45 ml/min
     - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN
     - Other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy which must be reviewed and approved by the study medical monitor before study enrollment
2. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status:
   - of 0 to 2 for subjects ≥ 75 years of age

   OR
   - of 0 to 3 for subjects between 18 to 74 years of age
3. Subject must have a projected life expectancy of at least 12 weeks.
4. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hours urine collection

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

Or, if serum creatinine is in µmol/L:

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

5. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 3.0 × ULN*
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN*
   - bilirubin ≤ 1.5 × ULN*
     - Subjects who are < 75 years of age may have bilirubin of ≤ 3.0 × ULN

   * Unless considered to be due to leukemic organ involvement.
6. Female subjects must be either postmenopausal defined as:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

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

     OR
   - A Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control starting at Study Day 1 through at least 180 days after the last dose of study drug.
7. Male subjects who are sexually active must agree, from Study Day 1 through at least 180 days after the last dose of study drug, to practice protocol-specified methods of contraception (Section 5.2.4). Male subjects must agree to refrain from

sperm donation from initial study drug administration through at least 180 days after the last dose of study drug.

8. Females of childbearing potential must have negative results for pregnancy test performed:
   - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
   - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.
   - Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
9. Subject must voluntarily sign and date an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

1 – 5	In order to select the appropriate subject population with appropriate disease characteristics for evaluation
6 – 8	The impact of venetoclax on pregnancy is unknown
9	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has received any prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment. **Note:** Prior treatment for Myelodysplastic Syndrome is allowed except for use of cytarabine.
2. Subject had an antecedent myeloproliferative neoplasm (MPN) including myelofibrosis, essential thrombocytosis, polycythemia vera, or chronic

myelogenous leukemia (CML) with or without BCR-ABL1 translocation and AML with BCR-ABL1 translocation.

3. Subjects that have acute promyelocytic leukemia (APL).
4. Subject has known CNS involvement with AML.
5. Subject has known HIV infection (due to potential drug-drug interactions between antiretroviral medications and venetoclax). HIV testing will be performed at Screening, if required per local guidelines or institutional standards.
6. Subject is known to be positive for hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals (non-exclusionary medications) are not excluded.
7. Subject has received strong or moderate CYP3A inducers 7 days prior to the initiation of study treatment.
    - Chinese subjects are excluded from receiving strong and/or moderate CYP3A inhibitors 7 days prior to the initiation of study treatment through the end of intensive PK collection (24 hours post dose on Cycle 1 Day 10).
8. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within 3 days prior to the initiation of study treatment.
9. Subject has cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease which subjects are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain. Class 3 is defined as cardiac disease which subjects are comfortable at rest but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class 4 is defined as cardiac disease which subjects have an inability to carry on any physical activity without discomfort, symptoms of heart failure at rest, and if any physical activity is undertaken then discomfort increases.
10. Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic,

immunologic, hepatic, cardiovascular disease, any other medical condition or known hypersensitivity to any of the study medications including excipients of LDAC that in the opinion of the investigator would adversely affect his/her participating in this study.

11. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.

12. Subject exhibits evidence of other clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial or fungal).

13. Subject has a history of other malignancies 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.

14. Subject has a white blood cell count > 25×10^9/L. (Note: Hydroxyurea administration or leukapheresis is permitted to meet this criterion).

15. Previous treatment with venetoclax and/or current participation in any other research study with investigational products.

Rationale for Exclusion Criteria

1 – 7	In order to ensure safety of the subjects throughout the study
8 – 15	In order to avoid bias for the evaluation of efficacy and safety, including concomitant use of other medications

5.2.3 Prior and Concomitant Therapy

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

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

Vaccination with a live vaccine should be avoided. Killed or inactivated vaccines may be administered; however the response to such vaccines may be diminished. General guidelines regarding excluded, cautionary and allowed medications are summarized in Table 1 and Appendix I.

Table 1. Excluded Food/Medications

Excluded Food (from 3 Days Prior to Study Administration Until Last Day of Treatment)
• Grapefruit and grapefruit products • Seville Oranges (including marmalade containing Seville oranges) • Starfruit
Excluded Drugs
• **Strong CYP3A inducers (During Ramp-Up and Throughout the Study)**
Cautionary, Additional Guidance Noted
• **Strong and Moderate CYP3A Inhibitors^** Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax as described in Table 2. • **Moderate CYP3A Inducers^** Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications, use with caution and contact AbbVie Medical Monitor or designee (refer to Section 6.1.7) for guidance. • **P-gp inhibitors** Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 2-fold (see Table 2).
Cautionary
• Warfarin and coumarin derivatives* • P-gp substrates** • BCRP substrates • OATP1B1/1B3 substrates • BCRP inhibitors

^ Chinese subjects are prohibited to take strong CYP3A inhibitors, moderate CYP3A inhibitors and inducers 7 days prior to the initiation of study treatment through the end of intensive PK collection (24 hours post dose on Cycle 1 Day 10).

* Closely monitor International Normalization Ratio (INR).

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

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

Assigned Venetoclax Dose	Modified Dose if Co-Administered with a Moderate CYP3A or P-gp Inhibitor	Modified Dose if Co-Administered with a Strong CYP3A Inhibitor
100 mg	50 mg	10 mg
200 mg	100 mg	20 mg
400 mg	200 mg	50 mg
600 mg	300 mg	50 mg

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

A sample list of excluded medications and cautionary medications that fall into the categories within this section of the protocol can be found in Appendix I. It is not possible to produce a comprehensive list of medications that fall into these categories, so if in question, please refer to the appropriate local product label and/or FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and notify the AbbVie Medical Monitor and discuss the investigator's intended use of these medications with the subject in question and the investigator's plans to medically monitor the potential study subject.

Commonly used anti-infective agents for prophylaxis (including ciprofloxacin and azole anti-fungal medications) and calcium channel blockers (diltiazem and verapamil) have CYP3A inhibitory properties and dose reductions of venetoclax/placebo are required.

Steroid therapy during study participation should be limited to lower dose and short duration if medically indicated. Intrathecal chemotherapy or radiation therapy for CNS prophylaxis is not permitted during study participation.

5.2.4 Contraception Recommendations

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

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) or a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 180 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1. Also, subjects must use a barrier method during this study from initial study drug administration to 180 days after the last dose of study drug.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1. Also, subjects must use a barrier method during this study from initial study drug administration to 180 days after the last dose of study drug.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, vasectomy occurred more than 3 months prior to screening, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

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

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 180 days after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Additionally, male subject agrees not to donate sperm from Study Day 1 through at least 180 days after the last dose of study drug. Prior to starting treatment, counselling on sperm storage will be provided to all eligible male subjects.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Biomarkers, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

This study is designed to assess Pharmacokinetic, Biomarker, Exploratory Research, and Safety data. Exploratory efficacy analyses may be performed on all subjects enrolled unless otherwise specified and may not be included in the clinical study report. Study procedures described in this protocol are summarized in Appendix C.

5.3.1.1 Study Procedures

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

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

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.

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

A subject who has signed the informed consent, has had at least one study procedure conducted, and is determined to be a screen failure, will not proceed into the study. Rescreening may be performed upon investigator discussion with the AbbVie Medical Monitor and subsequent agreement.

Informed Consent

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

Medical and Oncologic History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical conditions

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

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

Adverse Event and Prior/Concomitant Medication Assessment

All concomitant medications (prescription or over-the-counter, including vitamins and/or herbal supplements) and AE assessments will be performed per Appendix C. On Cycle 1 Day 1, any events observed from the time of signing of the informed consent but prior to initial study drug administration will only be recorded as a serious or non-serious adverse event if considered by the Investigator to be causally related to the study-required procedures. At each visit, including the Final Visit and the 30-day Safety Follow-Up Visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded on the adverse event eCRF.

Cytogenetic Assessment

Cytogenetic analysis must be performed locally from diagnostic bone marrow (preferred) or from peripheral blood if an adequate number of circulating blasts (> 10^9/L) are present. Historic cytogenetic data will be accepted if done within 1 month prior to screening.

Molecular Markers

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

Patient-Reported Outcome (PRO) Variables

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

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

PROMIS Fatigue SF 7a

PROMIS® is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being.[17] PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. Fatigue will be assessed using the PROMIS Fatigue SF that has been developed for use in oncology populations.[18,19] PROMIS Fatigue SF 7a is a seven-item questionnaire that assesses the impact and experience of fatigue over the past 7 days. The recommended minimum important difference range is 3 – 5 points; the lower bound (3) is being used as the minimum important difference in this study.[20] All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always.

