1.0 Title Page

Clinical Study Protocol M14-387

A Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy

Incorporating Administrative Change 1 and Amendments 1, 2, 3, 4, 5, 6 and 7

AbbVie Investigational Product:	Venetoclax (ABT-199/GDC-0199)
Date:	22 October 2020
Development Phase:	1/2
EudraCT	2014-002610-23
Study Design:	This is a Phase 1/2 open-label, non-randomized, multicenter study consisting of two phases. A Phase 1, or dose-escalation portion, which will evaluate the safety and pharmacokinetic profile of venetoclax (ABT-199/GDC-0199) administered orally in combination with low-dose cytarabine (LDC) with the objective of defining the maximum tolerated dose (MTD) and generating data to support the recommended Phase 2 dose (RPTD) in treatment-naïve subjects with Acute Myelogenous Leukemia (AML) who are ≥ 60 years of age and who are not eligible for standard induction therapy due to co-morbidity or other factors. A subsequent initial Phase 2 portion will evaluate if the RPTD has sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy. Subsequently, within Phase 2, Cohort C will evaluate the overall response rate (ORR) for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated.
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	05 August 2014
Amendment 1	11 November 2015
Administrative Change 1	25 November 2015
Amendment 2	28 November 2016
Amendment 3	31 May 2017
Amendment 4	24 January 2018
Amendment 5	22 March 2019
Amendment 6	27 February 2020

The purpose of this amendment is to:

- Section 3.3 - included information on the re-evaluation of the benefit and risk with consideration of Coronavirus Disease 2019 present in subject's region.
- Section 5.3.1 - added instructions for necessary changes to activities or procedures in the event of temporary study [drug] interruption/halt.
- Section 5.5.1 - included instructions that in the event the subject cannot pick up venetoclax onsite, DTP shipment can be done as needed and permitted by local regulations.
- Section 7.0 - clarified that protocol deviations may include modifications due to COVID-19.
- Section 9.2 - noted that AbbVie will modify the study protocol as necessary due to the pandemic. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 10.1 - noted that remote monitoring may be employed as needed.
- Modified the language for survival and post treatment follow up time frames to permit a shorter duration of follow up if all patients have discontinued and most patients have expired.
- Editorial changes throughout the protocol.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-387
Name of Study Drug: venetoclax (ABT-199/GDC-0199)	**Phase of Development:** 1/2
Name of Active Ingredient: ABT-199	**Date of Protocol Synopsis:** 22 October 2020
Protocol Title: A Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy	
Objectives: **Primary Objectives:** • The primary objectives of the Phase 1 portion are to assess the safety profile, characterize pharmacokinetics (PK), determine the dose schedule, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax (ABT-199/GDC-0199) in combination with LDC in treatment-naïve subjects with AML who are ≥ 65 years of age and who are not eligible for standard induction therapy due to co-morbidity or other factors. • The primary objectives of the initial Phase 2 portion of the study are to evaluate the preliminary estimates of efficacy including the overall response rate (ORR) and to characterize the toxicities of the combination at the RPTD. • The primary objective of Phase 2 Cohort C is to evaluate the ORR for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated. **Secondary Objective:** • The secondary objectives of the initial Phase 2 portion and Phase 2 Cohort C are to evaluate leukemia response (rates of CR, CRi, PR, and MLFS), duration of response (DOR) and overall survival (OS). **Exploratory Objective:** • Additional exploratory objectives of both phases of the study may be evaluated to find biomarkers that may serve as surrogates or predictors for clinical outcomes in future studies of venetoclax in AML.	
Investigators: Investigator information on file at AbbVie	
Study Sites: Approximately 10 sites globally	
Study Population: Adult subjects ≥ 65 years of age with untreated AML for whom standard induction therapy is not appropriate due to age, co-morbidity, or other factors. Additionally, in Phase 2 Cohort C only, subjects aged 60 – 64 may be enrolled if they have specified co-morbidities that preclude treatment with anthracycline-containing induction chemotherapy.	
Number of Subjects to be Enrolled: Up to 42 subjects will be enrolled in the Phase 1 portion. Approximately 50 subjects will be enrolled in the initial Phase 2 portion. In addition, approximately 20 subjects will be enrolled in Phase 2 Cohort C.	

Methodology:

This is a Phase 1/2, open-label, multicenter study that will evaluate the PK, safety and preliminary efficacy of venetoclax combined with LDC in treatment-naïve subjects with AML ≥ 65 years old and who are not eligible for standard induction therapy due to age, co-morbidity or other factors. This study will consist of two distinct portions or phases. The first portion of the study is a Phase 1, or dose-escalation portion, that will evaluate the safety and PK profile of venetoclax administered with LDC with the objectives of defining the MTD and generating data to support a RPTD. A subsequent initial Phase 2 portion will evaluate whether the RPTD has sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy. Subsequently, a cohort of subjects, Phase 2 Cohort C, will be enrolled permitting a broader range of supportive medication (strong CYP3A inhibitors) co-administration. Age entry criteria for these subjects will be ≥ 60 years.

For the Phase 1 portion, a classical 3 + 3 design is utilized to define the MTD of venetoclax in combination with a standard LDC regimen. Subjects are enrolled in cohorts of three. The first subject from the subsequent cohort should not begin their intended dosing regimen until it is declared by the sponsor that no dose limiting toxicities (DLTs) have occurred during Cycle 1 of the previous dose level. For this trial, a DLT is defined as experiencing a Common Terminology Criteria for Adverse Events (CTCAE) grade 4 or 5 toxicity, unless such events are in the common list of health events due to AML, or not recovering platelets to at least 25,000/μL and absolute neutrophil count (ANC) to 500/μL within 14 days of the last dose of venetoclax unless such cytopenias are due to residual leukemia effect. Should 1 subject experience a DLT, an additional 3 subjects will be enrolled at the same dose level (a total of 6 subjects at this dose level). Should 2 subjects at a dose level experience a DLT, that dose level is considered too toxic. The dose level below the too toxic dose level may be considered the MTD. Additional subjects are then enrolled at the putative MTD to bring the total number enrolled at the MTD to 6. If, during this cohort expansion, a total of 2 subjects at this dose level also experience a DLT, this level would also be considered too toxic and the method continues thusly until the maximal dose level is achieved where 6 subjects can be treated through Cycle 1 and no more than one subject experiences a DLT to define the MTD.

Biomarkers (such as cytogenetics, molecular markers, characterization of Bcl-2 and associated proteins or ex vivo testing of AML subject samples) that may be predictive of venetoclax will be assessed throughout the trial and may be used to enrich for subjects likely to respond to venetoclax.

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 the first day of therapy:

1. Subject must be ≥ 65 years of age in Phase 1 and initial Phase 2. Subjects enrolled in Phase 2 Cohort C must be either:
   - ≥ 75 years of age;

     OR
   - ≥ 60 to 74 years will be eligible if the subject has at least one of the following co-morbidities, which make the subject unfit for intensive chemotherapy:
     - 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 (calculated by Cockcroft-Gault formula)
     - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 ×ULN
     - Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the study medical monitor before study enrollment
2. Subject must have a projected life expectancy of at least 12 weeks.
3. Subject must have histological confirmation of AML and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity or other factors.
4. Subject must have received no prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment. **Note:** Subject may have been treated for prior Myelodysplastic Syndrome.
5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status;
   - of 0 to 2 for subjects ≥ 75 years of age
   - of 0 to 3 for subjects ≥ 60 to 74 years of age, if 0 – 1 another co-morbidity is required to make subject eligible.
6. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula.

   Note: Investigators should consider measuring a 24-hour creatinine clearance for subjects who are morbidly obese, have fluctuating renal function, or who in the investigator's clinical judgment may yield a more accurate clearance when measured than when calculated.
7. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 2.5 × ULN*
   - alanine aminotransferase (ALT) ≤ 2.5 × ULN*
   - bilirubin ≤ 1.5 × ULN for all subjects age 75 and older*
     - Subjects who are < 75 years of age must have a bilirubin of < 3.0 × ULN

   * Unless considered due to leukemic organ involvement.

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

Main Inclusion (Continued):

Note: Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN per discussion between the investigator and AbbVie medical monitor.

8. Male subjects must agree to refrain from unprotected sex and sperm donation from initial study drug administration until 180 days after the last dose of study drug.
9. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
10. If female, subject must be either:
    - Postmenopausal defined as no menses for 12 or more months without an alternative medical cause,

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

Main Exclusion:

A subject will be eligible for study participation if he/she does not meet the following criteria within 21 days prior to the first day of therapy:

1. Subject has received treatment with cytarabine for a pre-existing myeloid disorder.
2. Subject has acute promyelocytic leukemia (French-American-British Class M3 AML).
3. Subject has known active CNS involvement with AML.
4. Subject has tested positive for HIV (due to potential drug-drug interactions between antiretroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may potentially increase the risk of opportunistic infections). **Note:** HIV testing is not required.
5. Subject has received the following within 7 days prior to the initiation of study treatment:
    - Strong and moderate CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John's wort.
6. This criterion has been removed.
7. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.
8. Subject has a cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
9. Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the investigator would adversely affect his/her participating in this study.
10. Subject has chronic respiratory disease that requires continuous oxygen use.
11. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
12. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Uncontrolled systemic infection requiring IV therapy (viral, bacterial or fungal).
13. Subject has a history of other malignancies prior to study entry, with the exception of:

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** • Adequately treated in situ carcinoma of the breast or cervix uteri; • 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 is permitted to meet this criterion. 15. Subject is a candidate for a bone marrow or stem cell transplant within 12 weeks after study enrollment. 16. Subject has a history of myeloproliferative neoplasm (MPN) including polycythemia vera, myelofibrosis, essential thrombocythemia, or chronic myelogenous leukemia.	
Investigational Product:	Venetoclax
Dose:	20 mg QD to 2000 mg QD of venetoclax **Dose Level –2*** Cycle 1: Day 2: 20 mg, Day 3: 50 mg, Day 4: 100 mg, Day 5: 200 mg, Day 6 – Day 28: 200 mg Cycle 2 through Treatment Discontinuation: 200 mg QD, of a 28-Day Cycle **Dose Level –1*** Cycle 1: Day 2: 20 mg, Day 3: 50 mg, Day 4: 100 mg, Day 5: 200 mg, Day 6 – Day 28: 400 mg Cycle 2 through Treatment Discontinuation: 400 mg QD, of a 28-Day Cycle * These dose levels will only be implemented if Dose Level 1 (the initial dose level) is found to be above the MTD. **Dose Level 1 (STARTING DOSE LEVEL)** Cycle 1: Day 2: 50 mg, Day 3: 100 mg, Day 4: 200 mg, Day 5: 400 mg, Day 6 – Day 28: 600 mg Cycle 2 through Treatment Discontinuation: 600 mg QD of a 28-Day Cycle **Dose Level 2** Cycle 1: Day 2: 100 mg, Day 3: 200 mg, Day 4: 400 mg, Day 5: 600 mg, Day 6 – Day 28: 800 mg Cycle 2 through Treatment Discontinuation: 800 mg QD of a 28-Day Cycle **Dose Level 3** Cycle 1: Day 2: 100 mg, Day 3: 200 mg, Day 4: 400 mg, Day 5: 800 mg, Day 6 – Day 28: 1200 mg Cycle 2 through Treatment Discontinuation: 1200 mg QD, of a 28-Day Cycle

Dose (Continued):	**Dose Level 4** Cycle 1: Day 2: 100 mg, Day 3: 200 mg, Day 4: 400 mg; Day 5: 800 mg; Day 6: 1200 mg, Day 7 – Day 28: 1600 mg Cycle 2 through Treatment Discontinuation: 1600 QD of a 28-Day Cycle **Dose Level 5** Cycle 1: Day 2: 100 mg, Day 3: 300 mg, Day 4: 600 mg; Day 5: 1000 mg; Day 6: 1500 mg, Day 7 – Day 28: 2000 mg Cycle 2 through Treatment Discontinuation: 2000 QD of a 28-Day Cycle Note: Subjects will be hospitalized during the ramp-up period of study treatment devoted to venetoclax dose escalation (e.g., Day –1 to Day 7 for Dose Level –2 through Dose Level 3 and Day –1 to Day 8 for Dose Level 4 and Dose Level 5). **Phase 2 Cohort C**** Cycle 1: Day 1: 100 mg, Day 2: 200 mg, Day 3: 400 mg, Day 4 – Day 28: 600 mg Cycle 2 through Treatment Discontinuation: 600 mg QD of a 28-Day Cycle ** Applies to subjects enrolled in Amendment 2.
Mode of Administration:	Venetoclax will be self-administered orally QD within 30 minutes after the completion of a meal, preferably breakfast. Days 1 – 28 of all cycles, Cycle = 28 days
Reference Therapy:	Low-Dose Cytarabine
Dose:	20 mg/m^2/QD Days 1 – 10 of all cycles, Cycle = 28 days
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

Subjects with controlled disease who have tolerable side effects should continue to receive treatment with venetoclax and cytarabine up to 4 years after the last subject is enrolled or until subject discontinuation criteria are met.

Criteria for Evaluation:

Efficacy:

Bone marrow biopsies and aspirates must be performed at screening for all subjects. Cytogenetic and molecular profiling must be performed at screening. In addition, it is recommended that screening bone marrow aspiration samples be analyzed by flow cytometry. Bone marrow aspirate and biopsy must be performed prior to Cycle 2 Day 1, Cycle 4 Day 1, and then every 3 cycles thereafter until two consecutive samples confirm Complete Remission (CR), again if clinical suspicion of recurrence, and at the end-of-study visit for all subjects.

Based on these results, all dosed subjects will be assessed based on the International Working Group (IWG) criteria for AML (Cheson et al. J Clin Oncol. 2003) at each post-baseline visit by the investigators.

Criteria for Evaluation (Continued):

Efficacy (Continued):

CR: absolute neutrophil count ≥ 10^3/μL, platelets ≥ 10^5/μL, red cell transfusion independence, and bone marrow with < 5% blasts.

CRi: bone marrow with < 5% blasts, and peripheral neutrophils of < 10^3/μL or platelets < 10^5/μL.

PR: all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.

MLFS: less than 5% blasts in an aspirate and/or bone marrow core sample. There should be no blasts with Auer rods or persistence of extramedullary disease. The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.

RD: failure to achieve CR, CRi, PR; only including subjects surviving at least 7 days following completion of initial treatment cycle, with evidence of persistent leukemia by blood and/or bone marrow examination.

PD: one or more of the following: ≥ 50% decrement from maximum response levels in neutrophils or platelets, a reduction in hemoglobin by at least 2 g/dL, or transfusion dependence not due to other toxicities and bone marrow blast ≥ 5%.

In addition to the response determination using the above IWG AML response criteria, each subject will also be evaluated for Hematologic Response (HR) and complete remission with partial hematologic recovery (CRh).

CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission; MLFS = morphologically leukemia free status; RD = resistant disease; PD = progressive disease

Pharmacokinetic:

Venetoclax PK samples will be collected at 8 hours post-dose on the day of the first venetoclax dose administration and for each new escalated dose in all subjects enrolled in the study. Intensive PK samples will be collected for venetoclax in Phase 1. Sparse PK samples will be collected for venetoclax in both the Phase 1 and Phase 2 portions of the study. For the intensive PK days of venetoclax, values for the PK parameters including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) from 0 to the time of the last measurable concentration (AUC_t) and AUC over a 24-hour dose interval (AUC_{0-24}) will be determined using noncompartmental methods. Intensive PK samples will be collected for cytarabine in the dose escalation phase. For the intensive PK days of cytarabine, values for the PK parameters including C_{max}, T_{max}, half-life ($t_{1/2}$), AUC_t, AUC from 0 to infinity (AUC_∞) and clearance (CL/F) will be determined using noncompartmental methods. Additional analyses may be performed if useful in the interpretation of the data.

Criteria for Evaluation (Continued):

Pharmacodynamic and Predictive Biomarker Analysis:

A reduction in leukocytosis or blast counts may be evaluated as a measure of venetoclax-induced pharmacodynamic activity. Exploratory research may also be conducted to find biomarkers that may serve as surrogates for clinical endpoints in future venetoclax studies or that may be predictive of venetoclax activity. Peripheral blood and bone marrow aspirate samples will be obtained at study specified time points. Biomarker assays may include, but are not limited to, BH3 profiling and ex vivo sensitivity testing. Subject sub-populations (e.g., based on parameters such as cytogenetics, mutation profiles or ex vivo venetoclax sensitivities) may be enriched in Phase 2 of the study to increase the potential for response to venetoclax. If necessary, aliquots from PK samples will be utilized for biomarker analyses. Exploratory research analyses may not be included in the clinical study report.

Pharmacogenetics:

DNA samples may be analyzed for genetic factors contributing to the disease or the subject's response to venetoclax in terms of pharmacokinetics, tolerability and safety.

Safety:

Adverse event (AE) monitoring, vital signs, physical examination, electrocardiogram (ECG) and laboratory values will be assessed. Guidelines for Tumor Lysis Syndrome (TLS) management are provided. Note: All subjects will be hospitalized during dose ramp-up and longer as needed, per investigator judgment, for bone marrow recovery or for management of disease complications during the escalation from each subjects starting dose through at least 24 hours beyond each subject receiving their maximal venetoclax dose level. Chemistry labs pertinent to TLS (including potassium, calcium, uric acid, phosphorus, and creatinine) will be performed at pre-dose, 6, and 12 hours post-dose for the first dose and each escalated dose, and also as deemed necessary to monitor for TLS. Chemistries will also be performed at 24 hours after administration of the highest venetoclax dose level.

Statistical Methods:

Efficacy:

Analyses of ORR as defined by CR + CRi + PR, CR rate, CRi rate, CRh rate, CR + CRi rate, CR + CRh rate, duration of response (DOR), event free survival (EFS), overall survival (OS), the exploratory analysis of the proportion of all subjects who achieve minimal residual disease (MRD) negativity, the proportion of subjects who are transfusion independent post baseline, and the proportion of subjects who undergo subsequent stem cell transplant will be performed for subjects who received study drugs.

Pharmacokinetic:

Plasma concentrations and PK parameter values of venetoclax and cytarabine will be tabulated for each subject, visit, and dose regimen, and summary statistics will be computed for each sampling time and each parameter.

The dose proportionality of venetoclax and the potential interaction between venetoclax and cytarabine will be assessed using linear mixed effect model.

