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Protocol for Study M19-708

Acute Myeloid Leukemia: Venetoclax, Azacitidine, and Oral Azacitidine

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: Multicenter, Phase 3 Study of Venetoclax and Azacitidine as Maintenance Therapy for Patients with Acute Myeloid Leukemia in First Remission After Conventional Chemotherapy (VIALE-M)	
Background and Rationale:	Acute myeloid leukemia (AML) is an aggressive hematologic malignancy typically defined by the World Health Organization (WHO) as a myeloid neoplasm with 20% or more blasts in the peripheral blood or bone marrow. It is the most common form of acute leukemia in adults, with an estimated 19,520 new cases and 10,670 deaths in the United States (US) in 2018. Of all types of leukemia, AML has the lowest survival rate and accounts for the largest number of deaths. Venetoclax is a selective, potent, orally bioavailable, small molecule inhibitor of B-cell lymphoma (BCL)-2 that restores programmed cell death in cancer cells. Venetoclax was evaluated as a single agent in subjects with relapsed or refractory (R/R) AML or newly diagnosed subjects with AML who were unfit to receive intensive chemotherapy achieving a 19% objective response rate (ORR) with venetoclax monotherapy. Furthermore, ongoing studies in subjects with treatment-naïve AML who were ineligible for intensive chemotherapy reported complete remission (CR) + complete remission with incomplete blood count recovery (CRi) rates of 61% when subjects were treated with venetoclax in combination with hypomethylating agents and 54% in combination with low-dose cytarabine. For AML patients who are eligible, intensive chemotherapy during induction and consolidation is a standard-of-care treatment. Patients who are fit enough to receive intensive therapy will often achieve remission; however, the majority of these patients will ultimately relapse. The prevention of relapse is a major therapeutic challenge in the treatment of AML and an unmet need remains for AML patients in remission. This study will determine the recommended Phase 3 dose (RPTD) of venetoclax in combination with azacitidine (AZA; subcutaneous [SC] or intravenous [IV] administration) as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional chemotherapy. This study will also determine the dose of venetoclax in combination with oral AZA (ONUREG®; orally [PO] administered AZA) that can be safely administered (RPTD) as maintenance therapy, and evaluate the safety and efficacy of venetoclax in combination with oral AZA in subjects with AML who have achieved CR or CRi after conventional chemotherapy.
Objectives and Endpoints:	Primary Objective • Part 1 (Dose Confirmation): To determine the RPTD of venetoclax in combination with AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy. • Part 3 (Dose Finding): To determine the RPTD of venetoclax in combination with oral AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy.

	Secondary Objectives • Part 3 (Dose Finding): To characterize the safety, efficacy, pharmacokinetic (PK), and toxicity profiles of venetoclax in combination with oral AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy. Primary Endpoint Part 1 (Dose Confirmation) • The primary endpoint is dose-limiting toxicities (DLTs) of venetoclax in combination with AZA. Part 3 (Dose Finding) • The primary endpoint is DLTs of venetoclax in combination with oral AZA.
Investigators:	Investigator information on file at AbbVie.
Study Sites:	Approximately 250 sites in approximately 17 countries including but not limited to [redacted]
Study Population and Number of Subjects to be Enrolled:	Subjects with AML who have achieved CR or CRi with conventional chemotherapy will be enrolled in the study; as of 26 August 2021, 66 subjects were enrolled in Part 1 (Dose Confirmation); as of 08 September 2022, 46 subjects were enrolled in Part 3 (Dose Finding).
Investigational Plan:	This is a Phase 3 multicenter, open-label study of venetoclax in combination with AZA administered PO (oral AZA) to establish the RPTD and safety of the combination in a dose escalation phase (Part 3 [Dose Finding]) followed by a safety expansion component in subjects with AML after first remission resulting from conventional (including both induction and consolidation) chemotherapy. This study will also have an open-label, dose-confirmation component to establish the recommended dose of venetoclax in combination with AZA (SC or IV) (Part 1 [Dose Confirmation]) in subjects with AML after first remission resulting from conventional (including both induction and consolidation) chemotherapy. Best supportive care (BSC) and expectant AML management for this patient population according to institutional standards, excluding any AML-directed therapy, is allowed throughout the study. BSC will be determined for each subject by the investigator. For Part 1, subjects enrolled in the dose-confirmation cohort will receive venetoclax + AZA at the proposed study dose levels. When at least 20 subjects have been treated for at least 28 days, an aggregate review of the toxicity data will occur to determine if the RPTD has been reached. For Part 3 (Dose Finding), subjects enrolled in the dose-escalation cohorts will receive venetoclax + oral AZA at the proposed study dose levels. When the RPTD has been reached, a safety expansion cohort will receive venetoclax + oral AZA at the preliminary RPTD identified from dose-escalation portion of Part 3 (Dose Finding).

	Note: Part 2 (open-label, randomized, 2-arm portion of the study with venetoclax + AZA + BSC versus BSC) was removed from Version 5.0 of this protocol. Part 3 (Randomization) was removed from Version 6.0 of this protocol.
Key Eligibility Criteria:	Subject must be ≥ 18 years old, have newly diagnosed AML with intermediate or poor risk cytogenetics, have confirmed CR or CRi following completion of intensive Induction and Consolidation chemotherapies, have achieved first CR or CRi (after induction) within 120 days of the first dose of study drug or be no more than 75 days since last dose of intensive conventional (including both Induction and Consolidation) chemotherapies until enrollment, and have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. The key laboratory requirements are as follows: • creatinine clearance ≥ 30 mL/minute; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection; • bilirubin < 3.0 × upper limit of normal (ULN) (adequate liver function) for Part 1, or bilirubin < 2.0 × ULN for Part 3; • absolute neutrophil count ≥ 1,500/µL; • platelets ≥ 100,000/µL.
Study Drug and Duration of Treatment:	Part 1: Venetoclax QD for each 28-day cycle for 24 cycles + AZA QD for 5 days (Days 1 to 5) of each 28-day cycle up to 6 cycles. At investigator's discretion, subjects benefiting from treatment at the end of Cycle 24 may continue on venetoclax for up to 48 cycles. Part 3 (Dose Finding): Venetoclax QD for each 28-day cycle up to 24 cycles + oral AZA QD for 14 days (Days 1 to 14) of each 28-day cycle up to 24 cycles.
Date of Protocol Synopsis:	26 April 2024

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

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

AbbVie and Genentech/Roche (sponsors) are jointly developing venetoclax for the treatment of subjects with hematological malignancies. Venetoclax is a selective, potent, orally bioavailable, small molecule inhibitor of B-cell lymphoma (BCL)-2 that restores programmed cell death in cancer cells. Venetoclax binds with high affinity (inhibition rate constant [K_i] < 0.010 nM) to anti-apoptotic protein BCL-2 and with lower affinity to other anti-apoptotic BCL-2 family proteins, like B-cell lymphoma extra large (BCL-X_L) and B-cell lymphoma - Walter and Eliza Hall Institute (BCL-w) (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to BCL-2, respectively).

Venetoclax was evaluated as a single agent (Study M14-212) in subjects with relapsed or refractory (R/R) AML or newly diagnosed subjects with AML who were unfit to receive intensive chemotherapy achieving a 19% objective response rate (ORR) with venetoclax monotherapy.[5] Furthermore, studies in subjects with treatment-naïve AML who were ineligible for intensive chemotherapy reported complete remission (CR) + complete remission with incomplete blood count recovery (CRi) rates of 61% in combination with hypomethylating drugs (HMAs; Study M14-358)[6] and 54% in combination with low-dose cytarabine (LDAC; Study M14-387).[7] In a Phase 3, randomized, double-blind, placebo-controlled study (Viale A: Study M15-656), newly diagnosed subjects with AML who were unfit to receive intensive chemotherapy were treated with venetoclax in combination with azacitidine (AZA) or placebo in combination with AZA. As of 04 January 2020, the median overall survival (OS) was 14.7 months [95% confidence interval (CI): 11.9, 18.7] in the venetoclax + AZA arm versus 9.6 months [95% CI: 7.4, 12.7] in the placebo + AZA arm (hazard ratio 0.66 [95% CI: 0.52, 0.85]; p < 0.001). The CR + CRi rate was 66.4% [95% CI: 60.6, 71.9] in the venetoclax + AZA arm versus 28.3% [95% CI: 21.1, 36.3] in the placebo + AZA arm (p < 0.001).[8] The safety profile of subjects treated with venetoclax in combination with AZA was consistent with the known side-effect profiles of both agents alone, and adverse events (AEs) were consistent with expectations for an older AML population. The most common AEs in both treatment arms were GI and hematologic events with a higher frequency of neutropenia and febrile neutropenia in the venetoclax + AZA arm;[8] these findings are consistent with those in previous studies.[9]