EORTC QLQ-C30

Health-related quality of life (HRQoL) and symptoms will be assessed with the EORTC-QLQ-C30 version 3.[21] The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language-cultural groups. A change of 5 to 10 points is considered a small change, and the lower bound (5) will be used to define the minimum important difference. A change of ≥ 10 to < 20 points is considered a moderate change.

EQ-5D-5L

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations.[22,23] The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five-point scale: no problems, slight problems, moderate problems, severe problems, and extreme

problems. The scores for the five dimensions are used to compute a single utility index score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health. The minimum important difference for the EQ-5D-5L utility index score in cancer patients is 0.08, and the minimum important difference for EQ-5D VAS is 7.[24,25]

Table 3. Patient-Reported Outcome Assessments

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

Physical Examination

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

- Screening
- Prior to discharge from the hospital after reaching designated cohort dose in Cycle 1
- Day 1 of every cycle
- Final Visit
- 30-Day Safety Follow-up

The targeted physical exam includes an assessment of heart, lung, and abdomen, as well as any body system, guided by the examiner's observations or subject complaints on new or changed conditions, symptoms, or concerns. Targeted exams can be performed by the Principal Investigator (PI) or delegated to qualified medical staff (e.g., a sub-Investigator, nurse, etc.).

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

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

Vital Signs

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

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

It is recommended that vital signs should be assessed after the subject has been seated quietly for at least 5 minutes. Vital Signs after Cycle 3 may be performed within 3 days before or after the scheduled visit.

ECOG Performance Status

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

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

- 30-Day Safety Follow-up

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

ECOG Performance Status after Cycle 3 may be performed within 3 days before or after the scheduled visit.

12-Lead Electrocardiogram (ECG)

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

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

Electrocardiograms will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (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 radiofrequency signals in the room.

Each ECG will be evaluated by an appropriately qualified physician at the study site (the "local reader") who will determine if any findings outside normal physiological variation

are clinically significant. The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and subject discontinuation from the study.

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

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

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

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

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

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

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

Pulmonary Function Tests

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

Bone Marrow Aspirate and Biopsy for Disease Assessments

Bone marrow aspirates and biopsies per Appendix C will be obtained for local assessment at the following time points until two successive samples indicate CR or CRi (bone marrow collection until two successive samples indicate CR or CRi is not required for subjects who are unblinded following the final analysis results):

- Screening (for baseline Disease Assessment)
- End of Cycle 1 (must be performed within ± 3 days of Cycle 1 Day 28 and resulted prior to the administration of treatment for Cycle 2).
- For subjects with resistant disease at end of Cycle 1 a repeat bone marrow must be performed at the end of Cycle 2 or Cycle 3 based on the hematologic recovery to assess for a response of CR/CRi.
- For subjects with a response of CRi on two successive bone marrow samples, an additional bone marrow aspirate and biopsy must be performed to confirm a CR once peripheral blood count recovery is noted. This is not required for subjects who are unblinded following the final analysis results.
- For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) thereafter. This is not required for subjects who are unblinded following the final analysis results. Bone marrow aspirate and/or biopsy can be completed as per institutional standard of care.
- Upon concern for relapse or progressive disease.

- Final Visit (if no BM collected within the last 6 – 8 weeks. Disease assessment is not required if relapse of disease has already been confirmed.)

A bone marrow aspirate and biopsy must be performed for all subjects during screening to confirm diagnosis and to collect mandatory samples for mandatory biomarker assessments. Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis may be used as baseline assessment to satisfy eligibility criteria if they were collected as standard of care within 30 days prior to randomization. During screening, after informed consent is signed, bone marrow aspirates and biopsies may be collected to confirm the diagnosis to satisfy eligibility criteria.

During screening, after informed consent is signed, a bone marrow aspirate must be performed for all subjects to collect samples for mandatory biomarker assessments *(biomarker collections are not applicable to subjects enrolled in China)*.

Bone marrow aspirate and biopsy samples must be collected for all subjects at each of the disease assessments. Bone marrow core biopsy sample collection will be considered an optional procedure for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects, if a bone marrow aspirate sample is inadequate or un-evaluable, a repeat aspirate sample and/or biopsy can be performed as per institutional standard of care. Bone marrow aspirates and/or biopsies performed in addition to those required per protocol as standard of care throughout the study should also be captured on an eCRF. The corresponding protected health information (PHI) redacted local laboratory pathology report/bone marrow report should be sent to the central laboratory for each local disease assessment which is conducted, until otherwise instructed by the Sponsor. The local laboratory's pathology report will be used by the IRC during their assessment of disease response. Detailed collection instructions for the local laboratory pathology/bone marrow report, which is to be utilized by the IRC, will be provided in the current Study M16-043 laboratory manual.

Flow cytometry may be used to detect the presence of abnormal cell phenotypes (based on the inappropriate expression of myeloid lineage markers). Minimal residual disease (MRD) status may be determined either using the phenotypic markers detected or specific mutations identified in the screening sample.

Note: For all study visits after Cycle 2 Day 1, bone marrow aspirates and/or biopsies may be performed within ± 14 days of the scheduled subsequent cycle and delays, counting from the start of the previous cycle. This may be appropriate for subjects whose platelets and neutrophils are continuing to recover from nadir.

Documentation of Non-Childbearing Status and Pregnancy Testing

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

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

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

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

  Day 1 of each additional cycle until all study drug are permanently withdrawn (performed by either urine or serum pregnancy testing)

Clinical Laboratory Tests

All subjects will undergo the laboratory assessments listed in Table 4 per the schedule in Appendix C. Certified local laboratories will be utilized to process and provide results for

all of the hematology, chemistry coagulation, labs and urinalysis listed in Table 4. These data will be used for all data analysis. The appropriate certifications will be collected from the local laboratories.

If there are travel restrictions and other changes in local regulations in light of the COVID-19 pandemic, all laboratory tests can be arranged in a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible for subject safety and to determine the next cycle of study treatment.

If laboratory samples cannot be obtained due to the COVID-19 pandemic, study drug administration cannot be continued unless the investigator has reviewed all prior laboratory results as close to the planned new cycle of study treatment, **assessed risk-benefit**, confirmed and discussed with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within 7 days from the scheduled visit.

Table 4. Clinical Laboratory Tests

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

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

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

Chemistry and Hematology

Chemistry and hematology per Appendix C will be performed, at a minimum, at:

- Screening
- Cycle 1 Days 1, 2, 3, 4, 5, 6,* 8, 15, 22
- Day 1 of Cycle 2 and Day 1 of every cycle thereafter. Starting with Cycle 3 Day 1 may be performed within 3 days before or after the scheduled visit.**
- Final Visit
- 30-Day Safety Follow-up
- As needed throughout study

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

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

Further, additional hematology and chemistry laboratory assessments will be performed based on the clinical indications per institutional guidelines and regional standards between Cycle 1 the beginning of Cycle 2 Day 1 and throughout the study for subjects who have not achieved and maintained a CR.

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

Coagulation

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

- Screening
- Cycle 1 Day 1

- Final Visit

Urinalysis

Urinalysis samples per Appendix C will be collected at:

- Screening
- Cycle 1 Day 1
- Final Visit

Subject Calendar/Diaries

Subject calendars/diaries will be provided at the time of discharge from the hospital. Subjects will be instructed to bring their calendars/diaries back to the site to be reviewed at each visit, including at any visit at which a dose level change may be required. If COVID-19 circumstances warrant a virtual visit, calendars/diaries should be reviewed virtually with the subject and site should collect a paper copy at the next on-site visit.

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

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

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

Randomization and Subject (Screening) Number Assignment

Interactive Response Technology (IRT) will be utilized to register (screen and randomize) subjects on study. The site will contact the IRT to obtain a screening (subject) number

once the subject has signed the informed consent and a study-specific procedure has been performed (e.g., labs are drawn). Subjects who meet all Inclusion Criteria and none of the Exclusion Criteria after Screening will proceed to being randomized. The site will contact the IRT to complete the randomization process and obtain study drug assignment. Subjects will be enrolled as described in Section 5.5.4 and will receive a separate unique randomization number that will be automatically recorded in the eCRF through the IRT system. This randomization number will be used only by AbbVie for loading the treatment schedule into the database. Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and will be captured in the IRT and eCRF. Study treatment should start within 5 days after randomization, however this window cannot exceed the allotted 21-day Screening period. All subsequent drug assignments and changes in subject status (e.g., treatment completion) will be registered in the IRT.