Safety:

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

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABT-199	Study Drug Compound, "venetoclax"
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Promyelocytic Leukemia
ALT	Alanine Aminotransferase (also called SGPT)
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASD	Amorphous solid dispersion
AST	Aspartate aminotransferase (also called SGOT)
Bcl	B-Cell Lymphoma
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CLL	Chronic lymphocytic leukemia
CML	Chronic Myelogenous Leukemia
CNS	Central Nervous System
COVID-19	Coronavirus Disease-2019
CR	Complete Remission
CRi	Complete Remission with Incomplete Blood Count Recovery
CRh	Complete Remission with Partial Blood Hematologic Recovery
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P450 1A2
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DLCO	Diffusion Capacity of Carbon Monoxide

DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DTP	Direct-to-patient
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event Free Survival
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
FEV1	Forced Expiratory Volume in One Second
GCP	Good Clinical Practice
HDPE	High Density Polyethylene
HR	Hematologic Response
hr	Hour
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
Kg	Kilogram
L	Liter
LDC	Low-dose cytarabine
LDH	Lactate Dehydrogenase
m	meter
MAD	Multiple Ascending Dose
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities

MLFS	Morphologically Leukemia Free Status
MM	Multiple Myeloma
µg	Microgram
mg	Milligram
µL	Microliter
mL	Milliliter
µM	Micromolar
MPN	Myeloproliferative Neoplasm
MPV	Mean Platelet Volume
MRD	Minimal Residual Disease
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NCS	Not clinically significant
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
NOAEL	No-observed-adverse-effect-level
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	Per Os Orally
PR	Partial Remission
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
SAD	Single Ascending Dose

SAE	Serious Adverse Event
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
SUSAR	Suspected Unexpected Serious Adverse Reactions
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
WBC	White Blood Cell

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
AUC_t	Area under the plasma concentration-time curve from time zero to the last measureable concentration
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

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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 (ABT-199/GDC-0199) 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).[3] 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 leukemias (AML).[3] Venetoclax was especially potent against Non-Hodgkin lymphoma (NHL) cell lines expressing high levels of Bcl-2 protein due to the t(14;18) chromosome translocation, amplification of the *Bcl-2* gene locus, or aberrantly activated signaling mechanisms. Venetoclax also demonstrated potent killing of multiple myeloma (MM) cell lines and primary tumor samples bearing the t(11;14) translocation, which tend to express high levels of Bcl-2 relative to Mcl-1.

Bcl-2 over-expression has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. In addition, high levels of Bcl-2 were associated with poor survival in a subset of patients with this disease.[4,5] 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[4] or azacitidine.[5] 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 G). The sensitivity of primary AML patient samples was comparable to that observed for primary CLL samples, with a median IC_{50} = 0.010 µM (n = 57) for AML[6] (Appendix G) 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.[6]

However, not all AML cell lines, primary patient samples, or patients 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[7,8] including in AML.[4] Therapeutic agents such as the DNA methyltransferase inhibitor azacitidine,[6] the DNA synthesis inhibitor cytarabine[9] and the anthracycline doxorubicin[10] 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.[4] Combinations of venetoclax and chemotherapeutic agents commonly used in the treatment of AML were 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 G). 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 patients with AML. In mouse, rat, monkey, and dog, the venetoclax PK profile was characterized by low plasma clearance (CLp = 0.02 to 0.27 L/hr•kg) and low volumes of distribution (Vss = 0.3 to 1.1 L/kg). Half-lives ranged from 2.2 hours in monkey to 12.0 hours in dog. Formulation-dependent oral bioavailability was noted in all species. Studies in both rat and dog have defined the behavior of the amorphous solid dispersion (ASD) for both toxicology and first-in-human evaluation. Plasma concentrations obtained from fed dogs were 30% to 50% higher than those obtained from fasted animals.

Venetoclax is not a potent inhibitor of CYP3A4, CYP1A2, CYP2C19, CYP2B6, or CYP2D6 (IC_{50} > 30 µM). At concentrations of 1, 3, and 10 µM, venetoclax did not induce CYP3A4 or CYP1A2 expression in vitro. Venetoclax was metabolized by CYP3A4; thus its exposure could be affected when potent inhibitors or inducers of

CYP3A4 are co-administered. Venetoclax is a substrate for P-gp and BCRP. Active uptake of venetoclax or M27 was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor in vitro.

Venetoclax Preclinical Toxicology

The primary toxicities associated with repeat-dose oral administration of venetoclax were effects on the hematologic system (decreased lymphocytes and red blood cell mass) in mice, rats, and dogs, the male reproductive system (testicular germ cell depletion) in dogs, and embryo-fetal toxicity in mice. Other noteworthy findings in dogs were epithelial single cell necrosis in multiple tissues and hair coat color change towards white. In general, the primary toxicities and other noteworthy findings were consistent with the expected pharmacologic effects of venetoclax, a selective Bcl-2 inhibitor.

In mice, rats, and dogs, venetoclax produced decreases in lymphocytes in the peripheral blood (up to –75% in mice, –64% in rats, and –81% in dogs) and in lymphoid tissues, generally following 2 to 4 weeks or more of daily dosing (but after a single dose in dogs). Lymphocyte decreases were expected on the basis of venetoclax pharmacology and, when sustained over periods of 6 to 9 months in chronic venetoclax toxicity studies, were not associated with opportunistic infections.[16]

In mice, total lymphocyte counts at the high dose of 600 mg/kg/day after 4 weeks of dosing were minimally decreased –21% to –26% relative to concurrent controls at the end of the 4-week recovery period, indicating partial recovery. In dogs, the recovery of peripheral blood decreases in total lymphocytes and lymphocyte subsets (CD4+ T-cells, CD8+ T-cells, and CD21+ B-cells) was prolonged, requiring up to 18 weeks after a single dose or 2 weeks of daily dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> –90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs; but, as with peripheral blood lymphocytes, required up to 18 weeks in dogs.

Venetoclax produced dose-related decreases in red blood cell (RBC) mass due to altered hemoglobinization and decreased RBC production in mice, rats, and dogs. Based on a criterion of hemoglobin decreases of ≥ –20% as compared to control and/or baseline, these effects were considered adverse at the highest dosages in the 4-week mouse and dog studies (observed decreases of –21 to –23%) but were reversible following a 4-week recovery period. In studies designed to select dose levels for possible carcinogenicity assessment, RBC mass decreases were also observed in rats and were generally more severe (hemoglobin decreases to –49%) than in mice or dogs.

Venetoclax produced adverse, non dose-related microscopic findings of testicular germ cell depletion (spermatogonial loss with maturation depletion) in dogs at all doses tested. Reversibility was assessed after 4 weeks of dosing and a 4-week recovery period; there was no evidence of reversibility. Testicular germ cell loss may be related to venetoclax pharmacology, as Bcl-2 plays a role in spermatogonial maintenance.[17,18] There were no testicular effects in mice or rats at venetoclax exposures overlapping those in dogs.

Venetoclax resulted in increased post-implantation loss and decreased fetal body weights in the mouse embryo-fetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect-level was defined at the mid-dose of 50 mg/kg/day. In mice and rabbits, venetoclax was not teratogenic, and there were no other effects on development or fertility.

Additional noteworthy effects of venetoclax included minimal to mild single cell necrosis in multiple epithelial tissues (gallbladder, exocrine pancreas, epididymides, prostate, and stomach) in dogs and a change in the hair coat towards white in dogs (occurring after approximately 3 months of dosing in the 9-month study). None of these effects was considered to be adverse. Hair follicle melanocytes are critically dependent on Bcl-2 for survival during the normal hair replenishment cycle in mice, suggesting that the decrease in hair pigmentation in dogs was a likely effect of Bcl-2 inhibition.[19] In regards to single-cell necrosis, Bcl-2 is expressed in epithelial tissues and may regulate survival in rapidly dividing cell populations.[20-22] Venetoclax appears to increase the rate of normally

occurring apoptosis without adversely affecting the normal tissue architecture or functions of these tissues.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity (tested in vivo in hairless mice). In a juvenile toxicity study, mice were administered venetoclax at 10, 30 or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor and hunched posture at ≥ 30 mg/kg/day. Mortality and body weight decreases occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at ≥ 10 mg/kg/day; these findings were consistent with those in adult mice and considered non adverse.

The major human metabolite of venetoclax, M27, was characterized at steady-state in R/R CLL patient plasma with an average metabolite to parent AUC ratio of 0.48 at the 400 mg venetoclax clinical dose. In contrast, ss plasma levels of M27 in mice and dogs were ≤ 5.1% of human exposure, making M27 a disproportionate human metabolite. The safety of M27 was evaluated by in vitro and in vivo studies. M27 was negative in Ames and chromosome aberration in vitro assays, has at least 58-fold less in vitro potency than venetoclax, and demonstrates low off-target toxicity potential based on in vitro secondary pharmacology assays. Additionally, no adverse effects were observed in a 4-week mouse toxicity study in which M27 was orally administered at dosages up to 300 mg/kg/day, achieving M27 AUC plasma exposures at or above those observed clinically.

Dogs at the high dosage of 150 mg/kg/day (AUC 572 µg•h/mL) in the 4-week toxicity study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hind paws. Most but not all animals (8 of 10 dogs) were affected, and in 3 dogs the swelling reaction was observed after the first dose. The clinical signs were limited to the 150 mg/kg/day dosage, were mild to moderate in severity and transient and sporadic in occurrence, and were absent during the 4-week recovery period. A mechanistic basis for the swelling reactions was not established, but a histamine-like reaction to copovidone, a primary excipient in the formulation, is possible.[23] There were no signs of anaphylaxis.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the CNS/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest dose of 600 mg/kg. To assess cardiovascular safety, venetoclax was tested in an in vitro human ether-a-go-go related gene (hERG) assay and in both conscious and anesthetized dogs. In hERG, a 50% inhibition constant (IC_{50}) could not be calculated due to limited solubility (1.5 µg/mL). Only minimal effects on QT interval corrected for heart rate (QTc) were observed up to a maximum plasma concentration of 46 µg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (C_{max} = 16 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (–6% to –13%) and cardiac output (–11% to –19%) at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (geometric mean C_{max} = 3.46 µg/mL at the 1200 mg dose).

On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, key potential mechanism-based toxicities may include lymphopenia and neutropenia,[16] signs of tumor lysis, reduction in RBC mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. The potential for development of hair color change in humans is unknown. No adverse events of changes in hair color, skin pigmentation, or eye color have been reported in the venetoclax clinical studies to date. Although no effects of venetoclax on female reproductive tissues have been observed in repeat-dose general toxicology studies, embryo-fetal toxicity studies in animals have identified a fetal toxicity risk. Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-X_L sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a DLT clinically. Overall, the toxicities observed in animals administered venetoclax are consistent with the expected pharmacologic effects of Bcl-2 inhibition.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[25]

Venetoclax Clinical Data

As of 28 November 2019, on the basis of data available in the clinical databases for company-sponsored studies with unblinded data, a total of 3974 subjects have been exposed to at least 1 dose of venetoclax across company-sponsored studies, as described in Section 8.0. Of these subjects, 3962 are included in the overall pooled analyses for reporting Reference Safety Information (RSI) (Appendix A): 3610 oncology subjects, 255 healthy volunteers, 12 from a study conducted outside the venetoclax development program, 24 subjects with hepatic impairment, and 73 SLE subjects. Of the 2590 oncology subjects, 3481 were adults in the venetoclax oncology program (1183 in monotherapy studies and 2298 in combination therapy studies): 1639 with CLL/SLL, 597 with AML, 483 with MM, 572 with NHL, 144 with myelodysplastic syndrome (MDS), and 44 with ALL, 1 with rhabdomyocarcoma, and 1 with Evans tumor. The remaining oncology subjects included 65 pediatric subjects in the venetoclax program (26 ALL/LL, 29 AML, 1 NHL, 6 neuroblastoma, 3 other solid tumors): 5 received monotherapy and 60 received combination therapy. 64 subjects from studies conducted under another investigational new drug (IND) compounds outside the venetoclax program (52 AML, 11 NHL, 1 unknown). An additional 1125 subjects with blinded data have been treated with either venetoclax combination therapy or a comparator treatment in company-sponsored venetoclax oncology studies. Based on nonclinical and clinical data available with venetoclax administration, important identified risks are tumor lysis syndrome (TLS), neutropenia, and serious infection. Tumor lysis syndrome is a risk associated with venetoclax treatment and it is highest in CLL and MCL. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including, anemia, thrombocytopenia, and lymphopenia). Events of anemia, neutropenia, and thrombocytopenia are also commonly observed with the underlying hematologic malignancies. Infections, including serious infections, although also common with the underlying malignancies, have been reported with venetoclax

treatment and their incidence is higher with combination treatments. Co-administration with CYP3A inducers and inhibitors can cause changes in venetoclax exposure. Decreased spermatogenesis has been observed in nonclinical studies with dogs. Embryofetal toxicity was observed in nonclinical studies; thus, venetoclax should not be used during pregnancy. In addition, as venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored. Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. The harmonic mean terminal phase elimination half-life ($t_{1/2}$) ranged from 17 to 41 hours following a single oral dose of venetoclax. In subjects with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (fu) < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%). Drug-drug interaction (DDI) studies of venetoclax with ketoconazole, rifampin, warfarin, ritonavir, azithromycin, and digoxin were conducted to provide dosing recommendations for patients concomitantly taking CYP3A and/or P-gp inhibitors, inducers, and/or warfarin. Pharmacokinetic studies were conducted in healthy Chinese subjects and in Japanese subjects to provide dosing recommendations for those specific populations. Additionally, a dedicated study to evaluate the pharmacokinetics of venetoclax in subjects with hepatic impairment was conducted. Based on the population pharmacokinetic analysis, age, sex, race, weight, and mild and moderate renal or hepatic impairment do not have an effect on venetoclax clearance.

Updated data are described in detail in the Investigator's Brochure.[25]

Acute Myelogenous Leukemia

Acute myelogenous leukemia is characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood and extramedullary tissues. It is the most common form of acute leukemia in adults. An estimated 18,500 adults will be diagnosed with

AML in 2014 and 10,000 deaths will be attributed to the disease.[26] The median age of diagnosis is 72 years, with individuals 80 – 85 years of age having the highest incidence rates.[27] Elderly AML is a biologically and clinically distinct disease with a diminished response to chemotherapy with low remission rates and short disease-free and overall survival compared to AML that occurs in younger patients. Higher proportion of unfavorable cytogenetics, higher frequency of antecedent hematologic disorders or prior therapy for previous malignancies, and more frequent expression of the multidrug resistance phenotype accounts for the poor outcomes associated with current therapy. Additionally, the presence and severity of comorbid conditions, compromised end organ function that enhance the toxicity of induction chemotherapy, and functional incapacity all decrease the ability for the elderly patient to tolerate induction chemotherapy and survive life-threatening infections often associated with AML therapy.[28] Several studies have 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 all patients diagnosed with AML.[29,30]

3.1 Study Rationale

Currently, there is no consensus as to a single optimal therapy for older patients with AML who are not candidates for conventional induction treatment though subcutaneous low-dose cytarabine (LDC) is a common therapeutic approach. A common approach that hemato-oncologists utilize to determine fitness for intensive induction therapy is to conduct a thorough clinical evaluation including history taking, physical examination, and review of pertinent laboratory and clinical tests. This "clinical judgment" approach was supported by findings from a prospective study of 157 subjects with hematological malignancies that found "clinical judgment" to be the strongest prospective predictor of survival and was superior to formalized geriatric assessment without clinical judgment.[31] Another approach, suggested by Ferrara and colleagues,[32,33] incorporates specified co-morbidity criteria in addition to clinical judgment. Conceptual criteria proposed to define subjects unfit for conventional intensive chemotherapy[32] are:

1. Advanced age (over 75 years)

2. Severe cardiac comorbidity
3. Severe pulmonary comorbidity
4. Severe renal comorbidity
5. Severe hepatic comorbidity
6. Active infection resistant to anti-infective therapy
7. Cognitive impairment
8. Low performance status (ECOG functional scale)
9. Any other comorbidity that the physician judges to be incompatible with chemotherapy

Low-dose cytarabine is a standard treatment option for patients with AML who are ineligible for intensive induction therapy due to comorbidities. Initial studies from the Acute Leukemia Group B, over 40 years ago, reported that 15% – 20% of patients with AML receiving LDC at dose of 10 – 30 mg/m^2 achieved a CR.[31] Subsequently, a meta-analysis including 293 previously untreated patients with newly diagnosed acute non-lymphocytic leukemia reported a CR rate of 32% with LDC.[35] More recently, a large, international trial for newly diagnosed patients ages 65 years and older with AML and poor prognostic features reported a combined CR rate (CR + CR with incomplete blood count recovery) of 11% for those patients receiving LDC using modern and more sensitive methods to determine the depth of clinical response.[30]

Though LDC has been available for decades, the low response rate and associated short expected survival leaves a significant unmet medical need for patients with treatment-naïve AML who are ≥ 60 with comorbidities making them poor candidates for standard, high dose, anthracycline-based induction chemotherapy. Single-agent clinical activity observed in other advanced hematologic malignancies (Study M12-175) and AML (Study M14-212), along with activity demonstrated using venetoclax alone and in combination with cytarabine in AML cell lines and primary patient samples, suggest the

possibility of significant clinical activity in AML for the combination of venetoclax with LDC. The clinical trial described in this protocol is designed to evaluate if venetoclax may be combined safely with LDC and whether potentially meaningful clinical activity can be observed.

3.2 Differences Statement

This is the first study of venetoclax in combination with LDC for subjects with AML. Venetoclax was tested in Phase 2 trial (Study M14-212) in subjects with relapsed, refractory AML or in a frontline setting in subjects who are unfit for intensive therapy to examine preliminary activity and safety as monotherapy. A Phase 1b/2 trial (Study M14-358) was also initiated testing the combinations of venetoclax with either azacitidine or decitabine in subjects with naïve AML who are aged 65 and older and not eligible for intensive induction chemotherapy. Clinical trials in other indications which employ venetoclax monotherapy include a Phase 1 clinical trial to ascertain the safety, PK, maximum tolerated dose, RPTD of venetoclax in subjects with relapsed or refractory CLL and NHL (Study M12-175) and a Phase 2 trial of venetoclax in subjects with relapsed/refractory CLL harboring 17 p deletion (Study M13-982).

3.3 Benefits and Risks

Based on the venetoclax studies, the regimen is designed to escalate the dose of venetoclax rapidly and safely with a standard dose and schedule of LDC to optimize the opportunity for achieving a response and enable close subject monitoring. The dosing regimen will also enable interruptions and slower intra-subject dose escalation to target assigned dose if rapid tumor lysis is observed. Based on the ex vivo testing of primary subject AML samples that has shown significant variability among subjects, initial signs of leukemia response may occur at different doses of venetoclax when combined with LDC for different subjects.

Venetoclax was administered to 32 subjects with AML as monotherapy in Study M14-212. Safety data from 28 (87.5%) subjects who experienced adverse events of grade 3 and above, showed the most common events being febrile neutropenia (31.3%), malignant

neoplasm progression, (25.0%), hypokalemia, and pneumonia (21.9% each). Serious adverse events were reported for 27 (84.4%) subjects, including febrile neutropenia (9 subjects), malignant neoplasm progression (8 subjects), pneumonia (5 subjects), abdominal pain, sepsis, urinary tract infection, failure to thrive, renal failure acute, and hypotension (2 subjects each). All other events occurred in 1 subject each.