For AML patients who are eligible, intensive chemotherapy during induction and consolidation is a standard-of-care treatment.[5-7,10,11] Patients who are fit enough to receive intensive therapy will often achieve remission; however, the majority of these patients will ultimately relapse. The prevention of relapse is a major therapeutic challenge in the treatment of AML.[12-14] No post-consolidation treatment for prevention of relapse was previously established except for the use of allogeneic hematopoietic

stem cell transplant for a select group of relatively fit patients.[15-17] Although there has been a long-standing interest in maintenance therapies such as interleukin-2,[18-20] LDAC,[21] HMAs,[22-30] and gemtuzumab ozogamicin[26] after intensive induction treatment, the clinical benefits of such maintenance therapies have remained unclear.[19] In 2020, ONUREG® (CC-486; orally [PO] administered AZA) was approved for continued treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and were not able to complete intensive curative therapy. Data from the QUAZAR AML maintenance trial (CC-486-AML-001), a randomized, double-blind, placebo-controlled study, showed that the median OS in subjects receiving ONUREG was superior (median OS: 24.7 months) to subjects who received placebo (median OS: 14.8 months) and the subgroup analysis showed consistency in the OS benefit for subjects who achieved either CR or CRi. Adverse reactions in ≥ 10% subjects receiving ONUREG were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.[31]

The BCL-2 family of proteins is overexpressed in leukemic stem cells. Leukemia stem cells drive the initiation and perpetuation of AML, are quantifiably associated with worse clinical outcomes, and often persist after conventional chemotherapy resulting in relapse. In recent literature, analysis of leukemic stem cells from subjects undergoing treatment with venetoclax in combination with azacitidine (VIDAZA®) showed disruption of the tricarboxylic acid cycle manifested by decreased α-ketoglutarate and increased succinate levels suggesting inhibition of electron transport chain complex II. This leads to suppression of oxidative phosphorylation, which efficiently and selectively targets leukemic stem cells. These findings suggest that a therapeutic intervention can eradicate leukemic stem cells in patients with AML by disrupting the metabolic machinery, resulting in promising clinical activity in a patient population with historically poor outcomes.[32]

This study will determine the recommended Phase 3 dose (RPTD) of venetoclax in combination with AZA (subcutaneous [SC] or intravenous [IV] administration) as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional chemotherapy. This study will also determine the dose of venetoclax in combination with oral AZA that can be safely administered (RPTD) as maintenance therapy, and evaluate the safety and efficacy of venetoclax in combination with oral AZA in subjects with AML who have achieved CR or CRi after conventional chemotherapy.

2.2 Benefits and Risks to Subjects

Most patients with AML will achieve remission with induction chemotherapy. The majority of these patients will then go on to relapse. Maintenance therapy to prolong remission and increase cure is an approved approach in acute promyelocytic leukemia (APL). Maintenance strategies for non-APL AML are currently being tested.[33,34] No standard-of-care exists for maintenance therapy in non-APL AML.

It is hypothesized that a reservoir of leukemia stem cells that persist after primary therapy ultimately expand and drive relapse in AML. Curative therapy in AML must incorporate agents with activity against these cells either during induction and consolidation or during maintenance. Combined therapy with venetoclax + AZA has been shown to eradicate leukemia stem cells through disruption of oxidative phosphorylation and energy metabolism in preclinical models of AML.[32] These data support the conduct of a maintenance study incorporating both these agents.

Venetoclax in combination with AZA was highly active for newly diagnosed patients with AML who are unfit to receive intensive chemotherapy. Responses were deep and durable, and outcomes were superior compared with historical controls (Study M14-358). The reported CR or CRi rate was 71.4%. Median duration of response was 21.2 months. The most common treatment-emergent AEs were nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). No dose-limiting toxicities (DLTs) were reported. The most frequent serious AE (SAE) was febrile neutropenia (28%). These AEs were experienced by subjects treated with venetoclax in combination with an HMA; however, subjects who are already in morphologic remission may experience a lower frequency rate of AEs than newly diagnosed subjects with AML who were unfit to receive intensive chemotherapy.

CC-486 is an oral formulation of AZA with clinical activity in subjects with AML in Phase 1 studies. The Phase 3, randomized, double-blind, placebo-controlled QUAZAR AML maintenance trial (CC-486-AML-001) examines CC-486 maintenance therapy (300 mg/day for 14 days of 28-day treatment cycles) in subjects aged ≥ 55 years with AML in first CR. This trial investigated whether CC-486 maintenance can prolong remission and improve survival for older subjects with AML. CC-486 was the first maintenance therapy to provide statistically significant and clinically meaningful improvements in OS and RFS relative to placebo in a broad range of subjects with AML in remission following intensive induction chemotherapy. The median OS and RFS were prolonged by 9.9 months and 5.3 months, respectively. The safety and tolerability of oral AZA were manageable with no unexpected AEs.[33,35]

For further details, please see findings from completed and ongoing studies, including safety data in the current venetoclax Investigator's Brochure,[36] both the AZA and oral AZA Summaries of Product Characteristics (SmPC)[37,38], package inserts, prescribing information, and/or their equivalents.

Given the coronavirus disease 2019 (COVID-19) pandemic and based on the information to date, subjects receiving venetoclax in combination with AZA or oral AZA may be at an increased risk for COVID-19 or experience serious illness if infected. Management of these AEs will be made on a case-by-case basis with consideration of benefit/risk.

3 OBJECTIVES AND ENDPOINTS

Part 1 Objectives (Dose Confirmation)

Primary

- To determine the RPTD of venetoclax in combination with AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy.

Part 2 Objectives (Randomization)

Not applicable; Part 2 was removed from Version 5.0 of this protocol.

Part 3 Objectives (Dose Finding)

Primary

- To determine the RPTD of venetoclax in combination with oral AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy.

Secondary

- To characterize the safety, efficacy, pharmacokinetic (PK), and toxicity profiles of venetoclax in combination with oral AZA as maintenance therapy in subjects with AML who have achieved CR or CRi with conventional induction and consolidation chemotherapy.

Part 3 Objectives (Randomization)

Not applicable; Part 3 (Randomization) was removed from Version 6.0 of this protocol.

3.1 Primary Endpoint

Part 1 (Dose Confirmation)

The primary endpoint is DLTs of venetoclax in combination with AZA.

Part 3 (Dose Finding)

The primary endpoint is DLTs of venetoclax in combination with oral AZA.

Part 3 (Randomization)

Not applicable; Part 3 (Randomization) was removed from Version 6.0 of this protocol.

3.2 Secondary Endpoints

Part 3 (Randomization)

Not applicable; Part 3 (Randomization) was removed from Version 6.0 of this protocol.

3.3 Additional Endpoints

Part 3 (Dose Finding)

- Relapse free survival
- Overall survival
- Minimal residual disease conversion
- Time to deterioration GHS/QoL scale from the EORTC QLQ-C30

- Change in global fatigue score from baseline to post-baseline using the PROMIS Fatigue SF-7a global fatigue score
- Change from baseline to post-baseline in subscales and items from EORTC QLQ-C30 and EQ-5D-5L

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study treatment duration through 30 days after last dose of study drug.

3.5 Pharmacokinetic Endpoints

Sparse PK samples will be collected and analyzed for plasma concentrations of venetoclax and azacitidine (active ingredient of AZA and oral AZA) in Part 1 and Part 3. An analysis of venetoclax plasma concentrations may be performed using a nonlinear mixed-effect population PK modeling approach.

For the intensive PK sampling days in Part 3 (Dose Finding), values for the PK parameters of venetoclax and azacitidine including the maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), the area under the plasma concentration versus time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_t) for azacitidine, and AUC from time 0 to 24 hours postdose (AUC_{0-24}) for venetoclax will be determined using noncompartmental methods.

3.6 Biomarker Research Endpoints

Biospecimens (e.g., blood, plasma, serum, and bone marrow aspirate) will be collected at specified time points (Appendix H) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. This research may be exploratory in nature and the results may not be included in the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual Section 3.15 and Appendix J.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3 multicenter, open-label study of venetoclax in combination with oral AZA administered PO to establish the RPTD and safety of the combination with a dose escalation phase (Part 3 [Dose Finding]) followed by a safety expansion component in subjects with AML after first remission resulting from conventional (including both induction and consolidation) chemotherapy.

This study will also have an open-label, dose-confirmation component to establish the recommended dose of venetoclax in combination with AZA (SC or IV) (Part 1 [Dose Confirmation]) in subjects with AML after first remission resulting from conventional (including both induction and consolidation) chemotherapy.