Dispensing Venetoclax/Placebo

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

Subjects will be provided with venetoclax/placebo self-administration instructions. Subjects will be instructed to store venetoclax/placebo according to specific directions included in Section 5.5.2.2. Subjects are required to return bottles of venetoclax/placebo (empty, partially filled, or full) to the study site prior to the start of the next cycle and at the Final Visit.

Dispensing LDAC

The IRT will assign every vial of LDAC which was supplied by AbbVie to be dispensed for use by the site. Prior to each drug dispensation, site personnel must contact the IRT

for vial number assignment. **AbbVie supplied LDAC cannot be dispensed without contacting the IRT.** AbbVie or designee (refer to Section 7.0) will provide specific instructions on the use of the IRT.LDAC which is to be supplied locally will be dispensed and tracked per the normal practices of those sites.

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

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

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

Mandatory Samples for Biomarker Analysis

Blood Collections:

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M16-043 Laboratory Manual.

Blood Collection for Plasma:

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

- Screening visit (4 mL)
- End of Cycle 1 (20 mL)
- Response assessments: every 3 cycles after end of Cycle 1 assessment (20 mL). For subjects who are unblinded following the final analysis results, sample collection every 3 cycles after end of Cycle 1 visit is not required.
- Final Visit/Time of Relapse (20 mL)

Bone Marrow Aspirate and Biopsy Collections

Bone marrow aspirates should be drawn into appropriately labeled tubes in conjunction with the disease assessments. A portion of the aspirate must be processed according to the institutional standard procedures for diagnostic evaluation (locally); however, approximately 6 to 8 mL of the bone marrow aspirate should be collected for biomarker assessments to be shipped to the central laboratory. For subjects, where bone marrow aspirates are no longer required for response assessments, the bone marrow biomarker samples will also not be collected at those timepoints, but the peripheral blood biomarker samples will be collected. For subjects who are unblinded following the final analysis results, peripheral blood biomarker sample collection every 3 cycles after end of Cycle 1 visit is not required. Detailed processing will be outlined in the most current version of the Study M16-043 Laboratory Manual for the following:

Bone Marrow Collection for Disease Assessment by Flow Cytometry

NOTE: This specimen will be used for detection of residual blasts (i.e., MRD) at the response assessments and should be the first tube drawn from the bone marrow aspirate collection.

Approximately 1 to 2 mL of bone marrow aspirate at:

- Screening visit

- Response Assessments: End of Cycle 1 and every 3 Cycles after end of Cycle 1 visit. For subjects who are unblinded following the final analysis results, sample collection every 3 cycles after end of Cycle 1 visit is not required. Bone marrow aspirate completed as per institutional standard of care should continue to split for this assessment.
- Final Visit/Time of Relapse

Bone Marrow Collection for AML Mutational Profiling

Approximately 1 mL of bone marrow aspirate at:

- Screening visit
- Final Visit/Time of Relapse

Bone Marrow Collection for Translational Research:

Bone marrow aspirate will be collected at:

- Screening visit (4 mL)
- Response assessments: end of Cycle 1, and every 3 Cycles after end of Cycle 1 visit (1 mL). For subjects who are unblinded following the final analysis results, sample collection every 3 cycles after end of Cycle 1 visit is not required. Bone marrow aspirate completed as per institutional standard of care should continue to split for this assessment.
- Final Visit/Time of Relapse (4 mL)

Bone Marrow Biopsy for BCL-2 Family Analysis

Either an FFPE block or approximately 6 to 10 slides from the diagnostic/response assessment biopsy should be collected for immunohistochemistry analysis at:

- Screening visit
- Final Visit/Time of Relapse

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

Optional whole blood samples for DNA and RNA isolation will be collected on Cycle 1 Day 1, Cycle 3 Day 1 and Final Visit/Time of Relapse from each subject who consents to provide samples for exploratory research. Pharmacogenetic samples should be prepared, labeled, and shipped as outlined in the most current Study M16-043 laboratory manual.

5.3.1.4 Meals and Dietary Requirements

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

Subjects may not consume the following: grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction. It is expected that sites record if excluded food products are consumed by the subject during the study.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of venetoclax, cytarabine, and their possible metabolites will be collected by venipuncture at each study visit indicated in Appendix E. Blood samples must be protected from direct sunlight during collection, processing and storage. A total of approximately 7 blood samples (3 ml) for venetoclax will be collected per subject. A total of approximately 3 blood samples (4 ml) for cytarbine will be collected from approximately 75 subjects. The total number of venetoclax pharmacokinetic samples planned is 1225 and at minimum 225 cytarabine pharmacokinetic samples for analysis.

Additionally, for the Chinese subjects from China mainland sites, intensive pharmacokinetic samples will be obtained on Cycle 1 Day 10 as indicated in Appendix E.

5.3.2.2 Handling/Processing of Samples

Blood Samples for Venetoclax PK Assay

Detailed sample collection and processing instructions for the venetoclax PK will be provided in the current Study M16-043 laboratory manual.

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

Detailed sample collection and processing instructions for the cytarabine PK will be provided in the current Study M16-043 laboratory manual.

5.3.2.3 Disposition of Samples

The frozen plasma pharmacokinetic samples for venetoclax assays will be packed in dry ice sufficient to last during transport and shipped from the study site to a central lab designated by AbbVie. An inventory of the samples included will accompany the package. Please refer to current Study M16-043 laboratory manual for complete shipping instructions.

5.3.2.4 Measurement Methods

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

5.3.3 Efficacy Variables

Efficacy Assessments

Responses will be evaluated based on the revised guidelines by the modified International Working Group (IWG) for AML. Progressive disease is defined per European LeukemiaNet (ELN) recommendations. Subject's response is based on most recent physical examination, bone marrow results and recent hematology values. For subjects who require a delay in the next cycle of study treatment for blood count recovery after a bone marrow evaluation, hematology values up to pre-dose labs from Day 1 of the next cycle or 2 weeks from the bone marrow if there is no additional dosing can be used to determine the modified IWG response. As a significant number of the subjects in this study might have antecedent hematologic illnesses, hematologic response including transfusion independence will also be evaluated.

Criteria for evaluation are as follows:

- CR: No morphologic evidence of AML and absolute neutrophil count $\geq 10^3/\mu L$, platelets $\geq 10^5/\mu L$, red cell transfusion independence, and bone marrow with < 5% blasts, absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
- CRi: All criteria as CR except for residual neutropenia $< 10^3/\mu L$ (1,000/μL) or thrombocytopenia $< 10^5/\mu L$ (100,000/μL). If all criteria for CR are met except for RBC transfusion independence, this also fulfills CRi criteria.
- PR: All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
- MLFS: Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells, absence of circulating leukemia cells, absence of extramedullary disease, and absolute neutrophils $< 10^3/\mu L$ (1,000/μL) and thrombocytopenia $< 10^5/\mu L$ (100,000/μL).
- RD: Failure to achieve CR, CRi, PR; in subjects surviving at least 7 days following completion of Cycle 1 treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.

- MR: reappearance* of ≥ 5% blasts post CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
  * In cases with bone marrow blast percentages of 5% – 10%, a repeat marrow should be performed one week later to distinguish relapse from bone marrow regeneration.
- PD:
  - > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5×10^9/L [500/µL], and/or platelet count to > 50×10^9/L [50000/µL] non-transfused); or
  - 50% increase in peripheral blasts (WBC × % blasts) to > 25×10^9/L (> 25000/µL); or
  - New extramedullary disease

Reporting of Results

All dosed subjects will be assessed for response to treatment based on the published guidelines. Assessments will be performed at the end of Cycle 1 and every 3 cycles thereafter for response assessment. For subjects who are unblinded following the final analysis results, assessments every 3 cycles thereafter are not required. Bone marrow collection can be completed as per institutional standard of care. Subject will be assigned to one or more of the following categories by investigators:

1. complete remission;
2. complete remission with incomplete blood count recovery;
3. partial remission;
4. morphologic leukemia free state;
5. resistant disease;
6. progressive disease;

7. indeterminate (not assessable, insufficient data);
8. morphologic relapse;

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

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

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

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

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

Mandatory Biomarker Research Variables

Blood and bone marrow specimens will be collected to conduct exploratory biomarker analyses. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Evaluations may include the assessment of minimal residual disease levels present after therapy, analyses of biomarkers related to the pathway(s) targeted by the study drug (i.e., BCL-2 family protein expression levels) or biomarkers believed to be related to the disease or to drug response. The information learned from analyzing these samples may be used to investigate factors impacting

response to treatment, scientific questions related to AML or in the development of new therapies.