Study M14-212 has completed with efficacy data available for 32 subjects, the majority of them (30, 94%) with R/R AML. The ORR was 19% (6 of 32 subjects), with CR in 2 (6%) and CRi in 4 (13%) subjects. Anti-leukemic activity was observed in an additional 6 (19%) subjects.

For additional safety and efficacy data please refer to the current Investigator Brochure.[25]

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

4.0 Study Objective

The primary objectives of the Phase 1 portion are to assess the safety profile, characterize PK, determine the dose schedule, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RPTD) of venetoclax (ABT-199/GDC-0199) in combination with LDC in treatment-naïve subjects with AML who are ≥ 65 years of age and who are not eligible for standard induction therapy due to co-morbidity or other factors.

The primary objectives of the initial Phase 2 portion of the study are to evaluate the preliminary estimates of efficacy including the overall response rate (ORR), and to characterize the toxicities of the combination at the RPTD.

The primary objective of Phase 2 Cohort C is to evaluate the ORR for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated.

The secondary objectives of the initial Phase 2 portion and Phase 2 Cohort C are to evaluate leukemia response (rates of CR, CRi, PR, and MLFS), duration of response (DOR) and overall survival (OS).

Additional exploratory objectives of both phases of the study may be evaluated to find biomarkers that may serve as surrogates or predictors for clinical outcomes in future studies of venetoclax in AML.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 1/2, open-label, non-randomized, multicenter study that will evaluate the PK, safety and efficacy of orally administered venetoclax combined with LDC in treatment-naïve subjects with AML ≥ 60 years old and who are not eligible for standard induction therapy due to co-morbidity or other factors. This study is sponsored by AbbVie in collaboration with Genentech/Roche.

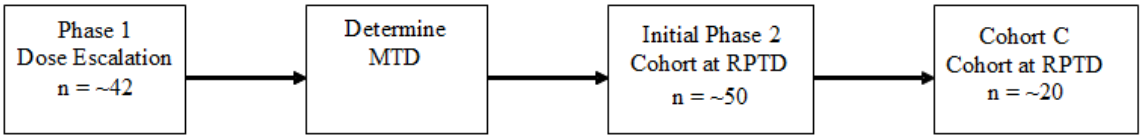
This study will consist of three distinct portions. The first portion of the study is a Phase 1, or dose-escalation portion, that will evaluate the safety and PK profile of venetoclax administered with LDC with the objective of defining the MTD and generating data to support a RPTD. A subsequent initial Phase 2 portion will evaluate if the RPTD has sufficient efficacy and acceptable toxicity to warrant further development of the combination therapy. Subsequently, Phase 2 Cohort C, will evaluate the ORR for subjects allowed additional supportive medications (strong CYP3A inhibitors) if medically indicated.

The study is designed to enroll up to approximately 42 subjects in Phase 1. For the initial Phase 2 portion, up to approximately 50 subjects will be treated at the RPTD and schedule

defined in the Phase 1 portion of the study. Phase 2 Cohort C will enroll approximately 20 subjects.

All efforts will be made to adhere to these specified enrollment numbers; however, recognizing the acute nature of the disease, it might not be possible to deny treatment to subjects in screening for ethical reasons or maintain individual subjects on therapy sufficiently long to evaluate safety or efficacy.

Figure 1. Overall Study Design



Biomarkers (such as cytogenetics, molecular markers, characterization of Bcl-2 and associated proteins or ex vivo testing of AML subject samples) that may be predictive of venetoclax activity will be assessed throughout the trial and may be used to enrich for subjects likely to respond to venetoclax.

Dosing Schedule Overview – Venetoclax – Phase 1 Portion

Venetoclax will be administered orally once daily (QD) on Days 2 through 28 of Cycle 1 of the 28-day cycle. Beginning with Cycle 2, venetoclax will be administered Days 1 through 28 of each 28-day cycle. Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast. The dose should be administered at the same time each day. On days the subject is given LDC, venetoclax should be given prior to LDC. The regimen is designed to escalate the dose of venetoclax in combination with LDC rapidly toward the target dose to optimize the opportunity for achieving a response and enable close subject monitoring. The dosing regimen will also enable interruptions, reductions (if necessary) and a slower intra-subject dose escalation if rapid tumor lysis or other toxicities are observed.

The initial period, approximately one week, of therapy until the target dose of venetoclax is achieved is considered the venetoclax ramp-up period (Day 1 through Day 4, 6 or 7 of Cycle 1, based on the escalation steps in the cohort).

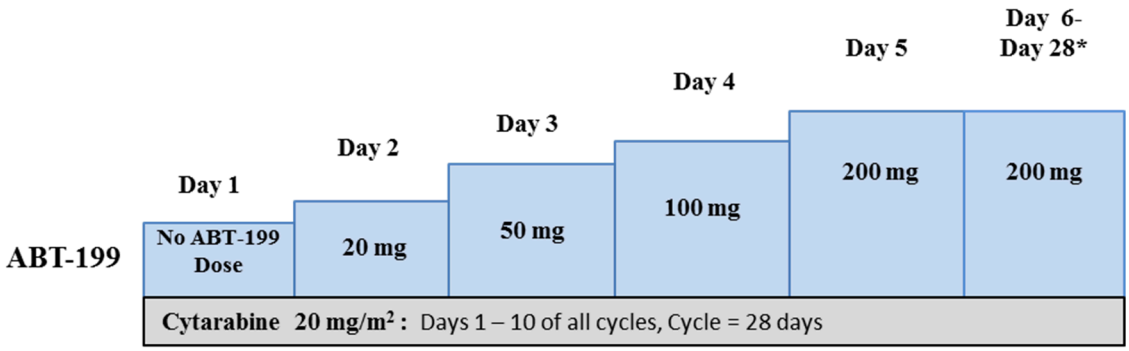
Dose modifications of venetoclax in the ramp-up period may be implemented for individual subject(s) at risk for TLS or any new adverse events > Grade 2. Dose reductions must follow original dosing schema. If the subject requires dose reductions or dose holds during the venetoclax ramp-up period, a discussion with the AbbVie medical monitor is required.

To mitigate the potential risk of TLS,[36] subjects will receive TLS prophylaxis prior to any venetoclax dose escalation in combination with LDC (See Appendix E for specific allopurinol and IV fluid dosing guidance). Subjects will be hospitalized during the ramp up period, with confinement recommended to begin by Study Day –1, and must occur by at least Day 1, through at least 24 hours after completion of the ramp-up period (e.g., Day –1 through Day 5 of Cycle 1 based on the escalation steps in Cohort C). Tumor lysis syndrome prophylaxis will be initiated in all subjects starting at least the day before the first dose of venetoclax. Refer to Section 6.1.8.2, Management of Tumor Lysis Syndrome, for the details on TLS prophylaxis, Appendix E – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome for procedures to follow, and Appendix H for information regarding how to recognize laboratory and clinical TLS.

If a subject develops any laboratory changes suggestive of TLS within the first 24 hours after either the first dose or during dose escalation, venetoclax dose escalation should be withheld or the dose should be reduced. Dose reductions and dose holds during the ramp-up period require notification of the AbbVie medical monitor as do any occurrence of clinical TLS.

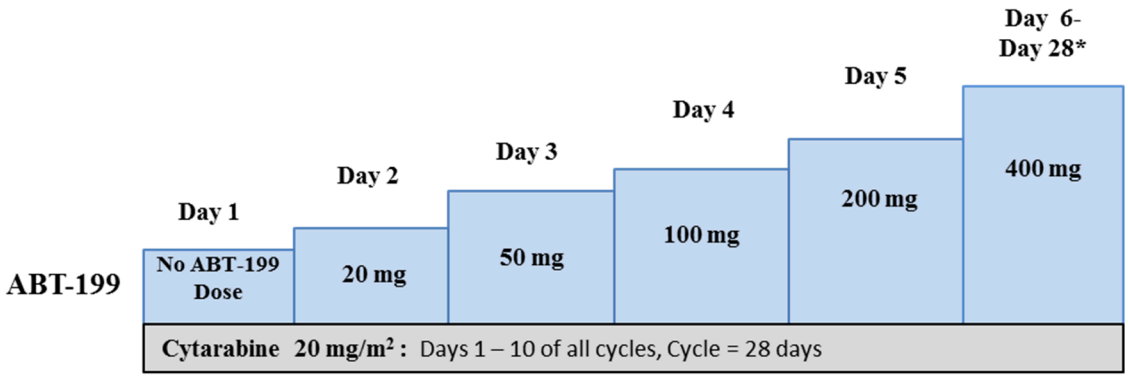
Dosing Schemas for Phase 1

Figure 2. Dose Level –2 Cycle 1



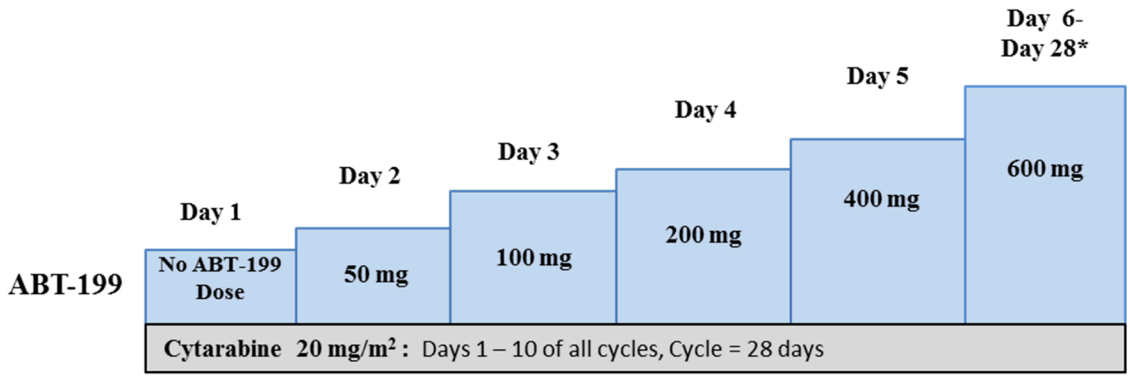
* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 200 mg.

Figure 3. Dose Level –1 Cycle 1



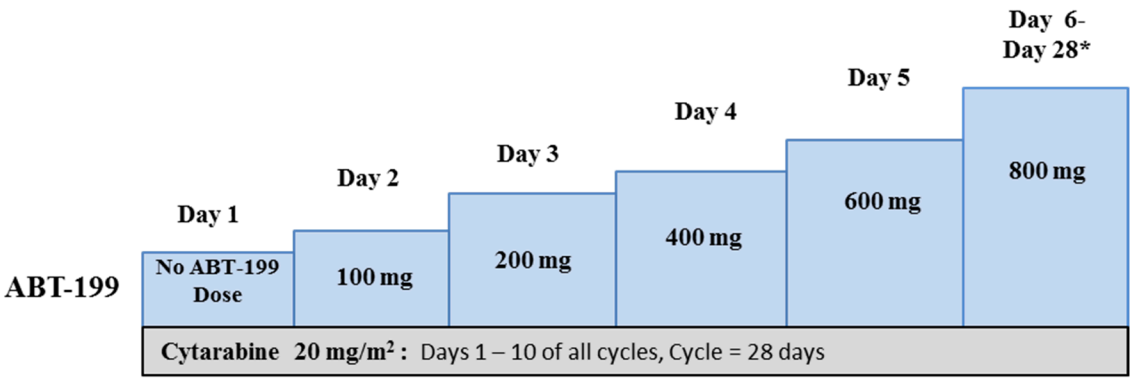
* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 400 mg.

Figure 4. Dose Level 1 Cycle 1 (Starting Dose Level)



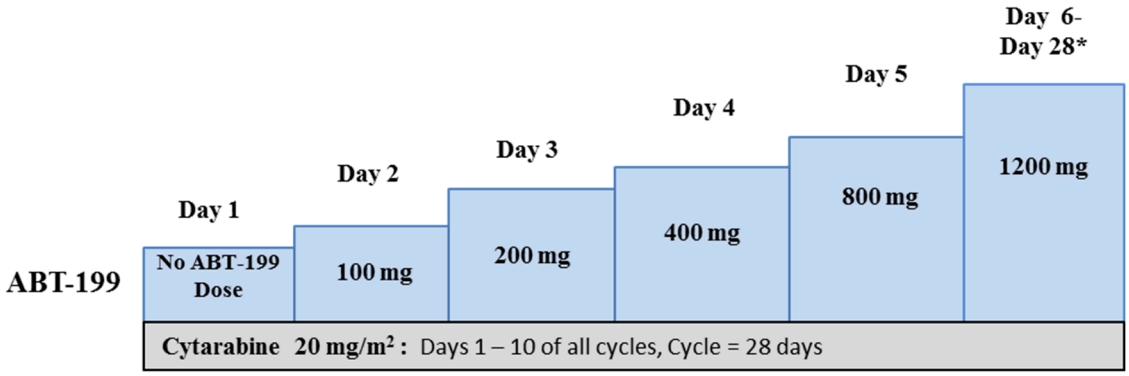
* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 600 mg.

Figure 5. Dose Level 2 Cycle 1



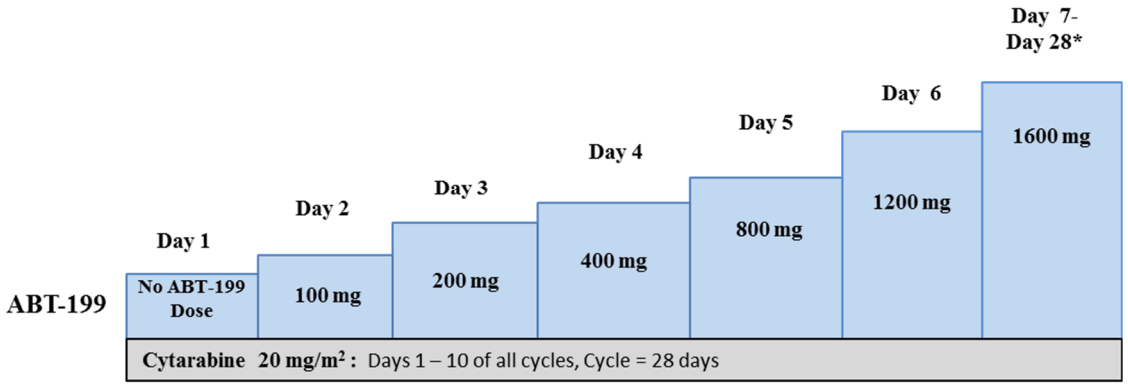
* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 800 mg.

Figure 6. Dose Level 3 Cycle 1



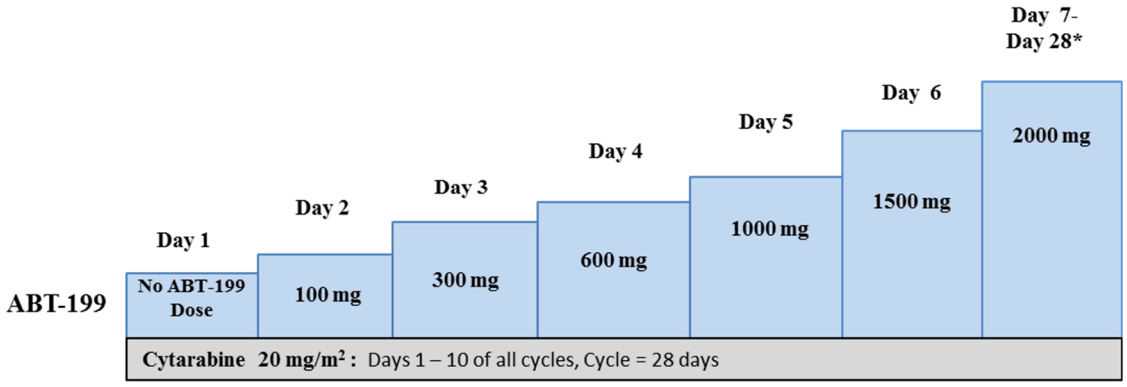
* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 1200 mg.

Figure 7. Dose Level 4 Cycle 1



* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 1600 mg.

Figure 8. Dose Level 5 Cycle 1



* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 2000 mg.

Low-Dose Cytarabine Dosing (Phase 1 and 2)

LDC (20 mg/m^2) will be administered subcutaneously for 10 consecutive days at the start of each cycle during both Phase 1 and Phase 2.

Dose Escalation and Modification Guidelines for Venetoclax – Phase 1

During Phase 1, modifications in the ramp-up period may occur based on tolerability of the first week dose escalation in earlier dose levels. Increases in starting dose and/or changes in the dosing increments may be implemented. The initial dose in subsequent cohorts may be lowered based on the tolerability, including the presence of signs of clinically significant laboratory or clinical tumor lysis. Dose escalation to the target dose may then occur in smaller increments. Decisions to modify the ramp-up period will be made by AbbVie following discussion between the investigators and AbbVie medical monitor. Historically, subjects receiving treatment for AML are at risk for developing TLS and accordingly TLS is an AESI in this protocol. If a subject experiences clinical TLS while receiving protocol therapy, AbbVie's medical monitor and safety team will review safety data (both pertaining to the individual subject and in aggregate) to determine if modifications to the first week dose escalation schedule or TLS prophylaxis are warranted.

Once 3 subjects are enrolled to a dose level, dose escalation or de-escalation decisions to the next designated dose level will be made after subjects have been evaluated to determine if each experienced a DLT during the first cycle of therapy or not. This will typically occur 28 ± 14 days from the last subject within a cohort starting therapy.

Subjects are enrolled in cohorts of three, and the first subject from the subsequent cohort should not begin their intended dosing regimen until it is declared by the sponsor that no DLTs have occurred during Cycle 1 of the previous cohort. All efforts will be made to adhere to these specified enrollment numbers (e.g., cohorts of three); however, recognizing the acute nature of AML, it might not be possible to deny treatment to subjects in screening for ethical reasons or maintain individual subjects on therapy sufficiently long to evaluate safety or efficacy. In the event that more than 3 subjects enroll into a cohort, only the first 3 subjects dosed and will be informative for defining the MTD. Should more than 3 subjects initially enroll into a dose level, subsequent subject data may be used to replace initial subjects if any of those subjects become non-evaluable due to non-adherence or other reasons.

For this trial, DLTs are defined as experiencing a CTCAE grade 4 toxicity, unless such events are in the common list of health events due to AML (Appendix F), or not recovering platelets to at least 25,000/µL and ANC to 500/µL within 14 days of the last dose of venetoclax unless such cytopenias are due to residual leukemia effect. Should 1 subject experience a DLT, an additional 3 subjects will be enrolled at the same dose level (a total of 6 subjects at this dose level). Should 2 subjects at a dose level experience a DLT, that dose level is considered too toxic. The dose level below the too toxic dose level is considered the MTD. Additional subjects are then enrolled at the MTD to bring the total number enrolled at the MTD to 6. If during this cohort expansion, a total of 2 subjects at this dose level also experience a DLT, this level would also be considered too toxic and the method continues thusly until the maximal dose level is achieved where 6 subjects can be treated through Cycle 1 and no more than one subject experiences a DLT. Additional subjects may be enrolled at the current dose level at the discretion of the AbbVie medical monitor, if enrolled subjects are not evaluable. In addition, significant

adverse events occurring after Cycle 1 in previous dose levels and ongoing PK assessments may inform dose escalation decisions and should such unanticipated occurrences necessitate a modification to the planned cohort dose assignments, decisions will be communicated in writing to all investigators.