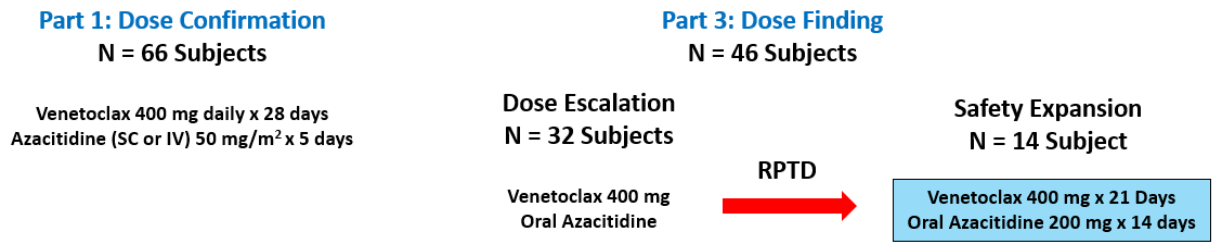
Best supportive care (BSC) and expectant AML management for this patient population according to institutional standards, excluding any AML-directed therapy, is allowed throughout the study in Part 1 and Part 3 (Dose Finding). BSC will be determined for each subject by the investigator.

As of 26 August 2021, 66 subjects were enrolled in Part 1 (Dose Confirmation); as of 08 September 2022, 46 subjects were enrolled in Part 3 (Dose Finding).

Note: Part 2 (open-label, randomized, 2-arm portion of the study with venetoclax + AZA + BSC versus BSC) was removed from Version 5.0 of this protocol. Part 3 (Randomization) was removed from Version 6.0 of this protocol.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix J).

Figure 1. Study Schematic



IV = intravenous(ly); PO = oral; RPTD = recommended Phase 3 dose; SC = subcutaneous(ly)

Screening

Consent will be obtained at the initial screening visit.

Unless otherwise specified, all other screening procedures must be performed within 28 days prior to start of study drug. Once screening procedures are complete and eligibility is confirmed, subjects will be enrolled into the study. Rescreening may be considered only once upon investigator discussion with the AbbVie Therapeutic Area Medical Director (TA MD) and subsequent agreement. Subjects who do not meet severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least **10** days since first **positive test** result have passed in asymptomatic patients or **at least 10** days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Subjects who rescreen must meet all eligibility criteria at the time of rescreen. See Section 5 for information regarding eligibility criteria.

Part 1: Dose Confirmation

For Part 1, the dose-confirmation cohort will enroll at least 20 subjects to receive venetoclax + AZA at the following dose levels: venetoclax 400 mg once daily (QD; Days 1 28) for each 28-day cycle up to 24 cycles and AZA 50 mg/m^2 SC or IV, QD for 5 days beginning on Cycle 1, Day 1 (Days 1 5) of each 28 day cycle up to 6 cycles.

When at least 20 subjects have been treated for at least 28 days, an aggregate review of the toxicity data will be made by the sponsor. If fewer than 20% of the subjects experience DLTs during Cycle 1, the RPTD will have been established. However, if 20% or more have DLTs during Cycle 1, an additional cohort of approximately 20 subjects will be treated with a reduced dose of AZA (36 mg/m^2, QD for 5 days) without dose modification of venetoclax (400 mg, QD) for 28 days. If 20% or more of these additional subjects experience DLTs during Cycle 1, a subsequent cohort of approximately 20 subjects may be treated with a reduced dose of AZA and/or reduced dosing duration per cycle of venetoclax. The recommended dose of venetoclax in combination with AZA will be such that fewer than 20% of subjects experienced a DLT during Cycle 1 in Part 1 (refer to Table 1).

Table 1. Dose Levels for Venetoclax + Azacitidine for Subjects in Part 1

Dose Level	Venetoclax Dose	Azacitidine Dose
1	400 mg × 28 days	50 mg/m^2 × 5 days
–1	400 mg × 28 days	36 mg/m^2 × 5 days
–2	400 mg × 21 days	36 mg/m^2 × 5 days
–3	400 mg × 21 days	20 mg/m^2 × 5 days

Subjects are considered to have completed the study treatment once they complete 24 treatment cycles. Subjects with controlled disease, who have not experienced a DLT, and who have tolerable side effects may continue to receive study drug for up to 48 cycles or until relapse, unacceptable toxicity occurs, or until the study closes. The investigator may discontinue a subject from the study as deemed appropriate.

As of 26 August 2021, 66 subjects were enrolled in Part 1 (Dose Confirmation).

Part 3: Dose Finding

Part 3 (Dose Finding) will follow a Bayesian optimal interval (BOIN) design to guide dose-escalation and de-escalation decisions based on the cumulative number of subjects experiencing a DLT at the current dose level. Table 2 gives the dose levels of venetoclax in combination with oral AZA to be explored. Venetoclax and oral AZA may be administered for up to 24 cycles.

In the dose-escalation portion, each dose level will initially enroll at least 6 DLT-evaluable subjects. The first cohort of subjects will be assigned to receive dose Level 1 (venetoclax [400 mg] QD on Days 1 to 21 in combination with oral AZA [200 mg] QD on Days 1 to 14 of each 28-day cycle) with dose escalation or de-escalation for the subsequent cohort of subjects guided by a BOIN design. Table 3 gives the BOIN

dose-escalation decision rule for a target toxicity rate of 20% and optimal interval of (16.9%, 25.1%). Approximately 12 subjects will be assigned to receive the preliminary RPTD identified during dose escalation.

The safety expansion portion will enroll at least 12 additional subjects to receive venetoclax in combination with oral AZA at the preliminary RPTD identified from dose-escalation portion of Part 3.

Subjects will be assessed for potential evidence of AML relapse through medical history, physical examination, and hematological laboratory review as detailed in the Operations Manual Section 3.14.

Subjects with controlled disease who have not experienced a DLT and who have tolerable side effects may continue to receive study drugs for 24 cycles or until relapse or unacceptable toxicity occurs. The investigator may discontinue a subject from the study as deemed appropriate.

Subjects who discontinue study drug but have not had an event of documented relapse will return for post-treatment follow-up visits. Subjects in Part 3 (Dose Finding) will return for post-treatment follow-up visits every 3 months (± 28 days) for 1 year and then every 6 months (± 28 days) thereafter starting from study drug discontinuation until documented relapse or the study ends, whichever occurs first. After relapse, survival information will be collected (e.g., via telephone calls and/or clinical visits) every 3 months (± 28 days) or more frequently at the sponsor's discretion for up to 2 years after relapse or until the sponsor's decision to stop follow-up.

Table 2. Venetoclax and Oral AZA Dose Levels

Dose Level	Venetoclax Dose	Oral AZA Dose
–1[a]	400 mg × 14 days	200 mg × 14 days
1[b]	400 mg × 21 days	200 mg × 14 days
2	400 mg × 21 days	300 mg × 14 days
3	400 mg × 28 days	300 mg × 14 days

a. Dose level -1 may be explored if the starting dose is not tolerated.

b. Starting dose level.

Table 3. Dose-Escalation Decision Rule

Action	Number of DLT-Evaluable Subjects at Current Dose Level								
	6	7	8	9	10	11	12	13	14
Escalate if # subjects with DLT ≤	1	1	1	1	1	1	2	2	2
Stay at current dose if # subjects with DLT =	-	-	2	2	2	2	3	3	3
De-escalate if # subjects with DLT ≥	2	2	3	3	3	3	4	4	4
Eliminate[a] if # subjects with DLT ≥	3	4	4	4	5	5	5	5	6

DLT = dose-limiting toxicity

a. Eliminate current and higher dose levels (i.e., venetoclax dose level and oral AZA dose level ≥ current dose).

As of 08 September 2022, 46 subjects were enrolled in Part 3 (Dose Finding).

Part 3: Randomization

Part 3 (Randomization) was removed from Version 6.0 of this protocol.

4.2 Discussion of Study Design

Appropriateness of Measurements

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

The PRO measures chosen for this study have been validated in cancer patients and include a generic health-related QoL measure (EQ-5D-5L), a cancer-specific health-related QoL measure that includes functional and symptom scales as well as a GHS scale (EORTC QLQ-C30), and a symptom-based measure to assess fatigue (PROMIS Fatigue SF 7a). The specific symptoms and functional aspects assessed by these measures are considered to be among the most impactful to AML patients.[4,39]

Suitability of Subject Population

Subjects with AML have poor survival and high relapse rates. The majority of patients with AML who achieve remission with induction chemotherapy will then go on to relapse. The prevention of relapse is a major therapeutic challenge in the treatment of AML. No post-consolidation treatment for prevention of relapse was previously established except for the use of allogeneic stem cell transplant for a select group of relatively fit patients and, more recently (2020), ONUREG (oral AZA) for patients with AML who achieved first CR or CRi following intensive induction chemotherapy and were not able to complete intensive curative therapy.[31]

It is hypothesized that a reservoir of leukemia stem cells that persist after primary therapy ultimately expand and drive relapse in AML. Combined therapy with venetoclax + AZA has been shown to eradicate leukemia stem cells through disruption of the metabolic machinery in AML. These data support the conduct of a maintenance study incorporating both these agents.