Given the exploratory in nature of these assessments, the biomarker analyzes may or may not be conducted in accordance with GLP/GCP guidelines and may not be included in the clinical study report.

Minimal or measurable residual disease (MRD), defined as persistence of leukemic cells after therapy, represents a potential biomarker for the depth of response to the therapy and a possible predictor for the response duration. Given the fact that AML is a phenotypic and molecularly heterogenetic disease, a single definition for meaningful measurable disease in this patient population has yet to be identified. Therefore, MRD may be explored in this study using two different technology platforms; multicolor flow cytometry (MFC) for a phenotypic assessment of residual disease and next generation sequencing (NGS) for a genetic assessment of leukemic-specific molecular abnormalities that would indicate residual disease. Another consequence of the disease heterogeneity in AML is the fact that the sensitivities of these MRD assays may vary for each subject depending upon the specific phenotypic or genetic aberrancy. Published literature suggests that most subjects are capable of achieving an MRD sensitivity of 10^{-3} (Araki 2016),[26] therefore, this cut-off as well as others may be explored as definitions of MRD negativity and correlated with outcome measures of efficacy and/or overall survival.

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

Optional Exploratory Research Variables

Pharmacogenetic DNA and RNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or the subject's response to venetoclax or other

study treatment in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, other genes believed to be related to drug response, or genes related to the disease state. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to venetoclax, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to venetoclax, drugs of this class, or the disease state. The results of PG analyses may not be reported with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects from Treatment

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

- The investigator believes it is in the best interest of the subject;
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug;
- The subject experiences toxicities related to study drug that require more than a 4-week (one cycle) dose interruption of venetoclax or LDAC, in the absence of clinical benefit;
- The subject requires any radiotherapy or alternate chemotherapy during the study period (with the exception of hydroxyurea [allowed in first month only]);
- The occurrence of an adverse event that precludes further LDAC administration;
- Noncompliance with the protocol.
- Treatment failure, defined as failure to achieve CR, CRi, PR, or MLFS.
- The subject becomes pregnant while on study drug.

Treatment will be continued as long as the patient continues to derive clinical benefit or until documented disease progression or develops unacceptable toxicity.

Accordingly, subjects may, in rare occasions, continue treatment after documented disease progression if the investigator believes it is in the best interest of the patient.

Following the final analysis results, the subjects will be unblinded by the Sponsor to the treatment assignment and subjects will be allowed to continue the assigned treatment arm as long as they derive clinical benefit from the treatment in the opinion of the investigator, or until transition to commercial supply is available, or until protocol criteria for discontinuation is met.

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

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

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

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

5.4.2 Discontinuation of Entire Study

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

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

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

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will take daily venetoclax or placebo orally in the form of tablets. Venetoclax or placebo should be dosed before LDAC on days of LDAC administration. Subjects will self-administer venetoclax or placebo by mouth QD. Tablets must be swallowed whole and must not be broken, chewed, or crushed.

LDAC must be prepared as per the applicable Summary of Product Characteristics (SmPC), package insert or prescribing information and administered subcutaneously by a trained provider meeting local qualifications for administration of subcutaneous cytarabine.

5.5.2 Identity of Investigational Products

Table 5. Identity of Investigational Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax	N/A	100 mg Tablet	Oral	AbbVie
Venetoclax	N/A	50 mg Tablet	Oral	AbbVie
Venetoclax	N/A	10 mg Tablet	Oral	AbbVie
Matching Placebo for Venetoclax (100 mg Tablet)	N/A	0 mg Tablet	Oral	AbbVie
Matching Placebo for Venetoclax (50 mg Tablet)	N/A	0 mg Tablet	Oral	AbbVie
Matching Placebo for Venetoclax (10 mg Tablet)	N/A	0 mg Tablet	Oral	AbbVie
Cytarabine	N/A	100 mg/5 ml vial 100 mg/ml vial	SC	Brand/Generic

AbbVie will provide venetoclax, and placebo for venetoclax, and may also provide cytarabine for the study. Sites located in countries where cytarabine is approved for AML may obtain cytarabine commercially via the site's pharmacy. AbbVie will provide cytarabine as a labeled investigational product to sites who do not supply their own commercially available cytarabine.

Identity of Non-Investigational Product(s)

Sites may be responsible for obtaining cytarabine. For operational or regulatory purposes, Abbvie may provide non-investigational products depending on local requirements. Cytarabine should be obtained from a licensed pharmacy or wholesaler.

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

5.5.2.1 Packaging and Labeling

Venetoclax tablets or placebo for venetoclax tablets will be packaged in high density polyethylene (HDPE) plastic bottles. Each bottle of the venetoclax 50 mg tablets or placebo for venetoclax 50 mg tablets will contain 28 tablets. Each bottle of the venetoclax 10 mg tablets or placebo for venetoclax will contain 5 tablets. Each bottle of the venetoclax 100 mg tablets or placebo for venetoclax 100 mg tablets will contain 186 tablets. All bottles will be labeled per local regulatory requirements.

LDAC will be provided as 100 mg/5 ml or 100 mg/ml per single use vial. Each vial and carton will be labeled per local regulatory requirements. Each vial must be administered per the applicable US prescribing information (USPI), Summary of Product Characteristics (SmPC) or local label.

5.5.2.2 Storage and Disposition of Study Drug(s)

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

5.5.3 Method of Assigning Subjects to Treatment Groups

The IRT will randomize subjects into the 2 treatment arms in a 2:1 ratio (venetoclax + LDAC or placebo + LDAC). A bottle (kit) number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IRT vendor.

Subject randomization will be stratified by AML status (secondary, de novo), age (18 – < 75, ≥ 75) and region (US, EU, China, Japan, Rest of world).

5.5.4 Selection and Timing of Dose for Each Subject

Venetoclax/placebo will be administered orally once daily (QD) Days 1 through 28, of a 28-day cycle, with a designated dose of 600 mg daily after ramp up in Cycle 1. During Cycle 1 Days 1 – 4, the dose will ramp up from 100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 and 600 mg on Day 4.

Each dose of venetoclax/placebo should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast. LDAC (20 mg/m^2) should be given QD following administration of venetoclax or placebo on Days 1 – 10 of every cycle.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

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

All subjects will be treated with open-label LDAC.

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

Following the final analysis results, the Investigator, the study site personnel, the subjects, and AbbVie personnel will be unblinded by the Sponsor to subjects' treatment assignment.

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

An IDMC will review safety and efficacy data for this study in an un-blinded fashion and provide recommendations to AbbVie as per the IDMC charter. Details of the IDMC, including IDMC membership, which will include individuals with experience in treatment of patients with AML, and member responsibilities, will be outlined in the IDMC Charter. Aggregate clinical safety data will be reviewed on a real-time basis throughout the course of the study.

5.5.6 Treatment Compliance

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

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

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

5.5.7 Drug Accountability

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

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

LDAC is a standard treatment option in many countries worldwide and is often referred to as low intensity therapy for AML. Low intensity therapy, such as LDAC, azacitidine, or decitabine are considered appropriate treatment approaches by the National Cooperative Cancer Network (NCCN)[26] and European LeukemiaNet (ELN)[28] for patients who are not candidates for intensive chemotherapy induction or HSCT. Two Phase 3 trials have compared azacitidine[29] and decitabine[30] to physician's choice therapy for older patients with newly diagnosed AML to evaluate if either provided a statistically significantly

longer survival when given as the initial treatment for AML. To date, neither agent has been found to provide a significantly longer survival for patients with newly diagnosed AML than for those randomized to physician choice. The most common treatment, in both studies, amongst the patients randomized to physician choice was LDAC. The response rates to LDAC when administered as monotherapy are substantially lower than what is seen in Study M14-387 in combination with venetoclax and preliminary projections for median survival times also appear better than for the aforementioned historical experiences with LDAC monotherapy.[31]

5.6.2 Appropriateness of Measurements

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

The PRO measures chosen for this study have been validated in cancer patients and include a generic HRQoL measure (EQ-5D-5L), a cancer-specific HRQoL measure that includes functional and symptom scales as well as a global health status scale (EORTC QLQ-C30), and a symptom-based measure to assess fatigue (PROMIS Fatigue SF 7a). The specific symptoms and functional aspects assessed by these measures are considered to be among the most impactful to AML patients.[32,33]

5.6.3 Suitability of Subject Population

Subjects who have histological confirmation of acute myeloid leukemia who are treatment naïve, greater than or equal to 18 years of age, considered ineligible for treatment with a standard induction regimen due to age and comorbidity, and appropriate for LDAC control arm may be enrolled. Study M14-387, which provides the experimental arm projections, enrolled a similar patient population.