Dose Escalation Guidelines

Number of Subjects with DLT	Dose Escalation
0 of 3	Begin enrollment in the next dose level
1 of 3	Enroll 6 subjects in current dose level
1 of 6 or < 33% DLTs	Begin enrollment in the next dose level
≥ 2 of 6 or ≥ 33% DLTs	Previous dose determined as the MTD or dose de-escalation

If a dose de-escalation occurs and < 33% of subjects enrolled experience a DLT at the reduced designated cohort dose, this dosing regimen will be declared the MTD. If ≥ 33% of the subjects enrolled at the reduced designated cohort dose still experience a DLT, dose de-escalation of the designated cohort dose regimen will continue to be explored.

The MTD will be defined as the highest designated cohort dose level (and corresponding ramp-up period regimen, if applicable) at which < 33% of the subjects enrolled experience a DLT.

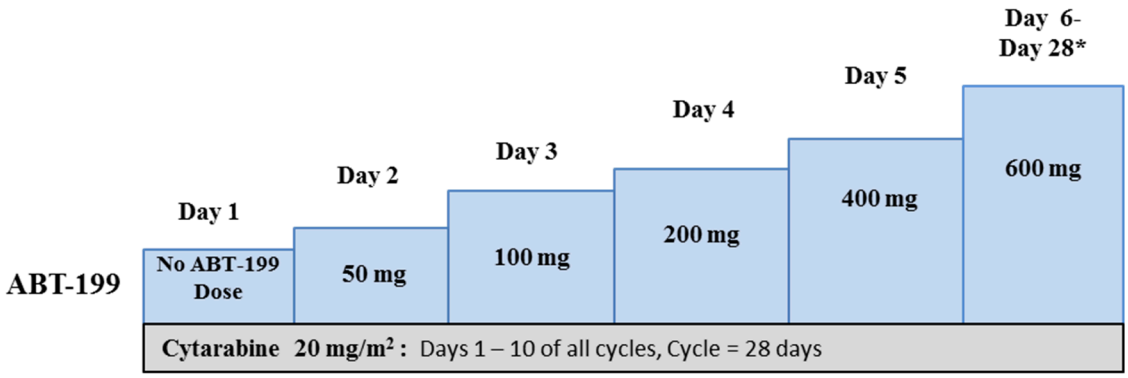
Subjects should experience a DLT and/or complete at least 80% of indicated venetoclax and cytarabine dosing in the first cycle to be considered evaluable regarding dose modification decisions.

Transition from Phase 1 to Phase 2

Once the MTD is determined, enrollment into the dose escalation portion of the study will end. The dose level for the Phase 2 cohort will be communicated to all participating investigators prior to the start of Phase 2 enrollment. Subjects from the dose escalation portion of the study are not eligible for enrollment in the Phase 2 portion of the study.

Dosing Schema for Initial Phase 2

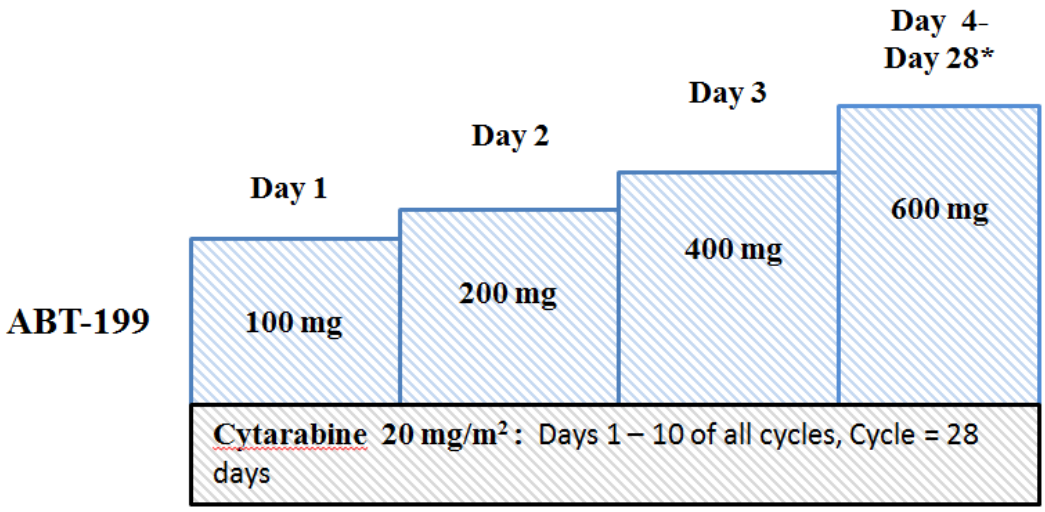
Figure 9. Dose Level 1 Cycle 1 (Starting Dose Level)



* Cycle = 28 days. Venetoclax dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 600 mg.

Dosing Schema for Phase 2 Cohort C

Figure 10. Phase 2 Cohort C**



* Cycle = 28 days. Venetoclax dose will be administered at the designated cohort dose of 600 mg on Day 4 – Day 28 of Cycle 1 and on Day 1 – Day 28 for all cycles starting Cycle 2.

** Applies to subjects enrolled in Amendment 2.

Dosing Schedule Overview – Venetoclax – Initial Phase 2 Portion and Phase 2 Cohort C

Once the MTD is declared, and the RPTD determined, a cohort of up to approximately 50 – 100 additional eligible subjects will be enrolled at the RPTD in order to further define the toxicity profile and to estimate the efficacy of the combination.

Subjects enrolled in the initial Phase 2 portion will receive the RPTD of venetoclax that will be administered orally once daily (QD) on Days 2 through 28 of Cycle 1 of the 28-day cycle. Beginning with Cycle 2, venetoclax will be administered Days 1 through 28 of each 28-day cycle. Cytarabine 20 mg/m^2/QD will be administered on Days 1 – 10 of each cycle.

Subjects enrolled in Phase 2 Cohort C will receive venetoclax on Days 1 through 28 of each 28-day cycle, including Cycle 1. Cytarabine 20 mg/m^2/QD will be administered on Days 1 – 10 of each cycle.

Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast. The dose should be administered at approximately the same time each day. On days the subject is given LDC, venetoclax should be given prior to LDC. The regimen is designed to escalate the dose of venetoclax in combination with LDC rapidly toward the target dose to optimize the opportunity for achieving a response and enable close subject monitoring. The dosing regimen will also enable interruptions, reductions (if necessary) and a slower intra-subject dose escalation if rapid tumor lysis or other toxicities are observed.

The initial period, approximately one week, of therapy until the target dose of venetoclax is achieved is considered the venetoclax ramp-up period (e.g., Day 1 through Day 4 of Cycle 1 in Phase 2 Cohort C).

Dose modifications of venetoclax in the ramp-up period may be implemented for individual subject(s) at risk for TLS or any new adverse events > Grade 2. Dose reductions must follow original dosing schema. If the subject requires dose reductions or dose holds during the venetoclax ramp-up period, a discussion with the AbbVie medical monitor is required.

To mitigate the potential risk of TLS,[36] subjects will receive TLS prophylaxis prior to any venetoclax dose escalation in combination with LDC. Subjects will be hospitalized during the ramp-up period, Day –1 through 24 hours post highest cohort dose (e.g., Day –1 through Day 5 of Cycle 1 in Cohort C). Tumor lysis syndrome prophylaxis will be initiated in all subjects starting at least the day prior to the first dose of venetoclax. Refer to Section 6.1.8.2, Management of Tumor Lysis Syndrome, for the details on TLS prophylaxis, Appendix E – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for procedures to follow, and Appendix H for information regarding how to recognize laboratory and clinical TLS.

If a subject develops any laboratory changes suggestive of TLS within the first 24 hours after either the first dose or during dose escalation, venetoclax dose escalation should be withheld or the dose should be reduced. Dose reductions and dose holds during the ramp-up period require notification of the AbbVie medical monitor as do any occurrence of clinical TLS.

Option to Continue Venetoclax Treatment

Subjects enrolled in either Phase 1 or Phase 2 portion may discontinue LDC but may continue receiving venetoclax once daily as monotherapy for up to 4 years following the first dose of the last subject enrolled on study provided they complete LDC dosing, continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation (Section 5.4.1). Additionally, should a subject discontinue venetoclax or LDC due to reasons other than progression or unacceptable toxicity, subjects may be allowed to subsequently resume treatment with venetoclax and/or LDC upon discussion between the AbbVie medical monitor and the investigator.

For subjects that continue to derive benefit after this 4 year period, AbbVie will work with the investigator to evaluate options for continuation of venetoclax. Approval of a subject to transition to monotherapy and dose/schedule determination will also be based on review of other laboratory parameters and discussion between the AbbVie medical monitor and the investigator.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 21 days prior to initial study drug administration. 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 the first day of therapy:

1. Subject must be ≥ 65 years of age in Phase 1 and initial Phase 2. Subjects enrolled in Phase 2 Cohort C must be either:
   - ≥ 75 years of age;
     OR
   - ≥ 60 to 74 years will be eligible if the subject has at least one of the following co-morbidities, which make the subject unfit for intensive chemotherapy:
     - 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 (calculated by Cockcroft-Gault formula)
     - Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN
     - Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the study medical monitor before study enrollment
2. Subject must have a projected life expectancy of at least 12 weeks.
3. Subject must have histological confirmation of AML and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity or other factors.
4. Subject must have received no prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment. **Note:** Subject may have been treated for prior Myelodysplastic Syndrome.
5. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status:
   - of 0 to 2 for subjects ≥ 75 years of age
   - of 0 to 3 for subjects ≥ 60 to 74 years of age, if 0 – 1 another co-morbidity is required to make subject eligible.

6. Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula:

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

Or, if serum creatinine is in µmol/L:

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

Note: Investigators should consider measuring a 24-hour creatinine clearance for subjects who are morbidly obese, have fluctuating renal function, or who in the investigator's clinical judgment may yield a more accurate clearance when measured than when calculated.

7. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN)*
   - alanine aminotransferase (ALT) ≤ 2.5 × ULN*
   - bilirubin ≤ 1.5 × ULN for all subjects age 75 and older*
     - Subjects who are < 75 years of age must have a bilirubin of < 3.0 × ULN

* Unless considered due to leukemic organ involvement.

Note: Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN per discussion between the investigator and AbbVie medical monitor.

8. Male subjects must agree to refrain from unprotected sex and sperm donation from initial study drug administration until 180 days after the last dose of study drug.
9. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
10. If female, subject must be either:
    - Postmenopausal defined as no menses for 12 or more months without an alternative medical cause,

OR

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

Rationale for Inclusion Criteria

(1 – 7) To select the appropriate subject population for the evaluation

(8, 10) The impact of venetoclax on pregnancy is unknown

(9) In accordance with Harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will be eligible for study participation if he/she does not meet the following criteria within 21 days prior to the first day of therapy:

1. Subject has received treatment with cytarabine for a pre-existing myeloid disorder.
2. Subject has acute promyelocytic leukemia (French-American-British Class M3 AML).
3. Subject has known active CNS involvement with AML.
4. Subject has tested positive for HIV (due to potential drug-drug interactions between antiretroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may potentially increase the risk of opportunistic infections). **Note:** HIV testing is not required.
5. Subject has received the following **within 7 days** prior to the initiation of study treatment:
   - Strong and moderate CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John's wort (see Appendix C for examples).
6. This criterion has been removed.

7. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit **within 3 days** prior to the initiation of study treatment.
8. Subject has a cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain.
9. Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the investigator would adversely affect his/her participating in this study.
10. Subject has chronic respiratory disease that requires continuous oxygen use.
11. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration.
12. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Uncontrolled systemic infection requiring IV 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 breast or cervix uteri;
    - 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 is permitted to meet this criterion.

15. Subject is a candidate for a bone marrow or stem cell transplant within 12 weeks after study enrollment.
16. Subject has a history of myeloproliferative neoplasm (MPN) including polycythemia vera, myelofibrosis, essential thrombocythemia, or chronic myelogenous leukemia.

Rationale for Exclusion Criteria

(1 – 5, 13 – 16)	To select the appropriate subject population for the evaluation
(7 – 12)	For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary, from the Screening Visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic case report form (eCRF).

The AbbVie medical monitor identified in Section 6.1.6 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

General guidelines regarding excluded and cautionary medications are summarized in Table 1.

Table 1. Excluded and Cautionary Medications and Dietary Restrictions (See Appendix C for Examples of the Medications)

Excluded Foods During Ramp-Up and Throughout Study
• Grapefruit and grapefruit products • Seville Oranges (including marmalade containing Seville oranges) • Starfruit
Excluded Medications During Venetoclax Ramp-Up Phase and Throughout Study:
• **Strong CYP3A inducers**
Cautionary
• **Moderate or Strong CYP3A inhibitors** - Consider therapeutic alternative medications whenever appropriate. -If a subject requires use of these medications, limit the duration to the minimal duration medically required and reduce the venetoclax dose by at least 2-fold for moderate inhibitors and by at least 8-fold for strong inhibitors (see Table 2). After discontinuation of a moderate or strong CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial target dose. • **Moderate CYP3A inducers** -Exclude during the ramp-up phase and consider alternative medications. -If a subject requires use of these medications at the cohort designated dose, use with caution and contact the AbbVie medical monitor for guidance.
• **Warfarin*** • **P-gp substrates** • **BCRP substrates** • **OATP1B1/1B3 substrates** • **P-gp inhibitors** • **BCRP inhibitors**

* Closely monitor the international normalized ratio (INR).

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

Assigned Venetoclax Dose	Dose if Co-Administered with a Moderate CYP3A Inhibitor	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

A sample list of excluded medications and cautionary medications that fall into the categories within Section 5.2.3 can be found in Appendix C. It is not possible to produce a 100% exhaustive list of medications that fall into these categories, so if in question, please notify the AbbVie medical monitor and discuss the investigator's use of these medications and the investigator's plans to medically monitor the potential study subject under consideration.

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

5.3.1 Safety and Efficacy Measurements Assessed and Flow Chart

This study is designed to assess pharmacokinetic, pharmacodynamic, pharmacogenetic, efficacy, and safety data. Study procedures described in this protocol are summarized in Table 3.

Table 3. Study Activities (Phases 1 and 2 {Including Cohort C})

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Informed Consent	X[b]											
Medical/Oncology History Assessment	X		X[c]									
Cytogenetic Assessment[d]	X											
AE/Concomitant Medication Assessment[v]	X	X	X	X	X	X	X	X		X	X	
Tumor Lysis Syndrome Prophylaxis[e]		X	X	X	X	X	X					
Physical Exam (including weight)[f,v]	X[h]		X				X[i]	X[j]		X[j]	X[j]	
Vital Signs[f,v]	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status[f,v]	X		X					X		X	X	
Hematology[f,g,v]	X		X	X	X	X	X	X		X	X	X
Chemistry[e,f,v]	X[k]		X	X	X	X	X	X[k]		X[k]	X	
Coagulation[f,v]	X		X					X[l]		X	X	
Urinalysis[f,v]	X											
12-lead ECG[m,v]	X									X[o]		
MUGA (preferred)/2D Echocardiogram w/Doppler[m,p]	X											
Clinical Disease Progression Assessment									X	X		X
Bone Marrow Aspirate and Biopsy for Response Assessment	X[q]								X[r]	X		

Table 3. Study Activities (Phases 1 and 2 {Including Cohort C}) (Continued)

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Dispense Subject Calendar/Diary							X[s]	X				
Collect Study Drug and Subject Calendar/Diary[w]								X		X		
Survival Assessments[t]												X

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

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

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

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

d. Cytogenetic testing should be performed if not completed within 3 months prior to Screening.

e. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.1.8.2 Management of Tumor Lysis Syndrome (TLS) and Appendix E – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

f. For all study visits beginning with Cycle 3, physical examination, vital signs, ECOG performance status, hematology, chemistry, coagulation and urinalysis may be performed within 72 hours before Day 1 of treatment for that cycle.

g. Hematology will be performed weekly (at the minimum, hematology should be performed weekly during Cycle 1 and Cycle 2).

h. Height will be measured only at Screening.

i. Only applies to Dose Level (–)2. Subjects should have Physical exam upon discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated cohort dose. Also, Dose Levels 4 and 5 would stay in hospital until Day 8, needing a Physical exam at Day 8.

j. A symptom-directed physical exam may be performed.

k. Amylase and lipase are required at Screening, Cycle 2 Day 1, and the Final Visit.

Table 3. Study Activities (Phases 1 and 2 {Including Cohort C}) (Continued)

l. Coagulation to be performed on Cycle 2 Day 1 and not required subsequently unless clinically indicated.

m. Additional ECGs and a MUGAs/Echos should be performed as clinically necessary per the discretion of the investigator.

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

o. May be obtained ± 2 days of the visit.

p. Should be performed provided that such assessment would not inappropriately delay therapy per discretion of the investigator.

q. Historical bone marrow aspirates at screening will not be sufficient; a bone marrow aspirate must be performed for study entry to collect mandatory biomarker assessments.

r. May be performed ± 7 days of the anticipated Day 1 of the subsequent cycle visit, for visits beginning with Cycle 2 Day 1. Assessments beginning with Cycle 4 Day 1 should be performed and resulted prior to the dispensation of the next cycle of drug.

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

t. Survival assessments should be performed every 12 weeks (± 1 week) for 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

u. Post Treatment visits will be performed every 12 weeks (± 1 week) for up to 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired. Survival assessments will be performed every 12 weeks, beginning when subjects develop progressive disease, for 1 year after the last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

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

Note: Refer to Table 4 for treatment schedule.

Table 4. Treatment Schedule (Phase 1 and Initial Phase 2)

	Cycle 1[a]			Cycle 2[a] and Subsequent Cycles[a]		Continuation of Venetoclax Monotherapy Only[a,b]
	Day 1	**Day 2 – 10**	**Days 11 – 28**	**Days 1 – 10**	**Days 11 – 28**	**Days 1 – 28**
Venetoclax		X	X	X	X	X
Cytarabine	X	X		X		

a. Cycle length = 28 Days.

b. Subjects enrolled in either Phase 1 or Phase 2 portions may discontinue LDC but continue receiving venetoclax once daily as monotherapy for up to 4 years following the first dose of the last subject enrolled on study provided they continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation (Section 5.4.1).

Table 5. Treatment Schedule (Phase 2 Cohort C)

	All Cycles[a]	
	Day 1 – 10	**Days 11 – 28**
Venetoclax[b]	X	X
Cytarabine[b]	X	

a. Cycle length = 28 Days.

b. Subjects enrolled in the Cohort C portion may discontinue LDC but continue receiving venetoclax once daily as monotherapy for up to 4 years following the first dose of the last subject enrolled on study provided they continue to tolerate venetoclax, have no evidence of disease progression, and do not meet any criteria for subject discontinuation (Section 5.4.1). Additionally, should a subject discontinue venetoclax or LDC due to reasons other than progression or unacceptable toxicity, subjects may be allowed to subsequently resume treatment with venetoclax and/or LDC upon discussion between the AbbVie medical monitor and the investigator.