Preliminary studies have demonstrated that both venetoclax and AZA can induce responses for subjects with AML and be dosed safely. Therefore, given the high relapse rates and current limited effective options, and the safety of venetoclax and AZA to date, the subject population (subjects with AML in first remission after conventional chemotherapy) is suitable for treatment with venetoclax + AZA as maintenance therapy.

Oral AZA was the first maintenance therapy to provide statistically significant and clinically meaningful improvements in survival relative to placebo in a similar patient population as this study with subjects who have AML in remission following intensive chemotherapy.[31] Therefore, given the safety and efficacy of venetoclax and oral AZA to date, the subject population (subjects with AML in first remission after conventional chemotherapy) is suitable for treatment with venetoclax + oral AZA as maintenance therapy.

Selection of Doses in the Study

The maximum-tolerated dose (MTD) for venetoclax monotherapy has not been reached; however, 1200 mg QD was safely dosed in Study M14-212 "A Phase 2 Study of ABT-199 in Subjects with Acute Myelogenous Leukemia (AML)." In Study M14-212, subjects who did not respond at the 800-mg dose were allowed to dose escalate to 1200 mg. None of the subjects who dose escalated to 1200 mg in Study M14-212 achieved a response upon escalation.

Part 1 of this study consists of a dose confirmation cohort which will confirm the dose selection. The target venetoclax dose for the initial cohort is 400 mg, a third of the dose safely administered to subjects with R/R AML as monotherapy in Study M14-212. A dose of 400 mg was selected as the target dose as this is the approved dose in chronic lymphocytic leukemia (CLL) as monotherapy and the US Food and Drug Administration (FDA)-approved dose used in combination with AZA in AML (newly diagnosed subjects who are ineligible for intensive chemotherapy). In the Phase 1b AML study, Study M14-358, subjects were safely administered 400 mg, 800 mg, and 1200 mg of venetoclax in combination with AZA.

Although venetoclax 400 mg in combination with AZA treatment (75 mg/m^2) in Study M14-358 was proven to be safe and is currently being administered in Study M15-656 "A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy" to subjects with active disease, subjects already in remission may benefit even greater from a regimen that is well tolerated. Therefore, to reduce the rates of AEs and because this dose or lower has been proven to be pharmacodynamically active, AZA will be administered at 50 mg/m^2 for 5 days (Days 1 - 5) for each 28-day cycle.[40] The lead-in phase to confirm the dose for venetoclax + AZA (Part 1) will ensure that the thresholds of safety will be met. In summary, venetoclax 400 mg QD in combination with AZA 50 mg/m^2 QD is expected to be efficacious with an acceptable safety profile.

Part 3 of this study consists of a dose-finding portion which will confirm the dose selection of venetoclax in combination with oral AZA. The target venetoclax dose for the initial cohort is 400 mg, QD for 21 days for each 28-day cycle. The target dose for the initial cohort for oral AZA is 200 mg (Days 1 to 14 for each 28-day cycle). Oral AZA has demonstrated a prolonged therapeutic activity over a 28-day cycle at this dose level when administered as a monotherapy.[41]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

A subject will be eligible for study participation if he/she meets the following criteria within 28 days prior to the first day of study drug administration.

Consent

- 1. Subjects or their legally authorized representative (if permitted per local regulations) must be capable of understanding and complying with parameters as outlined in the protocol and must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult individuals ≥ 18 years old.
- 3. Subject must meet the following laboratory parameters, per laboratory reference range within the **screening period <u>prior to study drug administration</u>**:
  - creatinine clearance ≥ 30 mL/minute; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection;
  - bilirubin < 3.0 × upper limit of normal (ULN) (adequate liver function) for Part 1, or bilirubin < 2.0 × ULN for Part 3;
  - absolute neutrophil count (ANC) ≥ 1,500/µL;
  - platelets ≥ 100,000/µL.
- 4. Subject is willing and able to comply with procedures required in this protocol.

Disease Activity

- 5. Diagnosis of newly diagnosed AML.
- 6. Subject meets the following disease activity criteria:
  - confirmation of AML by the WHO criteria (2016)
  - confirmation of CR or CRi following completion of intensive Induction and Consolidation chemotherapies (note: additional consolidation therapy on-study will be considered a protocol violation)
  - subject should be within one of the following time windows:
    - achieved first CR or CRi (after induction) within 120 days of the first dose of study drug (Cycle 1 Day 1), or

- be no more than 75 days since last dose of intensive conventional (including both induction and consolidation) chemotherapies until enrollment (Cycle 1 Day 1)

- AML has intermediate or poor risk cytogenetics per National Comprehensive Cancer Network (NCCN) 2016 criteria (Appendix E)[42]

✓ 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

Subject History

✓ 8. No history of APL.

✓ 9. No history of active central nervous system involvement with AML.

✓ 10. Subjects with human immunodeficiency virus (HIV) will be permitted provided that subjects have stable disease and are on antiretroviral medication (highly active antiretroviral therapy [HAART]) that are not strong or moderate cytochrome P450 (CYP)3A inducers. Appropriate dose adjustments for venetoclax will be made for HAART therapy implicated in drug-drug interactions.

✓ 11. No subjects with active hepatitis B virus (HBV) and/or hepatitis C virus (HCV) with high viral titers. Subjects with HBV inactive carrier status and/or HCV with low viral titers on antivirals (nonexclusionary medications) are eligible.

✓ 12. No known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, they should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen once (Section 4.1).

✓ 13. No cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease which subjects are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain.

✓ 14. No chronic respiratory disease that requires continuous oxygen or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, any other medical condition that, in the opinion of the investigator, would adversely affect his/her participating in this study.

✓ 15. No malabsorption syndrome or other condition that precludes enteral route of administration.

✓ 16. No evidence of other clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial, or fungal).

✓ 17. No psychiatric illness/social situation that would limit compliance with the study.

✓ 18. No history of **any malignancy** with the exception of:

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

- Prior history of malignancy which is considered to be cured by the investigator.

- 19. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 20. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 21. Subject must not have been treated with a medical product without any global regulatory approvals within 30 days or 5 half-lives of the drug (whichever is shorter) prior to Cycle 1 Day 1.
- 22. Subject must not be currently receiving AML treatment in any other clinical study.
- 23. No history of allogeneic stem cell transplantation and subject is not a candidate for allogeneic stem cell transplantation and will not proceed with transplantation as a decision has been made on the recommendation of the treating physician or subject's preference, or a suitable donor source cannot be identified.
- 24. No history of autologous stem cell transplantation for AML.

Contraception

- 25. For all females of childbearing potential; a **negative serum pregnancy test** at the screening visit and a negative urine pregnancy test at baseline prior to enrollment.
- 26. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** that is effective from Study Day 1 through at least 6 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax.
- 27. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** from Study Day 1 through at least 6 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax.
- 28. **If male**, and is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 3 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax, to practice the protocol-specified contraception.
- 29. Male who is not considering **fathering a child or donating sperm** from Study Day 1 through at least 3 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax.

Concomitant Medications

- 30. Subject must not have received **any live vaccine** within 4 weeks prior to enrollment or not be expected to need or to receive a live vaccination during study participation including within 3 months of last dose of an oncologic therapy or within 6 months of receiving any anti-B-cell antibodies or within 12 months after remission.
- 31. Subject must not have received a known **strong or moderate inducer of CYP3A** 7 days before study drug administration. Subject must not have known medical conditions requiring chronic therapy of moderate CYP3A inducers.

- 32. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days before study drug administration.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects receiving study drug must follow the following contraceptive guidelines as specified:

- Females, Nonchildbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of nonchildbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
  - Females who have not experienced menarche (at least 1 menstrual period).

- Females, Childbearing Potential

  If a female does not meet the definition of a female of non-childbearing potential above, she would be considered to be a female of childbearing potential.

  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 6 months after the last dose of AZA or oral AZA and at least 30 days after the last dose of venetoclax, when the last dose of AZA or oral AZA was at least 6 months prior.
  - Females of childbearing potential must use a contraceptive method listed below that is highly effective (with a failure rate of < 1% per year, when used consistently and correctly):

Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Day 1). Also, subjects must use a barrier method during this study from initial study drug administration to at least 30 days after the last dose of venetoclax and at least 6 months after the last dose of AZA or oral AZA.

- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Day 1). Also, subjects must use a barrier method during this study from initial study drug administration to at least 30 days after the last dose of venetoclax and at least 6 months after the last dose of AZA or oral AZA.

- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, one of the following should be used in addition to one of the birth control methods listed above (excluding true abstinence):

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1;
- male or female condom with or without spermicide;
- cap, diaphragm, or sponge with spermicide; or
- a combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier method).

  Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects are eligible to participate if they agree to the following from Study Day 1 and for at least 3 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax:

- Refrain from donating sperm

  PLUS, either:

- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable.

  OR

- Use a male condom (even with a successful vasectomy) with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% (when used consistently and correctly) per year

  AND

- Advise of the benefit for a female partner to use a highly effective method of contraception (as a condom may break or leak) if having sexual intercourse with a woman of childbearing potential who is not currently pregnant

Highly effective methods of birth control (with a failure rate of < 1%, when used consistently and correctly) are the following:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Day 1).
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study baseline (Day 1).
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).

5.3 Prohibited Medications and Therapy

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

- strong CYP3A inducers (consider alternative treatments with less CYP3A induction)
- grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) and star fruit
- adjuvant therapies, concomitant medications, or herbal substances that exert immunomodulating or antitumor activity

For subjects receiving Dose Level 1 or Dose Level 2 in the dose-escalation portion of Part 3 (Dose Finding), the following concomitant medications are also not allowed from Cycle 1 Day 7 through Cycle 1 Day 22:

- moderate CYP3A inducers
- strong or moderate CYP3A inhibitors
- P-glycoprotein (P-gp) inhibitors

For all subjects, the following are not allowed during the study (after enrollment on Cycle 1 Day 1):

- additional consolidation chemotherapy
- cytotoxic chemotherapy agents or experimental agents
- targeted therapy (e.g., FLT3 inhibitors) (note: subjects who received targeted therapies during Induction and/or Consolidation are allowed in the study)

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

5.4 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins, and/or herbal supplements or if administration of any medication becomes necessary, beginning with the screening visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded. The investigator should review all concomitant medications for any potential drug-drug interactions.

The following concomitant medications/therapy are permitted as needed and per institutional guidelines:

- supportive care medication;
- anti-infectives, antiemetics, antidiarrhea, and other standard supportive care medication;
- transfusion of blood and blood products; and
- granulocyte-colony stimulating factor (G-CSF; may be administered when Grades 3 to 4 neutropenia occurs per clinical practice).

In addition, the following apply (except for subjects receiving Dose Level 1 or Dose Level 2 in the dose-escalation portion of Part 3 [Dose Finding], from Cycle 1 Day 7 through Cycle 1 Day 22 which prohibit the following):

- Concomitant use of a moderate CYP3A inducer should be avoided. Alternative treatments with less CYP3A induction should be considered.
- Herbal supplements should be discouraged unless known not to be CYP3A active (inducers or inhibitors).
- If a P-gp inhibitor must be used, monitor closely for signs of toxicities or follow local label as applicable.
- Concomitant use of narrow therapeutic index P-gp substrates should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

CYP3A inhibitors and inducers should only be used when no appropriate therapeutic alternative exists. Co-administration of a strong or moderate CYP3A inhibitor requires a specified venetoclax dose reduction as presented in Table 4. The venetoclax dose that was used prior to concomitant use of a strong or moderate CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Table 4. Venetoclax Dose Modification when Co-Administered with Strong or Moderate CYP3A Inhibitors

Assigned Venetoclax Dose	Venetoclax Dose if Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose if Co-Administered with a Strong CYP3A Inhibitor
400 mg	200 mg	70 mg[a] or 100 mg[b,c]

CYP = cytochrome P450

a. United States, China, Israel, Taiwan, and Russia will dose reduce to venetoclax 70 mg when co-administered with Posaconazole.

b. All other countries will dose reduce to venetoclax 100 mg when co-administered with Posaconazole.

c. All countries will dose reduce to venetoclax 100 mg when co-administered with other strong CYP3A inhibitors.

Subjects who are taking a strong or moderate CYP3A inhibitor before Cycle 1 Day 1 would start venetoclax at a reduced dose on Cycle 1 Day 1 according to Table 4 and may receive venetoclax 400 mg 2 to 3 days after discontinuation of the CYP3A inhibitor.

Breast cancer resistance protein (BCRP) inhibitors are not expected to result in clinically relevant effects on venetoclax exposure.[43] When coadministered with a BCRP inhibitor, no dose adjustment for venetoclax will be necessary or follow local label as applicable.

Organic anion-transporting polypeptide (OATP) inhibitors are not expected to result in clinically relevant effects on venetoclax exposure.[43] When coadministered with an OATP inhibitor, no dose adjustment for venetoclax will be necessary.

In vitro, venetoclax is a BCRP inhibitor and a weak OATP1B1 inhibitor. When a BCRP or OATP substrate is coadministered with venetoclax, follow the local label as applicable.

Subjects should not receive live vaccines within 3 months of last dose of an oncologic therapy and within 6 months of receiving any anti-B-cell antibodies. Additionally, live vaccines should not be given within 12 months remission and lymphocyte count must be > 1,500/µL.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie TA MD. Information regarding potential drug interactions with venetoclax, AZA, or oral AZA can be located in the venetoclax Investigator's Brochure,[36] the AZA SmPC,[37] the oral AZA SmPC[38], package inserts, prescribing information, and/or their equivalents.

COVID 19 Pandemic Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger RNA [mRNA], non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of venetoclax on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug(s), when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in subjects with AML and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

Withdrawal from Study Treatment

A subject may voluntarily withdraw or be withdrawn from the study treatment at any time. These subjects will be included in the efficacy and safety analyses. Reasons for withdrawal from study treatment include, but are not limited to, the following:

- The investigator believes discontinuation is in the best interest of the subject.
- The subject requests withdrawal from the study or study treatment.
- Eligibility criteria violation was noted after the subject started the study and continuation on the study would place the subject at risk as determined by the investigator or the AbbVie TA MD.
- The introduction of prohibited medication putting the subject at undue risk that may lead to withdrawal from the study as determined by the investigator or the AbbVie TA MD.
- Clinically significant abnormal laboratory results or AEs which rule out continuation of the study drug with reductions in the lowest available dose, as determined by the investigator or the AbbVie TA MD.
- The subject becomes pregnant while on study drug.
- The investigator determines the subject is significantly noncompliant with study procedures.
- Disease relapse: reappearance of ≥ 5% blasts after CR or CRi in peripheral blood or bone marrow or development of extramedullary disease.

All subjects will complete the procedures outlined for the final visit, within 2 weeks of the last dose of study drug, and a 30-day follow-up visit, also calculated from the last dose of study drug.

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

Discontinuation of Study

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID 19 Pandemic Related Acceptable Protocol Modification

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

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

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

Interruption/Discontinuation of Study Drug Due to COVID 19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic subjects or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie TA MD, along with the possibility of premature discontinuation from the study drug dosing period. Follow guidelines in Section 5.6 for subjects who discontinue study drug.

5.6 Follow-Up for Subject Withdrawal from Study

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

Part 3 subjects who discontinue study drug prior to Cycle 24 or who have completed 24 cycles but have not had an event of documented relapse will return for post-treatment follow-up visits every 3 months (± 28 days) for 1 year and then every 6 months (± 28 days) thereafter starting from study drug discontinuation until documented relapse or the study ends, whichever occurs first. After relapse, survival information will be collected (e.g., via telephone calls and/or clinical visits) every 3 months (± 28 days) or more frequently at the sponsor's discretion for up to 2 years after relapse or until the sponsor's decision to stop follow-up.

If a Part 3 subject withdraws from study follow-up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that the patient has withdrawn consent and no longer wishes biomarker research to continue, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Study drugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the Investigational Product. Investigators will assess the relationship of AEs to the use of study drugs (see Table 5 for the list of study drugs).

Venetoclax manufactured by AbbVie will be administered orally, QD for each 28-day cycle beginning on Day 1 for subjects in Part 1 (Dose Confirmation) and Part 3 (Dose Finding).

If vomiting occurs after taking venetoclax, another dose should not be taken that day. In cases where a dose of venetoclax is missed or forgotten, the subject should take the forgotten dose as soon as possible, provided that the dose is taken within 8 hours of the missed dose and is taken with food and water. Otherwise, the missed dose should not be taken and the subject should take the next dose at the next scheduled dosing time.