5.6.4 Selection of Doses in the Study

The selected dosage of venetoclax is based on the results from Study M14-387, an ongoing Phase 1b/2 study of escalating doses of venetoclax in combination with LDAC in treatment naïve AML subjects greater than or equal to 65 years of age, and ineligible for

treatment with a standard cytarabine and anthracycline induction regimen. In the dose escalation phase, LDAC was administered subcutaneously at 20 mg/m^2 QD on Days 1 – 10 of each 28-day cycle of therapy. Venetoclax began on Day 2, to allow PK assessments of monotherapy LDAC of Cycle 1 followed by a ramp up to continuous daily dosing at the designated doses of 600 mg for Cohort 1 and 800 mg for Cohort 2. Eighteen subjects were enrolled in the Phase 1 dose escalation portion (10 subjects at the 800 mg dose and 8 subjects at 600 mg dose) and an additional 53 subjects were enrolled in the Phase 2 portion of the study at the 600 mg dose. Two of the 10 subjects enrolled to the 800 mg venetoclax cohort with LDAC experienced a dose-limiting toxicity identifying 600 mg venetoclax as the maximum tolerated dose (MTD) in co-administration with LDAC.

An exposure-response analysis was conducted across the 71 enrolled subjects to establish the relationship between venetoclax exposure and response rates to support venetoclax dose selection in Study M16-043. A statistically significant ($P < 0.05$) association of best responses was determined with increasing venetoclax exposures. Since 600 mg dose is the maximum tolerated dose for this combination, the probability of achieving CRi or better and CR was predicted for doses up to 600 mg. The predicted probability of achieving CRi or better was approximately 44% [90% CI: 34% – 54%] and 56% [90% CI: 42% – 68%] at exposures associated with the 400 mg and 600 mg dosage regimen given once daily, respectively. Similarly, the predicted probability of CR was approximately 24% [90% CI: 17% – 34%] and 34% [90% CI: 23% – 48%] at exposures associated with the 400 mg and 600 mg dosage regimen given once daily, respectively. Additionally, a multivariate logistic regression analysis was performed to evaluate the impact of other prognostic baseline variables such as age, ECOG scores, subjects with secondary AML and AML cytogenetics risk classification. A statistically significant association ($P < 0.05$) was found between complete response rates and venetoclax concentration while none of the other tested baseline variables achieved significance.

In summary, based on the preliminary results of exposure-response analysis and the observed tolerability data, the 600 mg dose of venetoclax in combination with LDAC was selected to maximize the response rates while avoiding dose-limiting toxicities.

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

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

The effect of two strong CYP3A inhibitors (posaconazole and ketoconazole) on the pharmacokinetics of venetoclax was evaluated in two separate studies. Study M13-364 was conducted to evaluate the effect of ketoconazole given once daily on pharmacokinetics of single dose of venetoclax in 12 subjects with NHL[34] and a cohort of 12 untreated elderly AML subjects in Study M14-358 was enrolled to assess the effect of posaconazole given twice daily on exposures of venetoclax given once daily.[35] Furthermore, prior studies indicated venetoclax bioavailability to be dependent on both food and dose. To account for the effect of covariates such as food and dose non-linearity on the bioavailability of venetoclax, a population PK model was used to simulate exposures of venetoclax in presence of strong CYP3A inhibitors.

The ramp-up scheme for venetoclax when given alone is 100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 and 600 mg QD from Day 4 onwards. To match the exposures (AUC) from these doses, venetoclax doses of 10 mg on Day 1, 20 mg on Day 2 and 50 mg QD from Day 3 onwards were chosen when co-administered with strong CYP3A inhibitors to mitigate any possible risk for TLS and ensure safety. Predicted venetoclax exposures when administered alone and in presence of strong CYP3A inhibitors at the recommended dose reductions are shown in Table 6.

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

	Venetoclax Alone					Venetoclax + Strong CYP3A Inhibitor				
	Ramp-up				Steady-State	Ramp-up				Steady-State
PK Parameter	Day 1 100 mg	Day 2 200 mg	Day 3 400 mg	Day 4 600 mg	Day 28 600 mg	Day 1 10 mg	Day 2 20 mg	Day 3 50 mg	Day 4 50 mg	Day 28 50 mg
AUC_{24} (µg•hr/mL)	4.22 (3.61 – 4.78)	8.76 (7.47 – 10.1)	15.7 (13.3 – 18.2)	22.9 (19.3 – 26.9)	28.1 (23.1 – 34.2)	1.19 (1.01 – 1.42)	3.14 (2.71 – 3.71)	6.96 (6.04 – 8.15)	10.2 (8.87 – 11.8)	26.3 (22.5 – 30.9)

6.0 Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution. The investigational product in this study is defined as venetoclax, LDAC or placebo.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, please refer to Sections 6.1 through 6.1.7.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

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

events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 6.1.7) regarding toxicity management and/or if the Investigator considers them to be adverse events.

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

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-

existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

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

Due to the COVID-19 pandemic and evolving local regulations, urgent safety measures may need to be employed in order to protect participating subjects from any immediate hazard. Such events and measures should be reported to the sponsor emergency medical contact listed in Section 6.1.5 immediately.

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. The following COVID-19 related supplemental eCRFs should be completed:

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

6.1.1.2 Serious Adverse Events

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

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

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

6.1.1.3 Adverse Events Expected due to Study Related Endpoints

Disease progression is an endpoint of this study. Disease progression should not be reported as an adverse event.

6.1.1.3.1 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within one hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03). When applicable, once the diagnosis is confirmed the medical term should

be reported for an event rather than the abnormal lab values as identified in CTCAE. If a reported adverse event increases in severity, the initial adverse event should be given final outcome date and a new adverse event must be reported to reflect the change in severity. If a reported adverse event increases in severity, the initial adverse event should be given final outcome date and a new adverse event must be reported to reflect the change in severity such that the dates on these AE's cannot overlap. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

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

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life-threatening requiring urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgement, 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 judgement, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

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

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

6.1.4 Adverse Event Collection Period

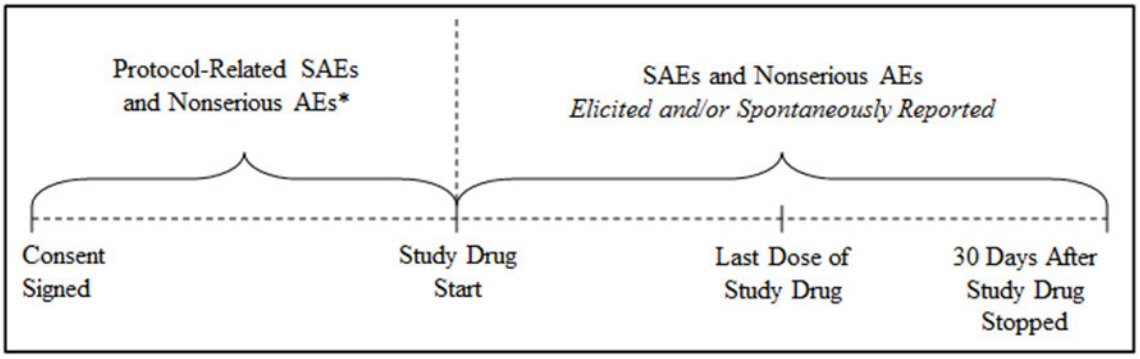
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

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

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

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

Figure 2. Adverse Event Collection



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

6.1.5 Adverse Event Reporting

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

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

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

Oncology Safety Management
Dept. R48S, [redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Safety Email: SafetyManagement_Oncology@abbvie.com

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

AbbVie TA Medical Monitor:

[redacted] MD, PHD
Oncology Development
Dept. R48K, [redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Phone: [redacted]
Fax:

In emergency situations involving study subjects when the AbbVie Medical Monitor 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 SDP:

Phone: +1 (973) 784-6402

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

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

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

6.1.6 Pregnancy

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

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancy in a subject's partner will be collected from the date of the first dose through 180 days following the last dose of study drug.