Table 6. Schedule of Biomarker/Pharmacogenetic/Pharmacodynamic Sample Collection (Phase 1 and 2 {Including Cohort C})

Sample Collections	Screening/ Cycle 1 Day 1[a]	Cycle 2 Day 1	Cycle 4 Day 1, Every 3 Cycles Thereafter, and as Clinically Indicated (± 7 Days)[c]	Final Visit/Time of Relapse	Comments
Mandatory Samples					
Bone Marrow Aspirate for Disease Assessment (MRD)[b]	X	X	X	X	1 – 2 mL bone marrow aspirate
Bone Marrow Aspirate for Mutational Profiling	X			X	1 – 2 mL bone marrow aspirate
Bone Marrow Aspirate for Ex Vivo sensitivity and translational research	X	X		X	3 mL bone marrow aspirate
Bone Marrow Aspirate for Bcl-2 Family Protein Analysis	X	X		X	1 mL bone marrow aspirate
Blood for Mutational Profiling	X			X	2.5 mL blood
Blood for Plasma	X	X	X[f]	X	4[d] mL blood OR 12[d] mL blood
Blood for Serum	X	X	X[f]	X	3.5 mL blood
Blood for Ex Vivo Sensitivity and Translational Research	X	X		X	8 mL blood
Blood for Bcl-2 Family Protein Analysis	X	X		X	2 mL blood
Pharmacogenetics	X[e]		X[e]	X	4 mL blood
Bone Marrow Core Biopsy for BCL-2 IHC	X			X	4 – 10 slides

a. Sample may be performed at Screening or Cycle 1 Day 1 prior to dosing.

Table 6. Schedule of Biomarker/Pharmacogenetic/Pharmacodynamic Sample Collection (Phase 1 and 2 {Including Cohort C}) (Continued)

b. This sample should be taken from the first bone marrow aspirate draw.

c. Only until 2 consecutive samples show a CR.

d. Blood for Plasma: 4 mL blood at Screening/Cycle 1 Day 1, Cycle 2 Day 1, and Final Visit/Time of Relapse; 12 mL blood at Cycle 4 Day 1 and every 3 Cycles Thereafter.

e. Pharmacogenetics should be collected on Cycle 1 Day 1, Cycle 4 Day 1, and Final Visit.

f. Subjects who achieve 2 consecutive CR assessments and no longer require a bone marrow aspirate/biopsy for disease assessment, will still have plasma and serum collections at every 3 cycles thereafter.

Table 7. Schedule of Blood Collection for Venetoclax and Cytarabine Assay (Pharmacokinetic Sampling) – Phase 1 Only

	Cycle 1				Cycle 2, Cycle 4 and Every 3 Cycles Thereafter (± 7 Days)
Procedures	**Day 1**	**Days 2 – 6**	**Day 10**	**Day 18**	**Day 1**
Venetoclax		8 hours post-dose[a]	0 (pre-dose), 2, 4, 6, 8 and 24 hours post-dose	0 (pre-dose), 2, 4, 6, 8 and 24 hours post-dose	0-hour (pre-dose)
Cytarabine[b]	0 hour (pre-dose) and at 15 and 30 min and 1, 3, 6 hours following the SC dose		0 hour (pre-dose) at and 15 and 30 min and 1, 3, 6 hours following the SC dose		

a. The 8-hour post-dose PK sample on Days 2 – 6 of Cycle 1 will be collected if venetoclax is initiated or escalated to a new dose level. If there is a delay in the escalation step, the 8-hour post-dose PK sample will be delayed accordingly. The PK collection performed 8 hours post-dose after each dose escalation may be taken up to 1 hour prior or up to 20 minutes after the scheduled time to allow for processing, if necessary. If the Day 2 – 6 PK draws fall on a weekend, collection is optional but strongly encouraged.

b. These samples are not optional, however, due to the complexity of the sample collection and processing for the cytarabine PK, AbbVie recognizes some centers may not have the capability to perform the PK samples. In those instances, the cytarabine PK samples will not be collected. Sites with these capabilities will be predetermined.

Table 8. Schedule of Blood Collection for Venetoclax Assay (Pharmacokinetic Sampling) – Initial Phase 2 Only

Procedures	**Cycle 1 Day 2**	**Cycle 2 Day 1**	**Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)**
Venetoclax	0 hour (pre-dose)	0 hour (pre-dose)	0 hour (pre-dose)

Table 9. Schedule of Blood Collection for Venetoclax Assay (Pharmacokinetic Sampling) – Phase 2 Cohort C

Procedures	Cycle 2 Day 1	Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)
Venetoclax	0 hour (pre-dose)	0 hour (pre-dose)

5.3.1.1 Study Procedures

All study procedures outlined in Table 3 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 due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow Table 3 on how to proceed.

Procedures performed at Screening will serve as baseline, unless repeated on Cycle 1 Day 1 prior to dosing, in which case the latter will serve as baseline.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in this study. The IEC/IRB approved informed consent 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. 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 and updated prior to the first dose of study drug on Cycle 1 Day 1:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use

- Detailed oncology history including:
  - Histology
  - Date of diagnosis of AML
  - Any surgical procedures
  - Treatments administered (including dates and type of modality)
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken.

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

Adverse Event and Prior/Concomitant Medication Assessment

On Cycle 1 Day 1, any events observed from the time of signing of the informed consent but prior to initial study drug administration will be recorded as a serious or nonserious 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 changes from baseline will be recorded on the adverse event eCRF.

All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of study drug.

Physical Examination

A complete physical examination (PE) will be performed at Screening. A symptom-directed PE including weight changes will be performed at visits as outlined in Table 3. Height will be measured only at Screening. The subject should wear lightweight clothing and no shoes during weighing.

Physical exams may be performed up to 72 hours prior to or after a scheduled study visit beginning with Cycle 3, if necessary. If the Screening PE is performed within 7 days of Cycle 1 Day 1, PE is not required on Cycle 1 Day 1, unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Vital Signs

Body temperature (oral), weight, blood pressure, pulse, and respiratory rate will be measured at the study visits as outlined in Table 3. Vital Signs may be performed up to 72 hours prior to or after a scheduled study visit beginning with Cycle 3, if necessary.

Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, weight, blood pressure, vitals and respiratory rate measurements may be performed by the subject or caregiver as needed.

ECOG Performance Status

The ECOG performance status[37] will be assessed at the study visits outlined in Table 3 as follows:

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 may be assessed up to 72 hours prior to or after a scheduled study visit beginning with Cycle 3, if necessary.

12-Lead Electrocardiogram (ECG)

A single 12-lead resting ECG will be obtained at Screening, Final Visit, and as clinically needed. The Final Visit ECG may be obtained within ± 2 days of the visit.

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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

ECG Safety Review

Each ECG will be printed and 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 decision on whether a subject will be discontinued 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 the ECGs will be entered into the electronic case report form (eCRF). If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval measurement will be documented in the eCRF only if a "prolonged QT" is observed. Correction by the Fridericia formula (QTcF) is preferred; however, correction by other methods may be acceptable based on discussion with the AbbVie medical monitor. The original ECG tracing will be retained as source documentation in the subject's records at the study site.

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

Assessment of ejection fraction will be made at Screening by either a MUGA (preferred method) or 2D echocardiogram with Doppler provided that such assessment would not inappropriately delay therapy per discretion of the investigator. Subsequent evaluation will be made as clinically indicated for subjects who develop signs of cardiac compromise. It is preferred that the same method of assessment is used for a given subject.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at Screening, at Cycle 2 Day 1, Cycle 4 Day 1, and every 3 cycles thereafter for response assessment until two successive bone marrow biopsies demonstrate CR then will be repeated if clinical evidence for recurrence occurs. Historical bone marrow aspirates at screening will not be sufficient, a bone marrow aspirate and biopsy must be performed for study entry to collect mandatory biomarker assessments. 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 status may be determined, based on the phenotypic markers

detected in the screening sample. Bone marrow aspirates and/or biopsies performed as standard of care throughout the study should also be captured on an eCRF.

Note: For all study visits after Screening, bone marrow aspirates and/or biopsies may be performed within 7 days of the anticipated Day 1 visit of the subsequent cycle. Bone marrow aspirates and/or biopsies should be performed and resulted prior to drug dispensation beginning with Cycle 4 Day 1 visit.

A sufficient bone marrow aspirate (biopsy) must be collected for clinical assessment and predictive biomarker assessments.

Bone marrow aspirates and biopsies performed as standard of care throughout the study, typically because the investigator has suspicion for improved response or progression, should also acquire bone marrow aspirate for MRD detection and blood for serum and blood for mutational profiling (per Table 6) and also be captured on an eCRF.

Due to differences in standard of care bone marrow core biopsy collection and analyses procedures amongst countries and individual sites, the core biopsy collection will be considered an optional procedure for subjects enrolled at sites where aspirate evaluation with cytometric and/or molecular diagnostics is considered standard of care. The aspirate samples should be collected for all subjects.

A sufficient bone marrow aspirate and/or biopsy must be collected for clinical assessment (pathology) performed by local laboratory as well as for shipment of a portion to AbbVie (or designee) for biomarker analyses as described in Section 5.3.1.5. The biopsy collection for biomarker analyses is only applicable to countries/individual sites where the procedure is performed as part of standard of care.

Clinical Laboratory Tests

Samples will be obtained at all study visits as outlined in Table 3 for, at minimum, the clinical laboratory tests outlined in Table 10.

Local laboratories will be utilized to process and provide results for the clinical laboratory tests. The principal investigator or sub-investigator, if delegated, will review, initial, and date all laboratory results. The laboratory test results will be collected on an eCRF. Laboratory normal ranges will be provided to the AbbVie Clinical Team, as requested.

All local laboratory measurements will be entered on the eCRF within **5 days** of report availability, unless the report reflects a Grade 3 or 4 test result in which case the results will be entered immediately on the eCRF **within 24 hours** of report availability.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

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

Table 10. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Blasts	Blood urea nitrogen (BUN) 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[a] Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Amylase (Screening, Cycle 2 Day 1 and Final Visit only) Lipase (Screening, Cycle 2 Day 1 and Final Visit only)	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination (as indicated)
Coagulation		
Prothrombin time (PT) Activated partial thromboplastin time (aPTT)		

a. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation.

Uric acid must be analyzed in plasma. Blood must be collected into pre-chilled tubes containing heparin anticoagulant. **Immediately immerse plasma samples for uric acid measurement in an ice water bath.** Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

For any laboratory test value outside the reference range that the investigator considers 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 6.1.8 regarding toxicity management), and/or if the investigator considers them to be adverse event.

Chemistry and Hematology

Chemistry and hematology will be collected at the following time points and as outlined in Table 3.

Starting with Cycle 3 Day 1, chemistry and hematology may be performed within 72 hours before or after the scheduled visit. However, there is no 72-hour window permitted for post-dose chemistry and hematology samples collected during Cycle 1 Day 1, Cycle 2 Day 1, or at the time of any dose escalation. Amylase and lipase are only required at Screening, Cycle 2 Day 1, and at the Final Visit. Refer to Section 6.1.8.2. If subject is taking rasburicase, the special sample handling procedure outlined in Table 10 must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase.

Refer to Section 6.1.8.2, Prophylaxis and Management of Tumor Lysis Syndrome, for monitoring required. If laboratory abnormalities consistent with TLS are observed, see Appendix E, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for procedures to follow.

Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) samples will be collected as outlined in Table 3 and as needed throughout the study. Beginning at Cycle 3, coagulation may be performed within 72 hours before or after the scheduled visit.

Urinalysis

Urinalysis samples will be collected as outlined in Table 3 and as needed throughout the study. Beginning at Cycle 3, urinalysis may be performed within 72 hours before or after the scheduled visit.

Clinical Disease Progression Assessment

Assessment of clinical disease progression will be made at visits as outlined in Table 3 and as deemed appropriate by the investigator at an interval of no greater than every 3 cycles. Subjects exhibiting disease progression should be discontinued from the study per Section 5.4.

Cytogenetic Assessment

Cytogenetic assessment will be done locally within 3 months prior to beginning therapy.

Molecular Markers

Profiling of common genetic abnormalities in AML may be explored at screening on a mandatory screening bone marrow sample and sent to a central laboratory designated by AbbVie. Although this is not a complete list, the following genes are commonly altered in AML subjects:

- fms-related tyrosine kinase-3 (FLT3), nucleophosmin1 (NPM1), CCAAT/enhancer-binding protein alpha (CEBPA), Isocitrate Dehydrogenase 1 (IDH1), Isocitrate Dehydrogenase 2 (IDH2), ten-eleven translocation 2, (TET2) and DNA methyltransferase 3A(DNMT3A).

Tumor Lysis Syndrome Prophylaxis

Tumor lysis syndrome prophylaxis will be initiated in all subjects starting at least the day before the first dose of venetoclax and continued through 24 hours post the first dose at the highest administered dose level of venetoclax per the guidelines in Section 6.1.8.2.

Subject Calendars/Diaries

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

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

Enrollment and Assignment of Subject Numbers

An Interactive Response Technology (IRT) system will be utilized to register subjects. Once the subject has signed the informed consent the site will obtain a screening (subject) number via the IRT system. Once the screening number is assigned, if the subject is not enrolled into the study, the reason for screen failure will be documented in the source document and will be captured in the eCRF.

The results of all screening evaluations must be within clinically acceptable limits, upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable.

Subjects who complete all screening procedures and meet the eligibility criteria in Section 5.2.1 and none of the exclusion criteria in Section 5.2.2 will proceed to enrollment.

Post-Treatment Follow-Up Visit(s)

For subjects who discontinue study treatment for reasons other than disease progression, the following post-treatment assessments will be performed every 12 weeks (± 1 week) until criteria are met for discontinuation from the study (e.g., disease progression, death or a subject's refusal of the Post-Treatment visits) for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired:

- Hematology
- Disease Assessment

Survival Assessment(s)

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

5.3.1.2 Confinement

Subjects will be hospitalized during dose escalation of venetoclax. Confinement is recommended to begin by Study Day –1 and must occur by at least Day 1 through at least 24 hours after completion of the ramp-up period for subjects in both Phase 1 and Phase 2 including Cohort C.

5.3.1.3 Meals and Dietary Requirements

Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast.

Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit 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.

5.3.1.4 Blood Samples for Pharmacogenetic Analysis

A 4 mL whole blood sample for DNA isolation will be collected on Cycle 1 Day 1, Cycle 4 Day 1, and the Final Visit. The sample collection tubes will minimally be labeled with "PG-DNA," protocol number, visit, and subject number. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) continues but no longer than 20 years. Sample collection and shipping information are detailed in the most current version of Study M14-387 Laboratory Manual.

5.3.1.5 Pharmacodynamic and Predictive Biomarker Testing

Blood Collections

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M14-387 Laboratory Manual.

Blood Collection for Mutational Profiling:

Approximately 2.5 mL for blood will be collected prior to dose at:

- Screening (preferred) or prior to the first dose of study drug
- Final Visit/Time of Relapse

Blood Collection for Plasma

Approximately 4 mL of blood or 12 mL of blood will be collected prior to dose at

- Screening (preferred) or prior to the first dose of study drug (4 mL blood)

- Cycle 2 Day 1 (4 mL blood)
- Response assessments:

  Cycle 4 Day 1, and every 3 cycles thereafter (12 mL blood)

  Subjects who achieve 2 consecutive CR assessments and no longer require a bone marrow aspirate/biopsy for disease assessment, will still have plasma and serum collections at every 3 cycles thereafter.
- Final Visit/Time of Relapse (4 mL blood)

Blood Collection for Serum

Approximately 3.5 mL of blood will be collected prior to dose at

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Response assessments:

  Cycle 4 Day 1, and every 3 cycles thereafter

  Subjects who achieve 2 consecutive CR assessments and no longer require a bone marrow aspirate/biopsy for disease assessment, will still have plasma and serum collections at every 3 cycles thereafter.
- Final Visit/Time of Relapse

Blood Collection for Ex Vivo Sensitivity and Translational Research (e.g., mutational analysis, BH3 profiling):

Approximately 8 mL of blood will be collected prior to dose at:

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Final Visit/Time of Relapse

Blood Collection for Bcl-2 Family Protein Analysis

Approximately 2 ml of blood will be collected prior to dose at:

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Final Visit/Time of Relapse

Bone Marrow Aspirate and Biopsy Collections

Bone marrow aspirates should be drawn into appropriately labeled tubes in conjunction with the clinical assessments. A portion of the aspirate must be processed according to the institutional standard procedures for diagnostic evaluation; however, approximately 6 to 8 mL of the bone marrow aspirate should be collected for biomarker assessments. Subjects, who achieve 2 consecutive CR assessments and no longer require a bone marrow aspirate/biopsy for disease assessment, will also not require bone marrow aspirates for biomarker collections. Detailed processing will be as outlined in the most current version of the Study M14-387 Laboratory Manual for the following:

Minimal Residual Disease Assessment

Minimal Residual Disease Assessment aspirate samples will be collected, processed and shipped to the central laboratory per the most current version of the Study M14-387 Laboratory Manual.

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

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Response assessments: Cycle 4 Day 1, and every 3 cycles thereafter
- Final Visit/Time of Relapse

Mutational Profiling

Mutational Profiling will be collected at:

- Screening (preferred) or prior to the first dose of study drug
- Final Visit/Time of Relapse

Bcl-2 Family Protein Analysis

Bcl-2 Family Protein Analysis will be collected at:

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Final Visit/Time of Relapse

Ex vivo sensitivity and Translational Research (e.g., BH3 profiling)

Ex vivo sensitivity and Translational research will be collected at:

- Screening (preferred) or prior to the first dose of study drug
- Cycle 2 Day 1
- Final Visit/Time of Relapse

Bone Marrow Core Biopsy for Bcl-2 IHC

A portion of the core biopsy (applicable only to counties/individual sites were this procedure is included as standard of care) must be processed for according to the institutional standard procedures for diagnostic evaluation: however, if tissue remains approximately 4 to 10 slides from the biopsy should be collected for immunohistochemistry analysis at:

- Screening (preferred) or prior to the first dose of study drug
- Final Visit/Time of Relapse

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

The timing of PK blood collections will take priority over all other scheduled study activities except for dosing. The order of blood collections will be maintained to the minute such that the time intervals relative to the preceding dosing will be the same for all

subjects. The date and time of each blood sample collection will be recorded to the nearest minute on the source documents.