AZA will be administered SC or IV, QD on Days 1 to 5 of each 28-day cycle, for up to 6 cycles (refer to Operations Manual Section 6.1) for subjects in Part 1. AZA must be prepared and administered by the route indicated in the package insert, prescribing information, local SmPC, or equivalent.

Oral AZA will be administered QD on Days 1 to 14 of each 28-day cycle for up to 24 cycles for subjects in Part 3. Subjects will be trained to self-administer oral AZA (refer to Operations Manual Section 6.1).

If vomiting occurs after taking oral AZA, a second dose should not be taken that day as subjects must not take 2 doses on the same day.

In cases where a dose of oral AZA is missed or forgotten, the subject should take the forgotten dose as soon as possible and resume the normal schedule in the following day.

The investigational medicinal products for this study are venetoclax, AZA, and oral AZA. AbbVie will supply venetoclax, AZA, and oral AZA. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie. AbbVie will not supply drugs other than venetoclax, AZA, and CC486. Non-investigational medicinal product (i.e., BSC) must be obtained commercially. AbbVie will not provide or reimburse for treatments administered for BSC.

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) study drug shipment can be made from the study site to the subject if allowed by local

regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix J for details on DTP shipment of study drug.

Subjects will record venetoclax dosing in a subject dosing diary. Subjects who are treated with oral AZA will also record oral AZA dosing in a subject dosing diary (refer to Operations Manual Section 3.17).

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

Study drug information is presented in Table 5.

Table 5. Study Drug Information

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Venetoclax	AbbVie	Oral	Film-coated tablet	100 mg, 50 mg, 10 mg
Azacitidine	Celgene or generic	Subcutaneous or intravenous	Powder for suspension or solution	100 mg (25 mg/mL or 10 mg/mL after reconstitution)
Azacitidine	BMS / Celgene / Fisher or generic	Oral	Film-coated tablet	200 mg, 300 mg

Note: Venetoclax, azacitidine, and oral AZA will be provided as open-label supplies for Part 1 and Part 3 (Dose Finding).

Venetoclax will be packaged in bottles with quantities sufficient to accommodate study design. AZA (IV/SC) will be in single-use vials packaged in cartons to accommodate the study design. Each vial must be reconstituted and administered by the route as per the local AZA label. Oral AZA will be packaged in blister cards with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept temperature monitored in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drugs will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

5.8 Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. All subsequent drug assignments and changes in subject status (e.g., study completion) will be registered in the IRT.

5.9 Protocol Deviations

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

5.10 Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

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

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned 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 AE.

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. 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.

All serious and nonserious AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related SAEs and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for a Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	A suspected SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is not listed in the applicable Reference Safety Information, and meets one of the above serious criteria. All individually reported SARs are considered suspected.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation.

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

Adverse Events of Special Interest

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

- tumor lysis syndrome (TLS)

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap. For all reported SAEs that increase in severity, the supplemental electronic case report forms (eCRFs) also need to be updated to reflect any changes due to the increase in severity.

For AEs not captured by the NCI CTCAE, the following should be used:

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

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 3 months after the last dose of AZA or oral AZA and 30 days after the last dose of venetoclax.

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

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described below. This includes AEs of neutropenia for venetoclax and known potential risks associated with AZA or oral AZA. Subjects will be

monitored for these events throughout the study and treatment may be discontinued or adjusted as appropriate.

Tumor Lysis Syndrome

Subjects in this study will have AML after first remission (CR or CRi) resulting from conventional chemotherapy. Therefore, although TLS is an identified risk with venetoclax treatment, TLS is highly unlikely to occur during this study because subjects will have relatively low levels of leukemic cells at the onset of venetoclax administration.

Management of Treatment Related Neutropenia

Venetoclax, AZA, and oral AZA may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies may be at a particularly high risk. Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax, AZA, and oral AZA. Subjects will be managed for neutropenia as detailed below.

Complete blood counts should be monitored throughout the treatment period. Supportive measures including anti-infectives for prophylaxis or any signs of infection and prophylactic use of growth factors (e.g., G-CSF) should be considered.

Management of Treatment Related Hematologic Toxicities

Treatment may be withheld for any therapy-related Grade 4 hematologic toxicity if subject had ≤ Grade 2 toxicity at baseline. Treatment may be restarted after the toxicity has resolved to Grade 1 or 75% of the baseline level (recovery) (Appendix D). If the toxicity recurs, the dose reduction guidelines outlined in Table 6, Table 7, and Table 8 should be followed when resuming study drug following resolution. Additional dose reductions may occur at the discretion of the investigator in consultation with the AbbVie TA MD.

Management of Treatment Related Nonhematologic Adverse Events

Treatment may be withheld for any clinically relevant ≥ Grade 3 nonhematologic AE. Once the AE has resolved to Grade 1 or baseline grade level (recovery), treatment may be restarted. If the toxicity recurs, the dose reduction guidelines outlined in Table 6, Table 7, and Table 8 should be followed when resuming study drug following resolution. Additional dose reductions may occur at the discretion of the investigator.

Management of Infection

Anti-infective prophylaxis for bacterial, viral, and fungal infections is recommended for all subjects with ANC of < 500/µL at any time point. Institutional infectious organisms and their drug resistance patterns should primarily be considered, and the choice of these agents should be based on regional guidelines or institutional standards. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions (Table 4).

All subjects should be monitored for new onset hematologic toxicity, with dose delay or reduction as appropriate.

Management of Decrease in Spermatogenesis

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

Management of Diarrhea Grade ≥ 3 (Part 3 only)

It is recommended that subjects experiencing diarrhea be managed according to the guidelines provided in Appendix F. Antidiarrheal medication may be administered as prophylaxis against diarrhea and for treatment of any AEs of diarrhea. In subjects not having problems during the first 2 cycles, the treating physician may discontinue use of antidiarrheal medications.

Management of Nausea and Vomiting Grade ≥ 3 (Part 3 only)

A serotonin (5-HT^3) receptor antagonist (e.g., ondansetron) or other comparable medication should be administered as an antiemetic approximately 30 minutes prior to administration of study drug. Antiemetic medication(s) should be administered for treatment of any AEs of nausea and/or vomiting. If there has been no nausea and/or vomiting during the first 2 cycles, the investigator may choose to omit antiemetic as required provided this is clearly documented in the eCRF.

Refer to Appendix G for recommendations for management of treatment-induced nausea and GI events.

Dose Modifications Based on Toxicities

Subjects who interrupt study drug for drug-related toxicities should resume treatment when the toxicity has resolved. Toxicity management guidelines and dose reductions will differ for subjects taking combination therapy (Table 7 and Table 8) compared to patients taking venetoclax monotherapy (Table 6).

Dose Modifications for Venetoclax Monotherapy

See Appendix D and Table 7 and Table 8 for dose interruptions and reductions for toxicities related to venetoclax + AZA or oral AZA and Table 6 for recommendations for reinitiating venetoclax treatment after interruption.

If ANC drops below 500/µL, venetoclax may be interrupted for ANC recovery until ANC ≥ 500/µL or up until 14 days. For subjects who have not recovered (ANC ≥ 500/µL) within or beyond 14 days of interruption, per investigator discretion, a bone marrow sample may be collected and analyzed to exclude relapse before proceeding. If relapse is confirmed, subjects should be withdrawn from the study treatment for alternative therapy. If relapse is excluded, per investigator discretion, growth factor support may be used to stimulate count recovery. If a subject presents with new onset Grade 4 neutropenia for more than 1 week during subsequent cycles, unless it is thought to be due to the underlying disease, venetoclax dosing may be interrupted until ANC recovery (≥ 500/µL) per investigator discretion and in consultation with the AbbVie TA MD. Venetoclax may be reinitiated at a lower dose based on Table 6. For subjects who require interruption or delay of study drug administration for cytopenia, venetoclax may be administered for 21 days out of 28 days during each of the subsequent cycles. If a subject continues to have persistent cytopenia (i.e., ANC < 1,000/µL and/or platelets < 50,000/µL) venetoclax may be administered for 14 days out of 28 days during each of the subsequent cycles. Subjects who develop cytopenias during subsequent cycles will have reduction in the duration of

venetoclax dosing as described in Table 6 beginning from whichever cycle cytopenias were first observed.

Venetoclax dose modifications for possible drug-drug interactions are provided in the Section 5.4.