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

6.1.7 Toxicity Management

Management of Cytopenias, Infections, and Other Adverse Events

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in both treated and untreated subjects with AML. Subjects with baseline neutropenia or have significant bone marrow involvement may be particularly at high risk. If a participant achieves a CRi or a morphologic leukemia free bone marrow, and has Grade 4 neutropenia or thrombocytopenia persisting beyond Day 28, venetoclax should be interrupted from Day 28 until ANC ≥ 500 – 1000/μL and platelet count ≥ 25 – 100 × 10^3/μL. Typically, if persistent AML remains in the bone marrow, concurrent cytopenias are thought to be attributable to the disease process of AML and continued treatment with venetoclax and LDAC may continue on schedule. In subsequent cycles, if a subject with previous CR presents with new onset Grade 4 neutropenia or thrombocytopenia lasting more than one week, unless it is due to the underlying disease, venetoclax dosing may be interrupted until ANC recovery to ≥ 500 – 1000/μL and platelet count ≥ 25 – 100 × 10^3/μL per investigator discretion in consultation with the AbbVie medical monitor. Venetoclax may be re-initiated at a lower dose, or discontinued if a minimal dose is not tolerable, per discussion with the AbbVie medical monitor.

Administration of venetoclax in subjects with lymphoproliferative disorders has been associated with clinically significant lymphopenia (B and T lymphocyte subtypes). Anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystis infections are required for all subjects with ANC of < 500/μL. Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of these agents should be based on regional guidelines or institutional standards. Potential for drug-drug interactions should be considered. Please refer to Table 1, Table 2, and Appendix I for a description of excluded and cautionary medications and implement dose reductions for venetoclax/placebo as necessary.

If a subject is continuing to respond based on the bone marrow assessment after Cycle 2 of treatment, but has persistent cytopenias (cytopenias that occur after Day 28 of a Cycle during Cycle 2 and beyond), venetoclax dose may be reduced as follows:

Table 7. Dose Reduction Guidelines for Management of Persistent Neutropenia or Thrombocytopenia

Venetoclax Dose/Duration	New Venetoclax Dose/Duration
600 mg daily × 28 day cycles	600 mg daily × 21 days with 7 day interruption
600 mg daily × 21/28 day cycles	600 mg daily × 14 days with 14 day interruption
600 mg daily × 14/28 day cycles	400 mg daily × 14 days with 14 day interruption

Cytopenias during Cycle 1 or 2 may be due to bone marrow involvement by AML and therefore dose reductions during Cycle 1 or 2 are not typically recommended. If an investigator believes a particular patient would benefit from a dose reduction during Cycle 1 or 2, the investigator should discuss with the medical monitor.

If dose reductions or interruptions for events other than cytopenias or infections are thought to be necessary by the investigator, a discussion with the AbbVie medical monitor is required and may be approved upon consultation. Delays greater than 21 days must be discussed with the AbbVie medical monitor or a designee.

Standard Therapy: Low – Dose Cytarabine

In a recent international clinical trial, subjects receiving LDAC experienced the following treatment emergent CTCAE grade 3 or 4 adverse events at a rate of at least 10%: thrombocytopenia 35%, anemia 27%, febrile neutropenia 25%, disease progression 22%, neutropenia 20%, pneumonia 19%, general physical health deterioration 16%, and leukopenia 10%.[36] It is unknown whether the aforementioned adverse events are attributable to receiving treatment with LDAC or were attributable to the underlying health condition of AML. Complications of myelosuppression, including infections and bleeding, may be exacerbated by treatment with LDAC. During Cycle 2 and subsequent

cycles, study treatments may be delayed at the discretion of the investigator, if the subject experiences myelosuppression associated complications, such as those described below:

- Febrile neutropenia (temperature ≥ 38.5°C and ANC < 1,000/µL)
- Active viral, bacterial or fungal infection (i.e., requiring IV anti-infectives or extensive supportive care)
- Hemorrhage (gastrointestinal, genito-urinary, pulmonary with platelets < 25,000/µL or any central nervous system hemorrhage)

Treatment with LDAC may be resumed once the above conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors).

Myelosuppression caused by LDAC is reversible. Complete blood and platelet counts should be performed regularly, as clinically indicated and prior to each treatment cycle. In the presence of myelosuppression or its complications, treatment with LDAC may be interrupted or supportive measures instituted.

LDAC dose reductions are not typically recommended. If a dose reduction is believed to be necessary a discussion with the AbbVie medical monitor is required.

6.1.7.1 Management of Tumor Lysis Syndrome (TLS)

There is a potential risk for TLS in subjects with AML, especially in those with elevated leukocyte count, circulating blasts, elevated pretreatment LDH levels, renal dysfunction, and dehydration. In addition, on-target effect of venetoclax could lead to rapid cell death and pose a risk of TLS. To mitigate the risk for TLS all subjects enrolled in the study will need TLS prophylaxis and monitoring. Prophylactic reductions of potassium, inorganic phosphorus or uric acid above normal range are recommended prior to beginning study treatment and continue based on the ongoing risk of TLS. For subjects at higher risk for TLS (i.e., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment LDH levels, or renal dysfunction), additional mitigation measures

including more intensive laboratory monitoring and interventions should be implemented. Lower starting dose of venetoclax/placebo may be considered (i.e., 50 mg).

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

- All subjects will be hospitalized on or before Day 1 of Cycle 1 prior to administration of the initial dose of study treatment and remain in the hospital for at least for 24 hours after reaching the final dose of venetoclax.
- All subjects must receive uric acid reducing agent, adequate oral and intravenous hydration as tolerated while monitoring the fluid status of the subject prior to and during the ramp up of venetoclax/placebo. The uric acid reducing agent, type of fluids and the rate of infusion will be determined by the investigator based on regional standards or institutional guidelines.
- TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax/placebo dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose.
- Additional laboratory assessments may be performed, per investigator discretion, post-dose during ramp up and up to 48 hours after reaching final dose if clinically indicated.
- Abnormal chemistry tests during ramp up should be corrected promptly.
- If a subject meets criteria for clinically significant laboratory or clinical TLS, please follow institutional guidelines or recommendations in Appendix G. No additional venetoclax/placebo dose should be administered until resolution. For continued dosing of venetoclax/placebo, monitor for evidence of TLS during study treatment, and manage abnormalities of serum creatinine and electrolytes promptly.

For continued dosing of venetoclax/placebo, monitor for evidence of TLS during treatment, and manage abnormalities of serum creatinine, uric acid and electrolytes

promptly. For subjects at higher risk (i.e., circulating blasts), more intensive measures should considered.

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]

AbbVie

[redacted]

MOBILE [redacted]

E-MAIL [redacted]

AbbVie Medical Monitor:

[redacted] MD, PHD

AbbVie

1 North Waukegan Road

North Chicago, IL 60064

Office: [redacted]

Cell:

Email:

Alternate Contact:

[redacted]

AbbVie

[redacted]

OFFICE [redacted]

FAX [redacted]

EMAIL [redacted]

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

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Definition for Analysis Populations

The safety analysis set consists of all subjects who take at least one dose of study drug (either venetoclax/placebo or LDAC). The safety analysis set will be used for safety analyses. The full analysis set consists of all randomized subjects. The full analysis set will be used for efficacy analyses.

8.1.2 Baseline Characteristics

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

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

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

8.1.3 Pharmacokinetics

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

8.1.4 Efficacy Endpoints

8.1.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is overall survival (OS).

Overall survival will be defined as the number of days from the date of randomization to the date of death. Subjects that have not died will be censored at the last known date to be alive. The distribution of overall survival will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using the log-rank test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75).

8.1.4.2 Secondary Efficacy Endpoints

Fixed sequence testing procedure will be used for analyses of the secondary efficacy endpoints. If statistical test is not significant for the primary efficacy endpoint of OS, then statistical significance will not be declared for any of the secondary efficacy endpoints. Secondary efficacy endpoints are CR + CRi rate, CR + CRh rate, CR + CRi rate by the initiation of Cycle 2, CR + CRh rate by the initiation of Cycle 2, CR rate, fatigue based on

the PROMIS Fatigue SF 7a, a global health status/quality of life scale (GHS/QoL) scale from the EORTC QLQ-C30, event free survival (EFS), transfusion independence rates for RBC or platelets, CR + CRi and MRD response rate, CR + CRh and MRD response rate, CR + CRi rate in biomarker subgroups (e.g., FLT3, IDH1/2), CR + CRh rate in biomarker subgroups (e.g., FLT3, IDH1/2), and OS in biomarker subgroups (e.g., FLT3, IDH1/2). To adjust for multiple testing of the key secondary efficacy endpoints, a fixed sequence testing procedure will be used. The key secondary efficacy endpoints and corresponding ranking will be specified in the statistical analysis plan (SAP).