Blood Samples for Venetoclax Assay

Blood samples (3 mL) for venetoclax (and possible metabolite[s]) assay will be collected by central venous catheter into evacuated potassium (K_2) EDTA tubes at the following times:

Phase 1 Cohorts

- Cycle 1 Day 2: 8 hours post-dose
- Cycle 1 Days 3 – 6 or 7: 8 hours post-dose (if escalation to a new dose level)
- Cycle 1 Day 10: 0 hour (pre-dose) and at 2, 4, 6, 8 and 24 hours post-dose
- Cycle 1 Day 18: 0 hour (pre-dose) and at 2, 4, 6, 8 and 24 hours post-dose
- Cycle 2 Day 1, Cycle 4 Day 1, and every 3 cycles thereafter (± 7 Days): 0 hour (pre-dose)

Initial Phase 2 Cohort

- Cycle 1 Day 2, Cycle 2 Day 1, Cycle 4 Day 1, and every 3 cycles thereafter (± 7 Days): 0 hour (pre-dose)

Phase 2 Cohort C

- Cycle 2 Day 1, Cycle 4 Day 1, and every 3 cycles thereafter (± 7 Days): 0 hour (pre-dose)

A total of approximately 17 blood samples (51 mL) will be collected per subject during Cycle 1 in Phase 1 portion. For a schedule of the blood collection for venetoclax assay, refer to Table 7 and Table 8. All 0 hour (pre-dose) samples are relative to the start of venetoclax administration. The PK collection performed 8 hours post-dose after each dose escalation may be taken up to 1 hour prior or up to 20 minutes after to allow for processing, if necessary.

The date and time (to the nearest minute) of each venetoclax dose and whether or not the venetoclax dose was taken within 30 minutes after the completion of a meal (preferably breakfast) will be recorded on the eCRF for each scheduled venetoclax PK day and for the 2 days prior to each scheduled venetoclax PK day (if applicable). Sites will ensure all information is captured through source documents (site or subject calendar/diary provided by AbbVie).

Blood Samples for Cytarabine Assay

Blood samples (4 mL) for cytarabine assay will be collected by central venous catheter in the Phase 1 cohorts at the following times:

- Day 1 and Day 10 of Cycle 1: 0 hour (pre-dose) and at 15 and 30 minutes and 1, 3, 6 hours following the SC dose.

For a schedule of the blood collection for cytarabine assay, refer to Table 7.

The start time of each cytarabine SC injection will be recorded to the nearest minute on the eCRF as applicable.

A total of 12 blood samples (72 mL) for cytarabine concentration determination are planned to be collected per subject.

The necessary anticoagulant and sample pre-treatment will be provided in the lab manual for the study. These samples are not optional, however, due to the expected complexity of the sample collection and processing for the cytarabine PK, AbbVie recognizes some centers may not have the capability to perform the PK samples. In those instances, the cytarabine PK samples will not be collected. Sites with these capabilities will be predetermined.

5.3.2.2 Handling/Processing of Samples

Blood Samples for Venetoclax PK Assay

Detailed sample collection and processing instructions for the venetoclax PK samples will be provided in the lab manual for this study.

Blood Samples for Cytarabine PK Assay

Detailed sample collection and processing instructions for the cytarabine PK samples will be provided in the lab manual for this study.

5.3.2.3 Disposition of Samples

The frozen plasma PK samples for venetoclax and cytarabine will be packed in dry ice sufficient to last during transport and shipped from the study site to the central lab according to instructions in the laboratory manual. An inventory of the samples included will accompany the package. The central lab will ship the samples to reference laboratories for analysis.

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

5.3.3 Efficacy Variables

Efficacy Assessments

Responses will be evaluated based on the revised guidelines by the International Working Group (IWG) for AML.[38] As a significant number of the subjects in this study might have antecedent hematologic illnesses, hematologic response will also be evaluated. Transfusion dependence is defined as having received ≥ 2 units of RBCs and or platelets

within 8 weeks prior to study treatment. Duration of Response will be measured from the time when all response criteria are first met until recurrent or progressive disease is documented.

Criteria for Evaluation is as follows:

- CR: Absolute neutrophil count $\geq 10^3/\mu L$, platelets $\geq 10^5/\mu L$, red cell transfusion independence, and bone marrow with < 5% blasts.
- CRi: bone marrow with < 5% blasts, and peripheral neutrophils of $<10^3/\mu L$ or platelets $< 10^5/\mu L$.
- 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 and/or bone marrow core sample. There should be no blasts with Auer rods or persistence of extramedullary disease. The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.
- RD: failure to achieve CR, CRi, PR; only including subjects surviving at least 7 days following completion of initial treatment cycle, with evidence of persistent leukemia by blood and/or bone marrow examination.
- PD: one or more of the following: ≥ 50% decrement from maximum response levels in neutrophils or platelets, a reduction in hemoglobin by at least 2 g/dL, or transfusion dependence,* not due to other toxicities and bone marrow blast ≥ 5%.

In addition to the response determination using the above IWG AML response criteria, each subject will also be evaluated for hematologic response and complete remission with partial hematologic recovery (CRh).

- HR: improvement in peripheral blood counts with all of the following: fewer absolute peripheral blood blasts than prior to initiating study treatment for subjects presenting with peripheral blood blasts, ANC ≥ 500 (cells/μL),

platelets $\geq 0.25 \times 10^5$ (platelets/μL), and no more than 2 units of packed red blood cells within a 28-day period.

- CRh: all of the following criteria are met: Bone marrow with < 5% blasts, peripheral neutrophils of $\geq 0.5 \times 10^3$/μL, and peripheral platelets $\geq 0.5 \times 10^5$/μL**

* Transfusion independence is defined as the absence of any RBC or platelet transfusion during any consecutive 8 weeks during the treatment period.[39]

** For a bone marrow sample collected before the last cycle of study treatment, the hematology lab results collected from the date of bone marrow sample collection up to 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.

Reporting of Results

All dosed subjects will be assessed for response to treatment based on the published guidelines. Assessments will be performed at Cycle 2 Day 1, Cycle 4 Day 1, and every 3 cycles thereafter for response assessment until two successive bone marrow samples document a CR. When additional bone marrow evaluations are routinely indicated for clinical management, additional collection of bone marrow aspirate and peripheral blood are strongly encouraged as these findings have the potential to define either remission status or potential progression of leukemia. NOTE: For subjects who achieve CR or CRi, MRD status may be determined.

Subjects will be assigned to one disease state for best IWG response assessment, achievement of protocol defined hematologic response, and minimal residual disease positivity at the time of the best response.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring and vital signs, physical examination, ECG and laboratory tests assessments.

5.3.5 Pharmacokinetic Variables

For the intensive PK days of venetoclax, values for the PK parameters including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) from 0 to the time of the last measurable concentration (AUC_t) and AUC over a 24-hour dose interval (AUC_{0-24}) will be determined using noncompartmental methods. For the intensive PK days of cytarabine, values for the PK parameters including C_{max}, T_{max}, half-life ($t_{1/2}$), AUC_t, AUC from 0 to the time of infinity (AUC_∞) and clearance (CL/F) will be determined using noncompartmental methods. Additional analyses may be performed if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced, and data analyzed for genetic factors contributing to the disease or to the subject's response to venetoclax (or other study treatment) in terms of PK, 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 pharmacogenetic analyses may not be reported with the study summary.

5.3.7 Pharmacodynamic Variables

Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of defining the relationship between drug concentration and disease status. Samples taken may be used for the assessment of specific biologic markers, including proteins and/or nucleic acids not currently known to be prognostic, in order to better understand the biology of AML and disease prognosis, to predict response to treatment

with venetoclax, or to assess venetoclax activity. Biospecimens collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study. These analyses are exploratory in nature and may not be conducted in GLP laboratories and may not be included in the clinical study report. The samples may also be used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) continues but no longer than 20 years.

Reduction in subject leukocytosis or blast counts may be evaluated as a measure of pharmacodynamics activity to venetoclax. Measurement of relevant nucleic acids and proteins (including but not limited to the Bcl-2 family members) in tumor cells in the blood, pre-treatment, and at time of disease progression, may be examined for putative stratification markers for correlation with efficacy.

For the study to be comprehensive, a determination of whether the cellular context influences response to this drug will need to be made; therefore both subject bone marrow and peripheral blood collections may be evaluated for a subset of the biomarker analyses which are planned. 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 subject populations (based on subject characteristics at baseline and relapse).

Venetoclax inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2. Preclinical studies have demonstrated a pattern of response to venetoclax based on the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of Mcl-1 and Bcl-X_L are generally predictive of response to this drug in vitro. The measurement of relevant DNA, RNA and proteins (including those in the Bcl-2 family and those related to AML disease biology) in leukemic blood and bone marrow as well as serum and protein may be examined pre-treatment, on therapy, and at the time of progression for putative stratification markers and correlation with efficacy. In addition, blood and bone marrow samples will be

collected and may be used to determine ex vivo sensitivity of leukemic cells by BH3 profiling and/or by treatment with venetoclax (IC_{50} values) to evaluate if response to venetoclax can be predicted in vitro. These methods may be further used along with subject cytogenetics and mutational profile to enrich for subjects likely to respond to venetoclax in the second portion of the study. Based on the ongoing assessment of data, the criteria for subject enrichment will be defined.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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;
- The subject requires more than two dose reductions, in two consecutive cycles, of venetoclax, in the absence of clinical benefit from the study treatment;
- The subject requires radiotherapy or alternate anti-neoplastic agents during the study period (with the exception of hydroxyurea [allowed in first month only]);
- The occurrence of an adverse event that precludes further investigational drug administration;
- Noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study and the primary reason will be recorded and a Final Visit and procedures listed in Table 3 will be performed as soon as possible after discontinuation from the study.

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.

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 any adverse event is achieved.

A separate 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.

Post-treatment assessment will be performed every 12 weeks (± 1 week) until discontinuation from the study (e.g., disease progression death or a subject's refusal of the Post-Treatment visits) for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

Additionally, in the event a subject withdraws from the study, PD and predictive samples stored for long term (up to 20 years) biomarker research will also be destroyed. In the event that destruction is not possible, they will no longer be linked to the subject. If the subject changes his/her mind, and the samples have already been tested, those results will still remain as part of the overall research data. In the event of a subject's death or loss of

competence, the samples and data will continue to be part of AbbVie's research, but will not be stored more than 20 years.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID 19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Refer to the Section 5.3.1.1, Study Procedures and Table 3 for details on how to handle study activities/procedures accordingly. Study drug interruptions due to COVID-19 restrictions should be captured in EDC.

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

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.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

Decisions to delay or interrupt any study treatment based on the current situation and any concern for active infection should be made by the treating investigator after considering the subject's current oncologic status and treatment tolerance, as well as their general medical condition. As a potentially serious infection, consideration for treatment interruption is advised. If needed, any questions can be discussed with the Therapeutic Area Medical Director (TAMD).

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be administered daily as follows:

Each dose of venetoclax will be taken with approximately 240 mL of water. Subjects will be trained to self-administer venetoclax orally QD within 30 minutes after the completion of a meal, preferably breakfast.

If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be taken and the second dose noted in the drug log. Otherwise, no replacement dose is to be taken. In cases where a dose of venetoclax is missed or forgotten, the subject should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

Low-dose cytarabine (20 mg/m^2) should be prepared per package insert and administered subcutaneously by a trained provider meeting local qualifications for administration of subcutaneous chemotherapy.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) venetoclax shipment can be made from the study site to the subject if allowed by local regulations. Cytarabine DTP are is not allowed by AbbVie. AbbVie will submit any required notifications to the regulatory authority as applicable.

Venetoclax may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of venetoclax is allowed by local regulations and the relevant ethics committee
- Venetoclax can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the venetoclax shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of venetoclax from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

5.5.2 Identity of Investigational Products

Information about the venetoclax and cytarabine formulations to be used in this study is presented in Table 11.

Table 11. Identity of Investigational Products

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax	N/A	10 mg Tablet	Oral	AbbVie
Venetoclax	N/A	50 mg Tablet	Oral	AbbVie
Venetoclax	N/A	100 mg Tablet	Oral	AbbVie
Cytarabine	generic	20 mg/mL solution for injection	SC	generic

AbbVie or designee will supply cytarabine.

5.5.2.1 Packaging and Labeling

The venetoclax tablets will be packaged in high density polyethylene (HDPE) plastic bottles. Each bottle will be labeled per local regulatory requirements. Cytarabine will be provided as one vial per carton. Each vial and carton will be labeled per local regulatory requirements.

5.5.2.2 Storage and Disposition of Study Drug

The venetoclax study drug must be stored at 15° to 25°C (59° to 77°F). Cytarabine must be stored at 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

There is no randomization schedule for this study. Subjects will be assigned at screening a unique subject number via IRT system beginning with 30101 for the Phase 1 portion of the study. For the Phase 2 portions of the study, subjects will be assigned at screening a unique consecutive subject number by an IRT system beginning with 30201.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. Venetoclax will be administered orally once daily (QD) on Days 2 through Day 28 of Cycle 1 (28-day cycle) for subjects enrolled into Phase 1 and the initial Phase 2 portion.

Venetoclax will administered orally once daily (QD) on Day 1 through Day 28 of Cycle 1 (28-day cycle) for subjects enrolled into Phase 2 Cohort C.

Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast.

5.5.5 Blinding

This is an open-label 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 of venetoclax to be dispensed to a subject during the study. Prior to each scheduled visit, site personnel must contact IRT for the next bottle number(s) for 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 as necessary, to the study coordinator at scheduled study visits. Compliance will be monitored and documented by the study coordinator on the appropriate form. The study coordinator 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 study drug) 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 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

Low-dose cytarabine is a commonly prescribed treatment within the United States for subjects who fulfill the entry criteria of this study. Venetoclax is undergoing testing in other clinical trials as a single-agent treatment for AML and in combination with other standard AML treatments. The ongoing single-agent study, Study M14-212, has

demonstrated that venetoclax has anti-leukemia activity for subjects with relapsed or refractory AML and therefore may be efficacious for subjects with previously untreated AML. This study consists of a Phase 1 portion to define the MTD and generate data to support a RPTD for the Phase 2 portion. The Phase 1 portion of the study is a dose escalation phase which will consist of up to 42 subjects who initiate therapy with venetoclax combined with cytarabine. In each cohort, a minimum of 3 and/or up to 6 subjects will be evaluated before making venetoclax designated cohort dose escalation decision. A subsequent Phase 2 portion will enroll approximately 50 subjects who will be administered venetoclax at the RPTD and schedule defined in the Phase 1 portion of the study. An additional Phase 2 cohort, Cohort C, will evaluate if the ORR for subjects enrolled with modified entry criteria and allowing additional supportive medications (strong CYP3A inhibitors) is substantially different than the ORR observed for subjects enrolled under the prior entry criteria in Phases 1 and 2. There are no direct control groups in this study although a recent historical control cohort of treatment naïve subjects age 65 and older with AML receiving LDC reported an 11% ORR utilizing the same response definitions.[30]

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Subjects who have histological confirmation of acute myelogenous leukemia who are treatment-naïve, greater than or equal to 60 years of age, and who are not eligible for standard induction therapy due to co-morbidity or other factors will be selected to participate in this study.

5.6.4 Selection of Doses in the Study

In the initial Phase 1 trial (Study M12-175) evaluating venetoclax monotherapy in subjects with CLL and NHL, the most significant toxicity was TLS in CLL subjects

during the initiation of dosing. Reductions in circulating CLL cells and electrolyte changes consistent with tumor lysis have been observed within 6 to 8 hours after initiation of therapy, a time consistent with the T_{max} for venetoclax. To minimize the risk of TLS[36] in Study M12-175, a dose titration scheme is being employed, starting at doses significantly lower than the final target dose. The response in CLL is dose-dependent, with incremental reductions in circulating CLL cells observed at the titration steps. Final target doses of up to 800 mg have been shown to be tolerable in subjects with CLL. Subjects with NHL have received target doses of 1200 mg without dose limiting toxicities.

Few DLTs for subjects at venetoclax target doses (≥ 600 mg) have been seen and include 2 events of neutropenia and 1 event of febrile neutropenia.

Preclinical studies evaluating the activity of venetoclax ex vivo in primary AML subject samples have shown sensitivities similar to those seen in primary CLL samples. Ex vivo sensitivity even greater than that in CLL cells has been observed in a small fraction of the primary AML cells with IC50 values < 1 nM.[8] Based on these data, rapid tumor lysis of AML may occur upon initiation of dosing with venetoclax. Therefore, a dose titration scheme based on that being used in CLL studies will be utilized in this study. The escalation steps are similar, but the timeline has been condensed due to more acute nature of AML versus CLL. No serious or nonserious AE of clinical TLS have been reported in the Phase 2 study of venetoclax monotherapy in AML. Phosphate and potassium laboratory changes have been observed and managed using the TLS electrolyte management guideline as described in Appendix E.

This combination regimen is designed to escalate the dose of venetoclax rapidly with LDC to optimize the opportunity for achieving a response and enable close subject monitoring. The dosing regimen will also enable interruptions and slower intra-subject dose escalations to the assigned target dose if rapid tumor lysis is observed. Based on the ex vivo testing of primary subject AML samples that has shown significant variability among subjects, it is expected that initial signs of tumor response will occur at different doses for different subjects. However, the Cycle 1 Day 2 dose and the final target dose

are anticipated to be the same for all subjects with modifications to the regimen permitted to respond to signals consistent with antitumor activity/tumor lysis.

Potential target daily doses of venetoclax are 200 mg, 400 mg, 600 mg, 800 mg, 1200 mg, 1600 mg and 2000 mg for dose levels (–)2 through 5 respectively. Based on potential dose limiting impurities, the dose of venetoclax for this protocol will not exceed 2000 mg/day.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.1.6). For adverse events, please refer to Sections 6.1 through 6.1.8.

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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 6.1.8 regarding toxicity management), and/or if the investigator considers them to be adverse events.

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 reported by a subject with onset or worsening from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug administration.

6.1.1.2 Serious Adverse Events

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

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

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. Deaths related to disease progression will not be recorded as serious adverse events (see Section 6.1.3.1).

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 (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention, etc.). Additional criteria for defining TLS are in Appendix H.

6.1.1.3 Adverse Events Commonly Associated with Acute Myelogenous Leukemia Study Population and/or Progression of Acute Myelogenous Leukemia

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

These events are listed in Appendix F (Adverse Events Commonly Associated with AML Study Population or Progression of AML).

These adverse events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of AML. Persistent cytopenias at the same CTCAE grade as at baseline are not to be reported as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the investigator had an identifiable cause other than the

underlying disease. However, all laboratory data should be entered regardless of whether an adverse event is reported.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, if an event commonly associated with AML or progression of AML meets seriousness criteria (as defined in Section 6.1.1.2) it must be reported to AbbVie within 24 hours of the site being made aware of the serious adverse event. For deaths related to disease progression, the date and cause of death will be recorded on the appropriate case report form, but the death will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

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 4.0).[40] If a reported adverse event increases in severity, the initial adverse event should be given final outcome date and a new adverse event must be reported to reflect the change in severity. The dates on the adverse events cannot overlap. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

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

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

6.1.3 Adverse Events Expected Due to Study Related Endpoints

6.1.3.1 Deaths

For this protocol, overall survival is an efficacy endpoint.