Table 6. Reduced Duration of the Venetoclax Dosing Schedule for Subjects (Part 1 Only)

Reduced Duration of Venetoclax[a]	Absolute Neutrophils/Platelets	Venetoclax Dosing Schema
First reduction	< 500/µL/< 25,000/µL	Venetoclax 400 mg Days 1 through 21 for each 28-day cycle
Second reduction	< 1,000/µL/< 50,000/µL	Venetoclax 400 mg Days 1 through 14 for each 28-day cycle
Subsequent reduction	< 1,000/µL/< 50,000/µL	Venetoclax 400 mg Days 1 through 10 for each 28-day cycle

a. Reduction in duration of venetoclax dosing should be followed sequentially in the order shown in the table above for subjects who require reductions in later treatment cycles.

Dose Modifications for Venetoclax + Azacitidine (Part 1 Only)

The use of venetoclax + AZA may exacerbate complications of myelosuppression which include infections and bleeding. Venetoclax + AZA treatment may be interrupted, delayed, or reduced (refer to Table 7 and Appendix D) 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 antiinfectives or extensive supportive care)
- hemorrhage (GI, genito-urinary, pulmonary with platelets < 25,000/µL, or any central nervous system hemorrhage)

Treatment with venetoclax + AZA may be resumed once the above conditions have improved or have been stabilized with adequate treatment (i.e., anti-infective therapy, transfusions, or growth factors) and the toxicity has resolved to ≤ Grade 1 or has returned to baseline level. Myelosuppression caused by venetoclax + AZA is reversible. Complete blood and platelet counts should be performed regularly, as clinically indicated, and prior to each treatment cycle. Subjects should not receive less than 400 mg for 7 days and 20 mg/m^2 for 5 days of venetoclax and AZA, respectively (Table 7).

Table 7. Dose Reduction for Venetoclax + Azacitidine for Subjects (Part 1 Only)

If Current Dose Level		Then Dose Reduction Level	
Venetoclax Dose	**Azacitidine Dose**	**Venetoclax Dose**	**Azacitidine Dose**
400 mg × 28 days	50 mg/m^2 × 5 days	400 mg × 28 days	36 mg/m^2 × 5 days
400 mg × 28 days	36 mg/m^2 × 5 days	400 mg × 21 days	36 mg/m^2 × 5 days
400 mg × 21 days	36 mg/m^2 × 5 days	400 mg × 21 days	20 mg/m^2 × 5 days
400 mg × 21 days	20 mg/m^2 × 5 days	400 mg × 14 days	20 mg/m^2 × 5 days
400 mg × 14 days	20 mg/m^2 × 5 days	400 mg × 7 days	20 mg/m^2 × 5 days
No further dose reductions			

Dose Modifications for Venetoclax + Oral AZA (Part 3 Only)

The use of venetoclax + oral AZA may exacerbate complications of myelosuppression which include infections and bleeding. Venetoclax + oral AZA treatment may be interrupted, delayed, or reduced (refer to Table 8 and Appendix D) 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 antiinfectives or extensive supportive care)
- hemorrhage (GI, genito-urinary, pulmonary with platelets < 25,000/µL, or any central nervous system hemorrhage)

Dose interruptions greater than 21 days in duration must be discussed with the AbbVie TA MD to determine if the subject may continue on study treatment.

Treatment with venetoclax + oral AZA may be resumed once the above conditions have improved or have been stabilized with adequate treatment (i.e., anti-infective therapy, transfusions, or growth factors) and toxicity has resolved to ≤ Grade 1 or has returned to baseline level. Study treatment should not be resumed for at least 3 days following resolution of fever. Complete blood and platelet counts should be performed regularly, as clinically indicated, and prior to each treatment cycle.

In the event of toxicity, a maximum of 1 dose reduction to a daily dose of 400 mg for 14 days is permitted for venetoclax. If toxicity persists in the subsequent cycle, a maximum of 1 dose reduction to a daily dose of 200 mg for 7 days is permitted for oral AZA. The decision to modify a subject's treatment schedule of venetoclax from 21 to 14 days and oral AZA from 14 to 7 days should first be discussed with the TA MD. Subjects should not receive less than 400 mg for 14 days and 200 mg for 7 days of venetoclax and oral AZA, respectively (Table 8).

Table 8. Dose Reduction for Venetoclax + Oral AZA for Subjects – Part 3: Dose Finding

If Current Dose Level		Then Dose Reduction Level	
Venetoclax Dose	**Oral AZA Dose**	**Venetoclax Dose**	**Oral AZA Dose**
400 mg × 21 days	300 mg × 14 days	400 mg × 21 days	200 mg × 14 days
400 mg × 21 days	200 mg × 14 days	400 mg × 14 days	200 mg × 14 days
400 mg × 14 days	200 mg × 14 days	400 mg × 14 days	200 mg × 7 days
No further dose reductions			

Any time during the study, if the subject must undergo emergency surgery, the study drug(s) should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug(s) once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.3 Dose-Limiting Toxicity Criteria

Part 1 (Dose Confirmation) and Part 3 (Dose Finding)

Any of the following events during Cycle 1, which are considered possibly or probably related to the administration of venetoclax, will be considered a DLT:

- Hematologic toxicities
  - any Grade ≥ 3 neutropenia lasting more than 7 days
  - any Grade ≥ 3 thrombocytopenia lasting more than 7 days
- Nonhematologic toxicities
  - any Grade 3 AE lasting ≥ 72 hours except for Grade 3 hypersensitivity reactions or Grade 3 localized injection-site toxicities
  - Grade ≥ 3 nausea, diarrhea, or vomiting despite adequate/maximal medical intervention lasting more than 7 days (Part 3 only)
  - any Grade ≥ 4 AE
  - any Hy's law cases defined as elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × ULN with concurrent elevated total bilirubin ≥ 2 × ULN in the absence of elevated alkaline phosphatase or other conditions that could cause these laboratory abnormalities

In addition, AEs not meeting above criteria but lead to omitting > 20% of the scheduled dose within the cycle should be considered as a DLT unless clearly related to underlying disease.

Treatment delay due to toxicity lasting greater than 14 days since the last dose of venetoclax will also be considered DLT.

Any DLT will require an interruption and possible discontinuation of venetoclax or AZA. Venetoclax may be reintroduced at a reduced dose if the toxicity grade returns to ≤ Grade 1 or to baseline if Grade 2 at study entry. If the subject is considered to be acceptable for resumption of venetoclax dosing at the same dose or reduced dose on Day 7 of the dose interruption, the event should not be designated as a DLT.

To be considered DLT-evaluable in Part 3, subjects must complete at least 80% of assigned venetoclax dosing and oral AZA dosing in Cycle 1 or experience a DLT in Cycle 1.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

7.2 Definition for Analysis Populations

The treated population includes all enrolled subjects who received at least one dose of both venetoclax and AZA in Part 1, as well as all subjects who received at least one dose of both venetoclax and oral AZA in Part 3. Unless otherwise noted, the treated population will be used for all safety, efficacy, and baseline analyses.

7.3 Statistical Analyses for Efficacy

Efficacy Analyses

Relapse Free Survival

RFS is the time from drug assignment to the date of relapse or the date of death from any cause, whichever comes first. If a subject does not experience an RFS event, the subject's data will be censored at the date of the subject's last disease assessment date (e.g., last bone marrow or hematology laboratory date) or date of drug assignment if the subject does not have any postbaseline disease assessment. The distribution of RFS will be estimated using Kaplan-Meier methodology.[44]

Overall Survival

OS is defined as time from drug assignment to death from any cause. OS data from subjects who have not died will be censored at the last known alive date. The distribution of OS will be estimated for each study arm using Kaplan-Meier methodology.[44]

MRD Conversion Rate

The MRD conversion rate is defined as the proportion of subjects deemed MRD-positive ($\geq 10^{-3}$) at screening who convert to MRD $< 10^{-3}$ after drug assignment. Subjects who are MRD $< 10^{-3}$ at screening

will be excluded from the analysis. The MRD conversion rate (95% CI) will be estimated using binomial distribution (Clopper-Pearson exact method).[45]

Time to Deterioration in GHS/QoL Score

Time to deterioration in GHS/QoL score is defined as time from drug assignment to death from any cause, or the first-time decrease of ≥ 10 points from baseline, whichever occurs first.[46] Subjects without any of the specified events will be censored at subject's last EORTC QLQ-C30 assessment. The distribution of time to deterioration in GHS/QoL will be estimated using Kaplan-Meier methodology.[44]

Change in Global Fatigue Score from Baseline to Post baseline

Fatigue will be assessed using the global fatigue score as measured by PROMIS Fatigue SF 7a. Scores will be computed according to the PROMIS fatigue scoring manual. Descriptive summaries will be provided for the change in fatigue score from baseline to post-baseline visits. Subjects without baseline score or any postbaseline score will be excluded from the analysis.

Additional Efficacy Analyses

Details on other efficacy analyses (i.e., analysis based on ELN[47] criteria if data are available) are provided in the SAP.