The proportion of subjects with complete remission or complete remission with incomplete blood count recovery (CR + CRi) will be calculated based on the modified IWG criteria for AML. CR + CRi rate will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR + CRi.

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

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

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

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

The proportion of subjects with complete remission or complete remission with partial hematological recovery (CR + CRh) will be calculated based on the modified IWG criteria for AML. CR + CRh rate will be compared between treatment arms using CMH

test stratified by AML status (secondary, de novo) and age (18 - < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR + CRh.

The proportion of subjects with complete remission or complete remission with incomplete marrow recovery (CR + CRi) by the initiation of Cycle 2 will be calculated based on the modified IWG criteria for AML. CR + CRi rate by the initiation of Cycle 2 will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR + CRi rate by the initiation of Cycle 2.

The proportion of subjects with complete remission will be calculated based on the modified IWG criteria for AML. CR rate will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR.

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

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

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

The distribution of EFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using the log-rank test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75).

Post baseline transfusion independence rate will be calculated as the portion of subjects who achieved transfusion independence post baseline. Transfusion independence is defined as a period of at least 56 days with no transfusion between the first dose of study drug and the last dose of study drug plus 30 days. In addition, the rate of conversion will be calculated as proportion of subjects being post-baseline transfusion independent from baseline transfusion dependence. The transfusion independence rate will be evaluated for 1) RBC and 2) platelets. All randomized subjects will be included to estimate the post-baseline transfusion independence rate.

Post baseline transfusion independence rate will be estimated as the proportion of subjects known to achieve transfusion independence during the evaluation period. Transfusion independence rate will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed for transfusion independence rate.

The rates of conversion from baseline transfusion dependence to post-baseline transfusion independence will be estimated. The conversion rate will be evaluated for 1) RBC and 2) platelets.

The proportion of subjects with complete remission or complete remission with partial hematologic recovery (CR + CRh) by the initiation of Cycle 2 will be calculated. CR + CRh rate by the initiation of Cycle 2 will be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed for CR + CRh rate by the initiation of Cycle 2.

The proportion of subjects achieving CR + CRi and MRD or CR + CRh and MRD response status may be calculated. All randomized subjects will be included in the

analyses. Subjects who are randomized but have no MRD assessment will be considered as non-negative for the calculation of MRD response status. MRD response will be defined using a threshold of less than 10^{-3} of residual blasts per leukocytes as measured in bone marrow. The MRD response rates may be compared between treatment arms using CMH test stratified by AML status (secondary, de novo) and age (18 – < 75, ≥ 75). In addition, 95% confidence interval will be constructed.

The response rates (e.g., CR + CRi, CR + CRh, or CR) and overall survival in molecular subgroups (e.g., IDH1/2, FLT3) may be evaluated.

8.1.4.3 Exploratory Efficacy Endpoint

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

8.1.5 Efficacy Endpoints per Independent Review Committee

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

8.1.6 Timing of Efficacy Analyses

An interim analysis will be performed at the time of the 100th death event. Final analysis will be performed at the time of the 133rd death event.

8.1.7 Safety

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

8.1.7.1 Study Drug Exposure

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

8.1.7.2 Adverse Events

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

8.1.7.3 Serious Adverse Events

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

8.1.7.4 Deaths

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

8.1.7.5 Laboratory Tests and Vital Signs

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

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

8.2 Determination of Sample Size

The primary endpoint of the study is overall survival and sample size calculation is based on the following assumptions:

- Median OS of 6 months for placebo plus LDAC arm
- Median OS of 11 months for venetoclax plus LDAC arm (hazard ratio of 0.545)
- Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary
- 2:1 randomization ratio to venetoclax plus LDAC, and placebo plus LDAC arm

With the above assumptions, a total of 133 death events will provide 90% power to detect statistically significant different between treatment arms at alpha level of 0.05. A total of approximately 210 subjects (140 in venetoclax plus LDAC arm and 70 in placebo plus LDAC arm) will be randomized into the study to obtain the 133 death events.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

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

9.3 Subject Information and Consent

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

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

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

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

9.3.1 Informed Consent Form and Explanatory Material

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

9.3.2 Revision of the Consent Form and Explanatory Material

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

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

10.2 Case Report Forms

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

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

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

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

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

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

Internet access to the ePRO data will be provided by Signant Health for the duration of the study. This access will be available for the duration of the study to the site

investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected electronically via a tablet device into which the patient will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients to complete more than one of the same assessments at any one visit. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by Signant Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive. If the PRO data is collected by phone interview, the delegated staff will enter the subject's responses into TrialManager. Paper record of the subject's responses will be maintained as original source. IRBs/EC should be notified of completion of PROs by phone interview and approved by the site's IRB/EC (if required).

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.

11.0 Data Quality Assurance

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

The AbbVie monitor will monitor the study site throughout the study. Source document review will be made against entries on the case report forms and a quality assurance check

will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after the case report forms are retrieved, a review of the data will be conducted by a physician or representative at AbbVie.

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

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

12.0 Use of Information

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

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

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

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

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

13.0 Completion of the Study

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

The Investigator (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

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

14.0 Investigator's Agreement

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

Protocol Title:	A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax Co-Administered with Low Dose Cytarabine Versus Low Dose Cytarabine in Treatment Naïve Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy
Protocol Date:	01 March 2022

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Statistics
		Statistics
		Biomarkers
		Bioanalysis
		Therapeutic Area
		Therapeutic Area
		Clinical Pharmacology and Pharmacometrics

Appendix C. Study Activities

Procedures	Screening[a]	D –1	Cycle 1										D 15, 22	Day 1 of Each Cycle*	Day 1 of Every Other Cycle*	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10							
Informed Consent	X[d]																		
Medical/Oncology History Assessment	X		X[e]																
AE/Concomitant Medication Assessment[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytogenetic Testing[f]	X																		
Tumor Lysis Syndrome Prophylaxis[g]		X	X	X	X	X	X	X											
Physical Exam (including weight)[h,v]	X[i]		X				X[j]							X			X	X	
Vital Signs[h,v]	X		X											X			X	X	
Pregnancy Test[v]	X		X[s]											X					
ECOG Performance Status[h,v]	X		X											X			X	X	
Hematology/Chemistry[k,h,v]	X		X	X	X	X	X	X[t]		X			X	X			X	X	
Coagulation[h]	X		X														X		
Urinalysis[h]	X		X														X		
12-lead ECG[v]	X																X[l]		
Pulmonary Function Test[m]	X																		
MUGA or 2D	X																		

Procedures	Screening[a]	D –1	Cycle 1										D 15, 22	Day 1 of Each Cycle*	Day 1 of Every Other Cycle*	End of Cycle 1 and Every 3 Cycles Thereafter	Final Visit[b]	30-Day Safety F/U	PT F/U[c]
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10							
Echocardiogram w/Doppler[m]																			
Disease Assessment	X[u]															X[o]	X		X
Bone Marrow Aspirate and Biopsy for Local Disease Assessment	X[n]															X[n,o,p]	X		
PROMIS Fatigue SF 7a[q,w]			X												X		X		
EORTC QLQ-C30[q,w]			X												X		X		
EQ-5D-5L[q,w]			X												X		X		
Dispense Venetoclax/Placebo														X					
Dispense Subject Calendar/Diary												X[r]		X					
Collect venetoclax and Subject Calendar/Diary														X			X		
Administer LDAC*			X	X	X	X	X	X	X	X	X	X							
Survival Assessments																			X

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

* LDAC will be administered for 10 days for each cycle starting with Day 1.

a. Screening procedures must be performed within 21 days prior to randomization. Bone marrow samples and peripheral blasts used for AML diagnosis can be collected within 30 days prior to randomization.

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

c. Post Treatment and survival visits will be performed every 4 months after the last study visit until the end of the study.

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

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

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

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

h. For all study visits after Cycle 3, physical examination, vital signs, ECOG performance status, hematology and chemistry, coagulation and urinalysis may be performed within 3 days before or after the scheduled visit. PROs can be completed within 3 days prior to Cycle 1 Day 1 visit.

i. Height will be measured only at Screening.

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

k. Only hematology required for disease assessment.