Deaths that occur during the protocol-specified adverse event reporting period (see Section 6.1.5) that are attributed by the investigator solely to progression of AML should be recorded only on the Study Completion and Death eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 6.1.6).

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 1 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.

6.1.3.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.4 Relationship to Study Drug

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

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

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.

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.

6.1.5 Adverse Event Collection Period

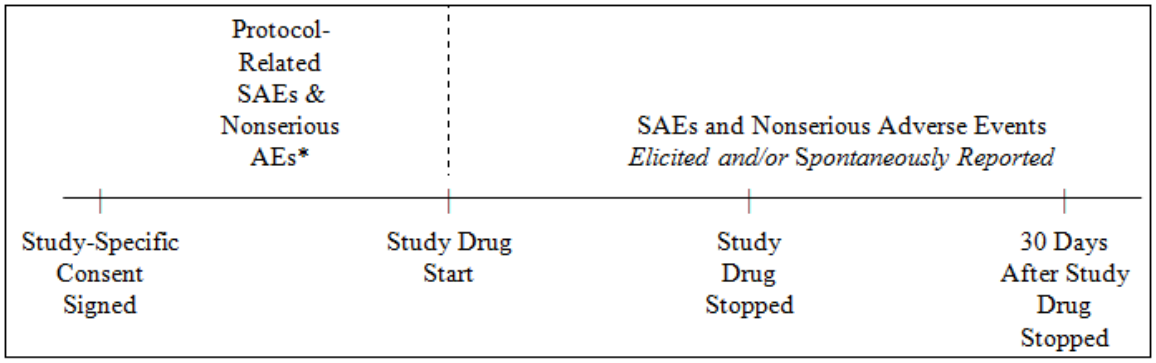
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study specific informed consent until study drug administration.

Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of study drug 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 solicited or spontaneously reported by the subject.

Adverse event information will be collected as shown in Figure 11.

Figure 11. Adverse Event Collection



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

6.1.6 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 the site or investigator being made aware of the serious adverse event.

FAX to: +1 (847) 938-0660
Email: PPDINDPharmacovigilance@abbvie.com

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

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

Safety Phone: (847) 935-2609
Safety Email: SafetyManagement_Oncology@abbvie.com

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

Primary Study Designated Physician:

[redacted]
Clinical Oncology
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Fax: [redacted]

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour **AbbVie Medical Escalation Hotline** where your call will be re-directed to a designated 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. The reference document used for SUSAR reporting in the EU

countries will be the most current version of the Investigator's Brochure or Summary of Product Characteristics (SmPC) for cytarabine.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

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

6.1.7 Pregnancy

Pregnancy in a study subject must be reported to an AbbVie representative (Section 6.1.6 or Section 7.0) within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects should be informed that contraceptive measures should be taken throughout the study and for 180 days after discontinuing study drug. Male subjects should be informed that contraceptive measures should be taken by their female partner. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.8 Toxicity Management

6.1.8.1 Definition – Dose Limiting Toxicity

Dose limiting toxicities (DLTs) for dose-escalation purposes will be determined during Cycle 1 (4 weeks) of study treatment. Adverse events that occur after the first cycle will also be evaluated by the investigator and the AbbVie medical monitor and may be considered as dose limiting.

Any of the following events, which cannot be attributed by the investigator to a clearly identifiable cause such as tumor progression, underlying illness, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 or 5 non-hematologic toxicity considered at least possibly related to the study drug, except those listed in Appendix F.
- Grade 4 or 5 pancytopenia with a hypocellular bone marrow and no greater than or equal to 5% marrow blasts lasting for 42 days or more.

Any DLT will require an interruption and possible discontinuation of venetoclax or LDC. Venetoclax and LDC therapy may be reintroduced at a reduced dose, if the toxicity grade returns to ≤ Grade 1 or to baseline if Grade 2 at study entry.

Any reduced dose level will be jointly defined by the investigator and the AbbVie medical monitor. The dose may be increased thereafter upon joint determination of the investigator and the AbbVie medical monitor. This dose is not to exceed the highest tolerated dose level. All decisions regarding continued dosing for individual subjects will

be medically managed by the investigator, per discussion with the AbbVie medical monitor, as appropriate. These decisions will be driven by the definition of DLTs as described above.

6.1.8.2 Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

There is a potential for TLS for patients with AML receiving induction therapy, especially for those with elevated pretreatment LDH levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk for TLS,[36] subjects will receive tumor lysis prophylaxis, including hydration (e.g., oral, intravenous) and treatment with an agent to reduce the uric acid level (e.g., allopurinol, rasburicase).[36,41]

TLS prophylaxis must be initiated in all such subjects prior to the first venetoclax dose or first new escalated dose.

Tumor Lysis Syndrome Prophylaxis and Management for Subjects Dose Escalated in Protocol Version 1 and Amendment 1

- Hospitalization recommended on Day –1 and mandated by Day 1 and for a minimum of 24 hours after any venetoclax dose escalation.
- Nephrology (or other acute dialysis service) should be available on each admission per institutional standards to ensure emergency dialysis is available.
- An agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 24 hours prior to venetoclax dosing. Treatment may need to be continued for up to 28 days based on the ongoing risk of TLS development. Subjects allergic to allopurinol must use another uric acid reducer starting at least 24 hours prior to venetoclax dosing or rasburicase on the day of treatment (prior to venetoclax dosing).
- Oral hydration (at least 1 to 2 liters) starting from at least 24 hours prior to first venetoclax dose or any dose escalation.
- Intravenous hydration (target 150 to 200 mL/hr, as tolerable) must be started upon admission and continued during hospitalization as appropriate. Urine output must be monitored.

- Chemistries on the first day of venetoclax dosing at 0 (within 4 hours prior to dosing), 4, 8 and 12 hours and each day of a new dose at 0 (within 4 hours prior to dosing), 4, 8 and 12 hours.*
- Chemistries at 24, 48, 72 hours after receiving the first designated target dose.*
- Collection of samples for venetoclax PK assay 8 hours after dosing on each day of new dose. The 8-hour post-dose PK sample may be collected up to 1 hour earlier or up to 20 minutes after the scheduled time, if necessary to facilitate sample processing.

* Chemistry samples (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) must be reviewed by the investigator real time and prior to the subject's next dose to ensure appropriate subject management. Based upon the results, subjects may need further monitoring or may need additional post-dose labs. Refer to Appendix E (Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome [TLS]) and Appendix H (Tumor Lysis Syndrome Classification) for toxicity management guidelines and procedures to follow for TLS prevention. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax doses should be administered until resolution.

Refer to Table 10 (footnote "a") for a special sample handling procedure that must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase.

Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS may be allowed and will not require a dose reduction. If the TLS has not resolved within 72 hours, then a dose reduction should be considered.

If TLS requires a dose hold or dose modifications, after resolution of electrolyte imbalances (Appendix E), venetoclax may be continued at the same dose per discussion between the investigator and the AbbVie medical monitor.

Tumor Lysis Syndrome Prophylaxis and Management in Phase 2 Cohort C – Applies to Subjects Enrolled in Amendment 2

Safety data from the 94 subjects treated in 3 AML studies demonstrated no events of clinical TLS; 40 subjects treated in the escalation phase of this study; 32 subjects in monotherapy study (Study M14-212) and 22 subjects in a combination study (Study M14-387) using low dose cytarabine. Based on this data, simplification of TLS prophylaxis and management will be followed for subjects enrolled into Cohort C.

All subjects enrolled into Phase 2 Cohort C will need TLS prophylaxis and monitoring. Below are the minimum requirements for TLS prophylaxis and management for subjects enrolled into the expansion phase. All other prophylaxis and monitoring procedures for TLS will be done as per institutional/regional 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 at least for 24 hours after reaching the final dose of venetoclax. TLS chemistry tests should be confirmed 24 hours after reaching the maximal dose of venetoclax.
- Administration of uric acid reducing agent, adequate oral and intravenous hydration while monitoring the fluid status of the subject prior to and during the ramp-up of venetoclax will be based on regional standards or institutional guidelines.
- Tumor Lysis Syndrome chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax 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 should be corrected promptly.
- If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution.
    - Prophylactic reductions of potassium, inorganic phosphorus and/or uric acid above normal range are recommended prior to beginning study treatment and continue based on the ongoing risk of TLS.

* Chemistry samples (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) must be reviewed by the investigator real time and prior to the subject's next dose to ensure appropriate subject management. Based upon the results, subjects may need further monitoring or may need additional post-dose labs. Refer to Appendix E (Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome [TLS]) and Appendix H (Tumor Lysis Syndrome Classification) for toxicity management guidelines and procedures to follow for TLS prevention. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax doses should be administered until resolution.

For continued dosing of venetoclax, monitor for evidence of TLS during treatment, and manage abnormalities in serum creatinine, uric acid and electrolytes promptly. For subjects at higher risk (e.g., circulating blasts), more intensive measures should be considered.

Refer to Table 10 (footnote "a") for a special sample handling procedure that must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase.

Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS may be allowed and will not require a dose reduction. If the TLS has not resolved within 72 hours, then a dose reduction should be considered.

6.1.8.3 Management of Myelosuppresion (Cytopenias)

Venetoclax

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 CR or CRi or is found to have a morphologically leukemia free bone marrow, and has Grade 4 neutropenia or thrombocytopenia, venetoclax should be held from Day 28 until ANC $\geq$ 500 – 1000/µL and platelets $\geq$ 25 – 100 $\times$ 10^5/µL. At the investigator's discretion, subjects may resume a subsequent cycle of therapy after a 2-week interruption if the investigator believes the risk of AML progression outweighs the risk of further treatment before cytopenia recovery. Typically, if morphologic AML remains in the bone marrow, concurrent cytopenias are thought to be attributable to the disease processes of AML. In subsequent cycles, if a subject in CR presents with new onset Grade 4 neutropenia or thrombocytopenia for more than 1 week, unless it is due to the underlying disease, venetoclax dosing may be interrupted until ANC recovery to $\geq$ 500 – 1000/µL or platelets $\geq$ 25 – 100 $\times$ 10^5/µL per investigator discretion in consultation with the AbbVie medical monitor. Venetoclax may be re-initiated at a lower dose 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). If clinically indicated in AML subjects treated in this study, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial or Pneumocystis infections. Potential for drug-drug interactions should be considered. Please refer to Table 1 and Appendix C for a description of excluded and cautionary medications.

If a subject is continuing to respond based on the bone marrow assessment beyond Cycle 2 of treatment but has persistent neutropenia or thrombocytopenia venetoclax dose may be reduced as follows:

Table 12. Dose Reduction Guidelines for Management of Persistent Neutropenia or Thrombocytopenia

Venetoclax Dose/Duration	Reduced 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

Standard Therapy: Low – Dose Cytarabine

In a recent international clinical trial, subjects receiving LDC 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%, leukopenia 10%.[35] It is unknown whether the aforementioned adverse events are attributable to receiving treatment with LDC or were attributable to the underlying health condition of AML. Complications of myelosuppression, including infections and bleeding, may be exacerbated by treatment with LDC. During Cycle 2 and subsequent cycles, LDC treatment 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 LDC 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 LDC 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 LDC may be interrupted or supportive measures instituted.

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

6.1.8.4 Management of Decreased Spermatogenesis

Based on findings in a preclinical study of venetoclax, there is a potential for decreased spermatogenesis. Male subjects should consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

6.1.8.5 Management of Other Toxicities

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

Subjects should be monitored for new onset hematologic toxicity and renal toxicities, with dose delay or reduction as appropriate. Please follow local, approved product label or applicable SmPC for monitoring guidelines.

6.1.8.6 Determination of the MTD

If a single subject within a cohort experiences a DLT, a total of 6 subjects will be enrolled and dosed at the same dose level. If these additional subjects do not exhibit a DLT, dose escalation may proceed. If any of the additional subjects exhibits a DLT, then dose de-escalation may occur to interrogate lower dose levels. The MTD, if identified, will be defined at the highest dose level at which less than 2 of 6 subjects or < 33% of (if cohort is expanded beyond 6) subjects experience a DLT.

6.1.8.7 Determination of the RPTD

If an MTD is reached, the RPTD will not be a dose higher than the MTD and will be selected by the sponsor based on the types of DLTs which occur and the MTD identified. If an MTD is not reached, then the RPTD will be defined based on the safety and PK data.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. 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 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

Office:
Fax:
Email: [redacted]

Medical Monitor:

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Fax:
Email: [redacted]

Alternative Contact:

[redacted]
AbbVie

Office:
Fax:
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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analysis Plans

Analysis will be performed separately for each phase of the study.

Efficacy and safety analyses will be performed on all subjects who receive at least one dose of venetoclax.

8.1.1 Baseline Characteristics

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

8.1.1.1 Demographics

Age, height, weight and gender will be summarized with means, standard deviation and range. Frequencies and percentages will be computed for the following parameters: race, smoking history, and performance status.

8.1.1.2 Medical History

Frequencies and percentages will be computed for each medical history parameter.

8.1.2 Pharmacokinetics

8.1.2.1 Tabulations and Summary Statistics

Plasma concentrations and PK parameter values of venetoclax and cytarabine will be tabulated for each subject, visit, and dose regimen, and summary statistics will be computed for each sampling time and each parameter.

8.1.2.2 Model and Tests

All analyses will be performed on the Phase 1 portion subjects only.

Dose Proportionality and Covariate Selection of Venetoclax

The following analysis will be performed separately on Cycle 1 Day 10 and Cycle 1 Day 18 venetoclax PK parameters.

An analysis will be performed for dose-normalized C_{max}, AUC_{24}, and other PK parameters provided that they can be adequately determined from the data. The model used for the statistical analyses will include designated cohort dose level. This may be done by

classifying subjects by dose level or, if appropriate, using dose level as a continuous variable. Covariates such as age, body weight, body surface area, gender, and perhaps others that might explain some of the variability in the population will be included in the model initially. However, a covariate may be dropped from the model if the regression coefficient is not significant at alpha level 0.10. The natural logarithmic transformation will be employed for C_{max} and the AUC's unless the data clearly indicate that other transformation or the untransformed variable provides more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels. Within the framework of the model, tests that have good power for a trend with dose will be performed on the effect of designated cohort dose level.

Venetoclax Effect on Cytarabine Pharmacokinetics Parameters

A linear mixed effects analysis will be performed for C_{max}, AUC_t and AUC_∞, to compare cytarabine PK parameters when co-administered with venetoclax (Cycle 1 Day 10) relative to cytarabine administered alone (Cycle 1 Day 1). For C_{max} and AUC, the logarithmic transformation will be used unless the data indicate that the logarithm has significant non-normality. The model will include effects for visit (Cycle 1 Day 1, Cycle 1 Day 10). To account for the correlation among visits, the repeated statement for the visit effect will be specified under SAS procedure mixed. The relative bioavailability of cytarabine co-administered with venetoclax relative to cytarabine alone will be estimated and a 90% confidence interval will be provided for each of C_{max} and AUC. The confidence intervals will be obtained by the antilogarithm of the endpoints of confidence intervals for the difference of mean logarithms obtained within the mixed modeling framework.

Cytarabine Effect on Venetoclax Pharmacokinetics Parameters

A similar analysis to venetoclax effect on cytarabine PK parameters will be performed on Cycle 1 Day 10 and Cycle 1 Day 18 venetoclax PK parameters.

8.1.2.3 Missing Values and Model Violations

All available data will be included the mixed effect analyses. Data exclusion, if any, will be documented and justification provided.

Normally distributed values of PK variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, simply using the available data, and if necessary doing the analysis with some missing values for a PK variable. However, if a missing individual concentration results in a value of a PK parameter that may be too low or too high to a meaningful degree, the value of the PK parameter will tentatively be considered missing. In this case, a value for the missing individual concentration may be imputed so that an appropriate value of the PK parameter can be included in the analysis. The imputed value will be obtained using appropriate methodology that takes into account the individual characteristics of the subject.

If an outlier is identified and/or a pronounced non-normal probability distribution is observed (after logarithmic transformation for C_{max} and AUC), then a non-parametric analysis may also be performed. Such a model violation may be identified by graphical methods, measures of non-normality (e.g., skewness, kurtosis) or other appropriate methods. If the regimens have unequal variances to the extent that conclusions might be affected, then approximate methods that allow for unequal variances will be used.

8.1.3 Efficacy Summaries

Efficacy will include analyses of ORR as defined by CR + CRi + PR, CR rate, CRi rate, CRh rate, CR + CRi rate, CR + CRh rate, DOR, EFS, OS, the exploratory analysis of the proportion of for all subjects who achieve MRD negativity, the proportion of subjects who are transfusion independent post baseline, and the proportion of subjects who undergo subsequent stem cell transplant. Transfusion support needs will be recorded to define ongoing transfusion dependence.

8.1.3.1.1 Overall Response Rates

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

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

*For a bone marrow sample collected before the last cycle of study treatment, the hematology lab results collected from the date of bone marrow sample collection up to 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.

CR + CRh rate will be defined as the proportion of subjects who achieve CR or CRh at any time point during the study. Subjects who never achieve CR or CRh or have not had IWG disease assessment will be considered to be non-responders in the calculation of CR + CRh rate.

Overall response rate will be defined as the proportion of subjects who achieve a CR, CRi, or PR at any time point during the study per the IWG criteria for AML. Subjects who do not achieve a response of CR, CRi, or PR will be considered to be non-responders participating in the calculation of the ORR rate.

In addition, the proportion of subjects who achieve CR, the proportion of subjects who achieve a CRi, the proportion of subjects who achieve a CRh, and the proportion of subjects who achieve CR + CRi will be summarized. The 95% confidence interval based on the binomial distribution will be provided for CR + CRh rate, ORR, CR rate, CRi rate, CRh rate, and CR + CRi rate.

8.1.3.1.2 Duration of Response

Duration of response will be defined as the number of days from the date of first response (CR, CRi, or PR) per the IWG criteria for AML to the earliest recurrence or PD. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will not be included unless otherwise indicated. Duration of response will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects who responded. Median DOR will be calculated and the corresponding 95% confidence interval will be presented.

8.1.3.1.3 Event-Free Survival

Event-free survival (EFS) will be defined as the number of days from the date of first dose to the date of earliest evidence of progression or relapse, subsequent treatment other than stem cell transplant while in composite complete response (CR + CRi), or death. If the specified event (relapse, start of subsequent treatment, or death) does not occur, patients will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the baseline visit will be censored at the date of first dose plus 1 day. Event-free survival (EFS) will be analyzed by Kaplan-Meier methodology. Median EFS will be calculated and 95% confidence interval for median EFS will be presented.

8.1.3.1.4 Overall Survival

Overall survival will be defined as number of days from the date of first dose to the date of death. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later. Overall survival will be analyzed by Kaplan-Meier methodology using data from all enrolled subjects. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

8.1.3.1.5 MRD Negativity Rate

The proportion of subjects who reach MRD negativity in this exploratory measurement and the duration of this status will be summarized.

8.1.3.1.6 Proportion of Subjects Who Undergo Transplant

The proportion of subjects who undergo a subsequent transplant will be summarized.