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

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

n. A bone marrow aspirate and biopsy must be performed for all subjects during screening to confirm diagnosis and to collect mandatory samples for mandatory biomarker assessments. Historical bone marrow aspirates and biopsies assessed locally to confirm the diagnosis may be used as baseline assessment to satisfy eligibility criteria if they were collected as standard of care within 30 days prior to randomization. During screening, after the informed consent is signed, bone marrow aspirates and biopsies may be collected to confirm the diagnosis to satisfy eligibility criteria. During screening, after informed consent is signed, a bone marrow aspirate must be performed for all subjects to collect samples for mandatory biomarker assessments *(biomarker collections are not applicable to subjects enrolled in China)*. Bone marrow aspirate and biopsy samples must be collected for all subjects at each of the disease assessments. Bone marrow core biopsy sample collection will be considered an optional procedure for subjects enrolled at sites in countries where an aspirate evaluation by morphologic assessment and flow cytometry is considered standard of care. For these subjects, if a bone marrow aspirate sample is inadequate or un-evaluable, a repeat aspirate sample and/or biopsy can be performed per institutional standard of care. Bone marrow aspirates and/or biopsies performed in addition to those required per protocol as standard of care throughout the study should also be captured on an eCRF. The corresponding PHI redacted local laboratory pathology report/bone marrow report should be sent to the central laboratory for each local disease assessment which is conducted, until otherwise instructed by the Sponsor.

o. End of Cycle 1 bone marrow aspirate and biopsy must be performed within ± 3 days of Cycle 1 Day 28. Assessments should be performed and resulted prior to the administration of study drugs for Cycle 2. For subjects who require a delay in study treatment for blood count recovery after a bone marrow evaluation, hematology values up to pre-dose labs from Day 1 of the next cycle or 2 weeks from the bone marrow if there is no additional dosing can be used to determine the IWG response. For all subjects a bone marrow aspirate and biopsy must be performed at end of Cycle 4 and every 3 cycles (± 1 week) and upon concern for relapse or progressive disease unless otherwise indicated in Section 5.3.1.1. For subjects who are unblinded following the final analysis results, bone marrow collection every 3 cycles starting at the end of Cycle 4 are not required. Bone marrow collection can be completed as per institutional standard of care. The corresponding PHI redacted local laboratory pathology report will be sent to the central laboratory for IRC review, until otherwise instructed by the Sponsor.

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

q. PRO assessments should generally be completed prior to any other procedures or clinical assessments and prior to dosing; however, they may be administered following confirmation that the subject is able to receive study treatment at the visit. PROs can be completed within 3 days prior to Cycle 1 Day 1 dosing.

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

s. Serum or Urine pregnancy test must be obtained at Cycle 1 Day 1, if it has been > 7 days since obtaining the pregnancy results at screening. Subjects with borderline serum pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

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

u. Disease Assessment at screening is to document baseline disease status; Disease Assessment at all other time points is to document disease response.

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

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

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

Sample Collections	Screening	Cycle 1 Day 1	End of Cycle 1, End of Cycle 4 and Every 3 Cycles Thereafter[a,c]	Cycle 3 Day 1	Final Visit/ Time of Relapse[a]
Plasma	X		X		X
Disease Assessment by Flow (MRD)	X		X		X
AML Mutational Profiling	X				X
Translational Research	X		X		X
Bone Marrow Biopsy for BCL 2 Family Analysis	X				X
Pharmacogenetics (DNA and RNA)[b]		X		X	X

a. Sample should be split from the bone marrow assessment for disease assessment.

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

c. For subjects, where bone marrow aspirates are no longer required for response assessments, the bone marrow biomarker samples will also not be collected at those time points, the plasma samples should still be collected. For subjects who are unblinded following the final analysis results, bone marrow and plasma sample collection at end of Cycle 4 and every 3 cycles thereafter is not required. Bone marrow aspirates completed as per institutional standard of care should continue to split for these assessments.

Notes:

- No result will be sent from the Central Laboratory, as all of them are "exploratory."
- The remainders of the biopsy sample will be returned to the site upon request

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

For Subjects Enrolled Outside China

Procedures	Cycle 1 Days 1 – 4	Cycle 2, 4 and 8 Day 5
Venetoclax	6 hours post-dose[a]	0 hour (pre-dose)
Cytarabine		15 minutes post injection

For Subjects Enrolled in China

Procedures	Cycle 1 Days 1 – 4	Cycle 1 Day 10 (Intensive PK Schedule)	Cycle 2, 4 and 8 Day 5
Venetoclax	6 hours post-dose[a]	0 hour (pre-dose), 2, 4, 6, 8 and 24 hours post-dose	0 hour (pre-dose)

a. The 6-hour post-dose PK sample on Days 1 – 4 of Cycle 1 will be collected if venetoclax is initiated or escalated to a new dose level. If there is a delay in the escalation step, the 6-hour post-dose PK sample will be delayed accordingly.

- All "pre-dose" samples in venetoclax PK sampling are relative to venetoclax/placebo administration and will be collected within 1 hour prior to dosing. Postdose samples for both venetoclax and cytarabine will be collected at the time points indicated with a window of ± 10%.
- The date and time (start and end times to the nearest minute) of each LDAC injection taken, will be recorded on the eCRF.
- The date and time (to the nearest minute) of each venetoclax/placebo dose taken will be recorded on the eCRF for every scheduled venetoclax PK day and for the 2 doses prior to every scheduled venetoclax PK day.

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

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

Appendix G. Tumor Lysis Syndrome Classification

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

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

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

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

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

*** Not directly or probably attributable to therapeutic agent.

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

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

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

Appendix H. Cell Lines Table

Venetoclax is potent against AML cell lines treated in vitro. AML cell lines were treated with increasing concentrations of venetoclax for 48 hours before assessing cell viability. Venetoclax cell killing IC_{50} values are shown for each cell line.

Cell Line	Venetoclax IC_{50} (µM)	Genetic Lesions
MOLM-13	< 0.100	MLL- and FLT3-mutant
GDM-1	< 0.100	nd
EOL-1	< 0.100	MLL-mutant
HL-60	< 0.100	N-Ras-mutant
MV4-11	< 0.100	MLL- and FLT3-mutant
ML-2	< 0.100	MLL-mutant
SIG-M5	< 0.100	nd
OCI-AML2	< 0.100	nd
MOLM-16	0.040	nd
OCI-AML5	0.110	nd
THP-1	0.820	MLL- and N-Ras-mutant
Kasumi-1	1.000	t(8;21) translocation
KG-1	1.200	nd
HNT-34	1.700	nd
PL-21	1.810	FLT3-mutant
SKM-1	2.530	nd
UKE-1	3.060	JAK2-mutant
SET-2	3.330	JAK2-mutant
HEL	3.370	JAK2-mutant
OCI-M2	4.050	nd
OCI-AML3	5.450	N-Ras-mutant
OCI-M1	5.610	nd
NOMO-1	6.950	MLL-mutant
ME-1	> 10	N-Ras-mutant and inv16

nd = not determined

Cell Line	Venetoclax Combination with 5-Aza
MOLM-13	0
RI-1	0
EOL-1	0
SUP-B15	0
MV4-11	0
ML-2	0
OCI-AML2	0
MOLM-16	0
OCI-AML5	0
KG-1	0
HNT-34	1.0
SKM-1	0
UKE-1	0
SET-2	0
HEL	0
OCI-M2	0
OCI-AML3	0.5
NOMO-1	1.0
KU812	0
PL-21	0.5

0 = additive; 0.5 = weak synergy; 1.0 = strong synergy; –1.0 = antagonism

3741402	0.170	NPM1- and IDH1-132-mutated
3804620	0.001	nd
3821772	< 0.001	CEBPA-mutant
3899418	0.003	FLT3-mutant
3873106	> 1.000	JAK2-mutant
3899936	> 1.000	New AML from MDS
3676198	> 1.000	nd
923xxx	< 0.001	CEBPA-mutant

Appendix I. Sample List of Excluded and Cautionary Medication

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

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

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

† If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 4-fold (Table 2). After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the target dose.

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

^ Closely monitor International Normalized Ratio (INR).

1 Moderate CYP3A inhibitor per venetoclax FDA USPI.

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

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

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

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

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). ○ If rasburicase is used, consider screening for G6PD deficiency prior to administration in patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting rasburicase. Please refer to local label for tests to be performed, contraindications and precautions. • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). • If rasburicase is used, consider screening for G6PD deficiency prior to administration in patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting rasburicase. Please refer to local label for tests to be performed, contraindications and precautions. • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.

Abnormality	Management Recommendations
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 – 2 hours STAT.

Appendix K. Japan Specific Information

1.0 Clinical Expense and Compensation

1.1 Expenditure of the Clinical Expense

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

1.2 Compensation for Health Impairment and Insurance

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

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

1.3 Pharmacogenetic Testing

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