8.1.3.1.7 Post Baseline Transfusion Independence (RBC/Platelet)

Post baseline transfusion independence is defined as a period of at least 56 days with no RBC or platelet transfusion between the first dose of study drug and the last dose of study drug + 30 days. Post baseline transfusion independence rate will be estimated as the portion of subjects who achieve transfusion independence post baseline. The corresponding 95% CI for transfusion independence rate will be provided based on the binomial distribution (Clopper-Pearson exact method).

In addition, the baseline transfusion dependence rate, which is defined as the portion of subjects who received either RBC or platelet transfusion within 56 days prior to the first dose of study drug, will be summarized.

8.1.4 Safety

The safety of Venetoclax and cytarabine will be assessed by evaluation study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

Safety analyses will be performed for all subjects who take at least one dose of study drug.

8.1.4.1 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug.

Analyses of adverse events will not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current MedDRA dictionary.[42] In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE Version 4.0[40] toxicity grade, and relationship to study drug will be provided.

8.1.4.2 Serious Adverse Events

Serious adverse events will be summarized using the same methods as adverse events described above.

8.1.4.3 Deaths

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

8.1.4.4 Longitudinal Analyses of Laboratory and Vital Signs Data

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 urinalysis and 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.

8.1.4.5 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry, hematology and lymphocyte enumeration determinations will be categorized according to NCI CTCAE Version 4.0[40] grades, and

shifts from baseline NCI CTCAE[40] 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.

Detailed listings of data for subjects experiencing NCI CTCAE[40] grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.2 Determination of Sample Size

This is a Phase 1/2 study where the Phase 1 portion is a dose escalation study and the Phase 2 portion is a dose expansion study.

For the Phase 1 portion of the study, the sample size is dependent upon the dose levels utilized and whether toxicities require and allow enrollment of 3 or 6 subjects to dose levels.

For the initial Phase 2 portion, approximately 50 subjects will be enrolled. With 50 subjects, the 95% confidence intervals for estimation of ORR would have a margin of error not exceeding ± 15%. Clopper and Pearson 95% confidence intervals for expected observed rates for a sample size of 50 subjects are shown in Table 13. With 50 subjects, an ORR rate of approximately 15% lower than the observed rate would be ruled out.

Table 13. 95% Confidence Intervals for Assumed Observed Rates Based on Sample Size of 50 Subjects

ORR Rate	No. of Subjects with Objective Response (95% CI for rate)
60%	30 (45%, 74%)
50%	25 (35%, 64%)
40%	20 (26%, 55%)
30%	15 (18%, 45%)

For Cohort C, approximately 20 subjects will be enrolled to assess the experience of dosing venetoclax with LDC to evaluate if the efficacy of the combination is still consistent with that observed in previously treated subjects. These factors include more objectively defined criteria with a lower age limit, modification to the venetoclax dose to account for strong CYP3A inhibitors, and potential reduction in liver/kidney function allowed for enrollment. With 20 subjects, the ORR and Clopper and Pearson 95% confidence interval are specified in Table 14.

Table 14. 95% Confidence Intervals for Assumed Observed Rates Based on Sample Size of 20 Subjects

ORR Rate	No. of Subjects with Objective Response (95% CI for rate)
70%	14 (46%, 88%)
60%	12 (36%, 81%)
50%	10 (27%, 73%)
40%	8 (19%, 64%)

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the

ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

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

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed.

In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Responsibilities of the clinical investigator are specified in Appendix A.

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 pharmacogenetic and pharmacodynamic 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 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.

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.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subject 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. Source document data may be transcribed onto case report forms (CRFs) as required. Data collected during this study must be recorded on the appropriate source document.

The investigator/institution 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 (CRF) 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 electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 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.

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.

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.

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.

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.

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. A review of all laboratory results will be conducted by the AbbVie or contract monitors, the investigator and other appropriate personnel from AbbVie.

12.0 Use of Information

All information concerning venetoclax and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing 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 pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic 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. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic 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 and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator 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.

The investigator must retain any records related to the study according to local requirements. If the investigator 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 multicenter study. Selection criteria for this signatory investigator will be based on level of participation, and significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for venetoclax (ABT-199/GDC-0199) and the product label for cytarabine.
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 Phase 1/2 Study of Venetoclax in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 60 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy
Protocol Date:	22 October 2020

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
		Clinical
		Clinical
		Pharmacokinetics

Appendix C. Sample List of Excluded and Cautionary Medications

Excluded During Ramp-Up Phase and Throughout Study:
Strong CYP3A inducers – avasimibe, carbamazepine (Tegretol®), phenytoin (Dilantin®), enzalutamine, mitotane rifampin (Rifadin®), St. John's wort
Cautionary (Additional Guidance Noted in Table 1):
Moderate CYP3A inducers – bosentan, efavirenz, etravirine, modafinil, nafcillin **Strong CYP3A inhibitors** – boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir/ritonavir combinations posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole **Moderate CYP3A inhibitors** – amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil
Cautionary:
Warfarin and Courmarin 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,* irinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, pitavastatin, pravastatin, repaglinide, simvastatin acid, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, captopril, carvedilol, felodipine, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors** geftinib*

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

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

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

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

Appendix D. NCCN Risk Categorization: Guidelines for AML Version 2.2014

Risk Category	Cytogenetic
Better Risk	inv(16) or t(16;16)
	t(8;21)
	t(15;17)
Intermediate Risk	Normal cytogenetics
	+8 alone
	t(9;11)
	Other non-defined
Poor Risk	Complex(> 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 E. 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 within normal limits (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, 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, 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.
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 F. Adverse Events Commonly Associated with Acute Myelogenous Leukemia Study Population and/or Progression of Acute Myelogenous leukemia

Fever
Fatigue
Dyspnea
Pain, all types
Thrombocytopenia
Anemia
Neutropenia
Infection (bacterial, viral, fungal)

- Neutropenic infection
- Neutropenic sepsis
- Oral candidiasis
- Stomatitis
- Periodontal infection
- Tooth infection, abscess
- Upper respiratory tract infection
- Sinusitis, Rhinitis
- Bronchitis (bacterial, viral)
- Bronchitis chronic
- Pneumonia (bacterial, viral, fungal)
- Catheter site cellulitis
- Herpes zoster disseminated, multi-dermatomal
- Herpes zoster
- Herpes simplex (oral, genital)
- Skin candida
- Urinary tract infection bacterial, fungal
- Genitourinary tract infection (viral, bacterial, fungal)

Gastroenteritis
Enterocolitis

Malignant disease progression, including death

Hyperleukocytosis, including the symptomatic form (leukostasis)
Leukaemic infiltration brain
Malignant pleural effusion
Chloroma/granulocytic sarcoma

Second primary cancers, all types

Bleeding

Gingival bleeding
Mouth haemorrhage
Epistaxis
Haematuria
Injection site haemorrhage
Petechiae
Skin haemorrhage
Retinal hemorrhage

Population-Related Comorbidities

Hypertension
Rheumatoid arthritis/osteoarthritis
Hyperlipidemia
Peptic ulcer
Inflammatory bowel disease
Coronary artery disease
Peripheral vascular disease

Cardiomyopathy
Valvular disease
Atrial fibrillation
Diabetes mellitus
Chronic obstructive pulmonary disease
Cerebrovascular accident
Transient ischemia attack

Appendix G. 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 IC50 values are shown for each cell line.

Cell Line	Venetoclax IC50 (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

Appendix H. 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.

Cross reference: Howard SC 2011[43]

Appendix I. Protocol Amendment: List of Changes

A summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add:

COVID-19	Coronavirus Disease-2019
DTP	Direct-to-patient

Section 3.3 Benefits and Risks
Add: new last paragraph

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

Table 3. Study Activities (Phases 1 and 2 {Including Cohort C})
Previously read:

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Informed Consent	X[b]											
Medical/Oncology History Assessment	X		X[c]									
Cytogenetic Assessment[d]	X											
AE/Concomitant Medication Assessment	X	X	X	X	X	X	X	X		X	X	
Tumor Lysis Syndrome Prophylaxis[e]		X	X	X	X	X	X					
Physical Exam (including weight)[f]	X[h]		X				X[i]	X[j]		X[j]	X[j]	
Vital Signs[f]	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status[f]	X		X					X		X	X	
Hematology[f,g]	X		X	X	X	X	X	X		X	X	X
Chemistry[e,f]	X[k]		X	X	X	X	X	X[k]		X[k]	X	
Coagulation[f]	X		X					X[l]		X	X	
Urinalysis[f]	X											
12-lead ECG[m]	X									X[o]		
MUGA (preferred)/2D Echocardiogram w/Doppler[m,p]	X											
Clinical Disease Progression Assessment									X	X		X

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Bone Marrow Aspirate and Biopsy for Response Assessment	X[q]								X[r]	X		
Dispense Subject Calendar/Diary							X[s]	X				
Collect Study Drug and Subject Calendar/Diary								X		X		
Survival Assessments[t]												X

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

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

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

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

d. Cytogenetic testing should be performed if not completed within 3 months prior to Screening.

e. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.1.8.2 Management of Tumor Lysis Syndrome (TLS) and Appendix E– Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

f. For all study visits beginning with Cycle 3, physical examination, vital signs, ECOG performance status, hematology, chemistry, coagulation and urinalysis may be performed within 72 hours before Day 1 of treatment for that cycle.

g. Hematology will be performed weekly (at the minimum, hematology should be performed weekly during Cycle 1 and Cycle 2).

h. Height will be measured only at Screening.

i. Only applies to Dose Level (–)2. Subjects should have Physical exam upon discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated cohort dose. Also, Dose Levels 4 and 5 would stay in hospital until Day 8, needing a Physical exam at Day 8.

j. A symptom-directed physical exam may be performed.

k. Amylase and lipase are required at Screening, Cycle 2 Day 1, and the Final Visit.

l. Coagulation to be performed on Cycle 2 Day 1 and not required subsequently unless clinically indicated.

m. Additional ECGs and a MUGAs/Echos should be performed as clinically necessary per the discretion of the investigator.

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

o. May be obtained ± 2 days of the visit.

p. Should be performed provided that such assessment would not inappropriately delay therapy per discretion of the investigator.

q. Historical bone marrow aspirates at screening will not be sufficient; a bone marrow aspirate must be performed for study entry to collect mandatory biomarker assessments.

r. May be performed ± 7 days of the anticipated Day 1 of the subsequent cycle visit, for visits beginning with Cycle 2 Day 1. Assessments beginning with Cycle 4 Day 1 should be performed and resulted prior to the dispensation of the next cycle of drug.

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

t. Survival assessments should be performed every 12 weeks (± 1 week) for 1 year after last subject's last dose.

u. Post Treatment visits will be performed every 12 weeks (± 1 week) for up to 1 year after last subject's last dose. Survival assessments will be performed every 12 weeks, beginning when subjects develop progressive disease, for 1 year after the last subject's last dose.

Note: Refer to Table 4 for treatment schedule.

Has been changed to read:

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Informed Consent	X[b]											
Medical/Oncology History Assessment	X		X[c]									
Cytogenetic Assessment[d]	X											
AE/Concomitant Medication Assessment[v]	X	X	X	X	X	X	X	X		X	X	
Tumor Lysis Syndrome Prophylaxis[e]		X	X	X	X	X	X					
Physical Exam (including weight)[f,v]	X[h]		X				X[i]	X[j]		X[j]	X[j]	

Procedures	Scr[a]	Day –1	Cycle 1					Day 1 of Cycle 2 and Day 1 of Every Cycle Thereafter (± 3 Days)	Cycle 2 Day 1, Cycle 4 Day 1, and Every 3 Cycles Thereafter (± 7 Days)	Final Visit[n]	30-Day Safety F/U	PT F/U[u] (± 1 Week)
			Day 1	Day 2	Day 3	Day 4	Day 5					
Vital Signs[f,v]	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status[f,v]	X		X					X		X	X	
Hematology[f,g,v]	X		X	X	X	X	X	X		X	X	X
Chemistry[e,f,v]	X[k]		X	X	X	X	X	X[k]		X[k]	X	
Coagulation[f,v]	X		X					X[l]		X	X	
Urinalysis[f,v]	X											
12-lead ECG[m,v]	X									X[o]		
MUGA (preferred)/2D Echocardiogram w/Doppler[m,p]	X											
Clinical Disease Progression Assessment									X	X		X
Bone Marrow Aspirate and Biopsy for Response Assessment	X[q]								X[r]	X		
Dispense Subject Calendar/Diary							X[s]	X				
Collect Study Drug and Subject Calendar/Diary[w]								X		X		
Survival Assessments[t]												X

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

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

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

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

d. Cytogenetic testing should be performed if not completed within 3 months prior to Screening.

e. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.1.8.2 Management of Tumor Lysis Syndrome (TLS) and Appendix E – Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome (TLS) for further information.

f. For all study visits beginning with Cycle 3, physical examination, vital signs, ECOG performance status, hematology, chemistry, coagulation and urinalysis may be performed within 72 hours before Day 1 of treatment for that cycle.

g. Hematology will be performed weekly (at the minimum, hematology should be performed weekly during Cycle 1 and Cycle 2).

h. Height will be measured only at Screening.

i. Only applies to Dose Level (–)2. Subjects should have Physical exam upon discharge from the hospital. Subjects should remain hospitalized no less than 24 hours post dosing of their designated cohort dose. Also, Dose Levels 4 and 5 would stay in hospital until Day 8, needing a Physical exam at Day 8.

j. A symptom-directed physical exam may be performed.

k. Amylase and lipase are required at Screening, Cycle 2 Day 1, and the Final Visit.

l. Coagulation to be performed on Cycle 2 Day 1 and not required subsequently unless clinically indicated.

m. Additional ECGs and a MUGAs/Echos should be performed as clinically necessary per the discretion of the investigator.

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

o. May be obtained ± 2 days of the visit.

p. Should be performed provided that such assessment would not inappropriately delay therapy per discretion of the investigator.

q. Historical bone marrow aspirates at screening will not be sufficient; a bone marrow aspirate must be performed for study entry to collect mandatory biomarker assessments.

r. May be performed ± 7 days of the anticipated Day 1 of the subsequent cycle visit, for visits beginning with Cycle 2 Day 1. Assessments beginning with Cycle 4 Day 1 should be performed and resulted prior to the dispensation of the next cycle of drug.

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

t. Survival assessments should be performed every 12 weeks (± 1 week) for 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

u. Post Treatment visits will be performed every 12 weeks (± 1 week) for up to 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired. Survival assessments will be performed every 12 weeks, beginning when subjects develop progressive disease, for 1 year after the last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

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

Note: Refer to Table 4 for treatment schedule.

Section 5.3.1.1 Study Procedures
Add: new second paragraph

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow Table 3 on how to proceed.

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, weight, blood pressure, vitals and respiratory rate measurements may be performed by the subject or caregiver as needed.

Section 5.3.1.1 Study Procedures
Subsection 12-Lead Electrocardiogram (ECG)
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Heading "COVID-19 Pandemic-Related Acceptable Protocol Modifications"
Add: new heading title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

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

Section 5.3.1.1 Study Procedures
Subsection Post-Treatment Follow-Up Visit(s)
First sentence previously read:

For subjects who discontinue study treatment for reasons other than disease progression, the following post-treatment assessments will be performed every 12 weeks (± 1 week) until criteria are met for discontinuation from the study (e.g., disease progression, death or a subject's refusal of the Post-Treatment visits) for a period of 1 year after last subject's last dose:

Has been changed to read:

For subjects who discontinue study treatment for reasons other than disease progression, the following post-treatment assessments will be performed every 12 weeks (± 1 week) until criteria are met for discontinuation from the study (e.g., disease progression, death or

a subject's refusal of the Post-Treatment visits) for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired:

Section 5.3.1.1 Study Procedures
Subsection Survival Assessment(s)
Previously read:

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose.

Has been changed to read:

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

Section 5.4.1 Discontinuation of Individual Subjects
Sixth paragraph previously read:

Post-treatment assessment will be performed every 12 weeks (± 1 week) until discontinuation from the study (e.g., disease progression death or a subject's refusal of the Post-Treatment visits) for a period of 1 year after last subject's last dose.

Has been changed to read:

Post-treatment assessment will be performed every 12 weeks (± 1 week) until discontinuation from the study (e.g., disease progression death or a subject's refusal of the

Post-Treatment visits) for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

Section 5.4.1 Discontinuation of Individual Subjects
Seventh paragraph previously read:

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose.

Has been changed to read:

Survival information (e.g., date and cause of death, post-treatment cancer therapies, including transplantation) will be collected once the subject's disease has progressed via telephone calls (e.g., to subject or family member) and/or clinical visits at 12 weeks intervals (± 1 week) after the subject's last study visit for a period of 1 year after last subject's last dose or possibly sooner if all patients have discontinued and most patients have expired.

Section 5.4.1 Discontinuation of Individual Subjects
Subsection <u>COVID-19 Pandemic-Related Acceptable Protocol Modification</u>
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID 19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Refer to the Section 5.3.1.1, Study Procedures and Table 3 for details on how to handle study activities/procedures accordingly. Study drug interruptions due to COVID-19 restrictions should be captured in EDC.

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

Section 5.4.2 Discontinuation of Entire Study
Subsection Interruption/Discontinuation of Study Drug Due to COVID-19 Infection
Add: new subsection title and text

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

Decisions to delay or interrupt any study treatment based on the current situation and any concern for active infection should be made by the treating investigator after considering the subject's current oncologic status and treatment tolerance, as well as their general medical condition. As a potentially serious infection, consideration for treatment interruption is advised. If needed, any questions can be discussed with the Therapeutic Area Medical Director (TAMD).

Section 5.5.1 Treatments Administered
Subsection COVID-19 Pandemic-Related Acceptable Protocol Modifications
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) venetoclax shipment can be made from the study site to the subject if allowed by local regulations. Cytarabine DTP are is not allowed by AbbVie. AbbVie will submit any required notifications to the regulatory authority as applicable.

Venetoclax may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of venetoclax is allowed by local regulations and the relevant ethics committee
- Venetoclax can be administered by the subject (or subject's caregiver) at home

- Subject agrees to have the venetoclax shipped directly to their home
  - Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of venetoclax from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
  - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Section 6.1.6 Adverse Event Reporting
Subsection <u>COVID-19 Pandemic-Related Acceptable Protocol Modifications</u>
Add: new subsection title and text

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

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

Section 7.0 Protocol Deviations
First paragraph, last sentence previously read:

If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Has been changed to read:

If a protocol deviation occurs (or is identified, including those that may be due to 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):

Section 9.2 Ethical Conduct of the Study
Last sentence previously read:

Responsibilities of the clinical investigator are specified in Appendix A.

Has been changed to read:

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

Responsibilities of the clinical investigator are specified in Appendix A.

Section 9.3 Subject Information and Consent
Add: new last paragraph

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.

Section 10.2 Case Report Forms
Add: new fourth paragraph

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.