7.4 Statistical Analyses for Safety

Safety analyses will only include subjects in the Safety Analysis Set as defined in Section 7.2.

Analysis of Adverse Events

Treatment-emergent AEs will be summarized by preferred terms within a System Organ Class according to the Medical Dictionary for Regulatory Activities (MedDRA). In addition, the percentage of subjects experiencing an AE at a given NCI CTCAE (version 5.0) toxicity grade and relationship to study drug will be provided. Treatment-emergent SAEs will be summarized similarly.

Analysis of Laboratory Data

Change from baseline will be analyzed for each scheduled postbaseline visit for blood chemistry and hematology parameters. Subjects who do not have a baseline measurement or do not have any postbaseline measurement will not be included.

Where it is applicable, blood chemistry and hematology laboratory determinations will be categorized according to the NCI CTCAE. Grades and shifts from baseline NCI CTCAE grades to maximum postbaseline grades will be assessed.

7.5 Multiplicity Adjustment and Overall Type I Error Control

Not applicable for this study.

7.6 Sample Size Determination

Part 1

The sample size for Part 1 is intended to provide an adequate safety evaluation. The probability of observing at least 1 AE in a cohort of 20 subjects for various true AE rates is provided in Table 9.

Table 9. Probability of Observing at Least One Adverse Event in a Cohort of 20 Subjects for Various True Adverse Event Rates

True AE Rate	Probability to Observe at Least 1 AE
0.05	0.64
0.10	0.88
0.15	0.96
0.20	0.99

AE = adverse event

Part 3 (Dose Finding)

The total sample size for Part 3 (Dose Finding) will depend on the DLTs observed during dose escalation in Cycle 1 and is intended to provide an adequate safety evaluation of the RPTD of venetoclax in combination with oral AZA. Approximately 24 subjects will be assigned to receive the RPTD of venetoclax in combination with oral AZA. The probability of observing at least 1 AE in a cohort of 24 subjects for various true AE rates is provided in Table 10.

Table 10. Probability of Observing at Least 1 Adverse Event in a Cohort of 24 Subjects for Various True Adverse Event Rates

True AE Rate	Probability to Observe at Least 1 AE
0.05	0.71
0.10	0.92
0.15	0.98
0.20	> 0.99

AE = adverse event

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed

consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

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

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

8.3 Subject Confidentiality

Before subject data are shared with AbbVie, the study investigator and staff will replace the subject's name, address, and contact information with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

For the personal data that AbbVie Deutschland GmbH & Co acting as sponsor of the submitted study ("AbbVie") controls and maintains, AbbVie Deutschland has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

AbbVie has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

AbbVie Deutschland as the sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority without undue delay and at the latest within 72 hours after becoming aware of such an incident. AbbVie Deutschland shall create and maintain appropriate records of such an incident.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original,

accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s), including EU Clinical Trial Regulation.

10 DATA QUALITY ASSURANCE

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

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

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

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-24}	AUC from time 0 to 24 hours postdose
AUC_t	AUC from time 0 to the time of the last measurable concentration
AZA	azacitidine
BCL	B-cell lymphoma
BCL-w	B-cell lymphoma - Walter and Eliza Hall Institute
BCL-X_L	B-cell lymphoma - extra large
BCRP	breast cancer resistance protein
BOIN	Bayesian optimal interval
BSC	best supportive care
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease – 2019
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
DTP	direct-to-patient
EC	Ethics Committee

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European LeukemiaNet
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30-item
EQ-5D-5L	European Quality-of-Life-5 dimensions-5-level
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GHS	Global Health Status
GI	gastrointestinal
GLP	Good Laboratory Practice
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HR	hazard ratio
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IE	intercurrent events
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
IVRS	Interactive Voice Response System

IWG	International Working Group
IWRS	Interactive Web Response System
K_i	inhibition rate constant
LDAC	low-dose cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
mRNA	messenger RNA
MTD	maximum-tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OATP	organic anion-transporting polypeptide
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral(ly)
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	prothrombin time
QD	once daily
QoL	quality-of-life
RFS	relapse-free survival
RNA	ribonucleic acid
RPTD	recommended Phase 3 dose
R/R	relapsed/refractory
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SF	short form
SmPC	Summary of Product Characteristics

SOC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to C_{max}
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-708: Multicenter, Phase 3 Study of Venetoclax and Azacitidine as Maintenance Therapy for Patients with Acute Myeloid Leukemia in First Remission After Conventional Chemotherapy (VIALE-M)

Protocol Date: 26 April 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP), as well as applicable laws, regulations, and guidelines. Certain laws, regulations, or guidelines may apply to conduct of the study at investigator's site even if such laws, regulations, or guidelines originate in a foreign jurisdiction. The investigator agrees and acknowledges that applicable laws or regulations may require AbbVie to submit inspection reports, instances of significant non-compliance with the study protocol, or other documents regarding conduct of the study at the investigator's site to regulatory authorities, and such documents may be publicly disclosed by such authorities. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting the following to AbbVie within 1 calendar day of becoming aware:
   - Any unanticipated problems involving risks to human subjects
   - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has affected or is likely to affect to a **significant** degree the following:
     - Rights, safety, physical or mental integrity of the subjects in the clinical trial
     - Scientific value of the clinical trial, reliability or robustness of data generated

   Where required by local regulation, inform relevant Ethics Committees / Institutional Review Boards and other appropriate individuals (e.g., Co-ordinating Investigator, Institution Director).
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
[redacted]	[redacted]	Statistics

APPENDIX D. RECOMMENDED DOSE REDUCTIONS RELATED TO DRUG TOXICITIES

Recommended Venetoclax/Azacitidine and Venetoclax/Oral AZA Dose Modifications for Toxicities

Event	Occurrence	Action
Nonhematologic Adverse Events[a]		
≥ Grade 3 nonhematologic toxicities	1st occurrence	Interrupt venetoclax + AZA or venetoclax + oral AZA. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax + AZA or venetoclax + oral AZA may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax + AZA or venetoclax + oral AZA. Follow dose reduction guidelines in Section 6.2 when resuming treatment with venetoclax + AZA or venetoclax + oral AZA after resolution. A greater dose reduction may occur at the discretion of the investigator after discussion with TA MD.
≥ Grade 3 diarrhea (Part 3 only)	1st occurrence	Interrupt venetoclax + oral AZA and provide adequate/ maximum medical intervention (refer to Appendix F). Resume venetoclax + oral AZA at same dose when toxicity resolves to ≤ Grade 1.
	2nd and subsequent occurrences	Interrupt venetoclax + oral AZA. Follow dose reduction guidelines in Section 6.2 when resuming venetoclax + oral AZA after resolution. A greater dose reduction may occur at the discretion of the investigator after discussion with TA MD.
≥ Grade 3 nausea and/or vomiting (Part 3 only)	1st occurrence	Interrupt venetoclax + oral AZA and provide adequate/maximal medical intervention. Resume venetoclax + oral AZA at same dose when toxicity resolves to ≤ Grade 1.
	2nd and subsequent occurrences	Interrupt venetoclax + oral AZA. Follow dose reduction guidelines in Section 6.2 when resuming venetoclax + oral AZA after resolution. A greater dose reduction may occur at the discretion of the investigator after discussion with TA MD.

Event	Occurrence	Action
Hematologic Toxicities[a,b]		
Grade 3 neutropenia and/or thrombocytopenia if lasts 7 days or longer; or Grade 3 neutropenia with infection or fever; or Grade 3 thrombocytopenia with hemorrhage; or All Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax + AZA or venetoclax + oral AZA. Treatment may be resumed at the same dose once the condition(s) have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors) and toxicity has resolved to ≤ Grade 1 or has returned to 75% of the baseline level, as assessed by investigator. Dose interruption in case of prolonged toxicity (≥ 14 days) should be discussed with the TA MD. Any dose reduction should be discussed with the TA MD when resuming treatment with venetoclax + AZA or venetoclax + oral AZA after resolution.
	2nd and subsequent occurrence	Interrupt venetoclax + AZA or venetoclax + oral AZA. Follow dose reduction guidelines in Section 6.2 when resuming treatment with venetoclax + AZA or venetoclax + oral AZA after resolution (resolved to ≤ Grade 1 or returned to 75% of the baseline level as assessed by investigator). Additional dose reductions may occur at the discretion of the physician and in consultation with the TA MD.
Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.		

AZA = azacitidine; TA MD = Therapeutic Area Medical Director

a. Once a dose has been reduced, the dose will not be increased again.

b. There is no increase in oral AZA dose independent of percentage of blasts in the bone marrow.

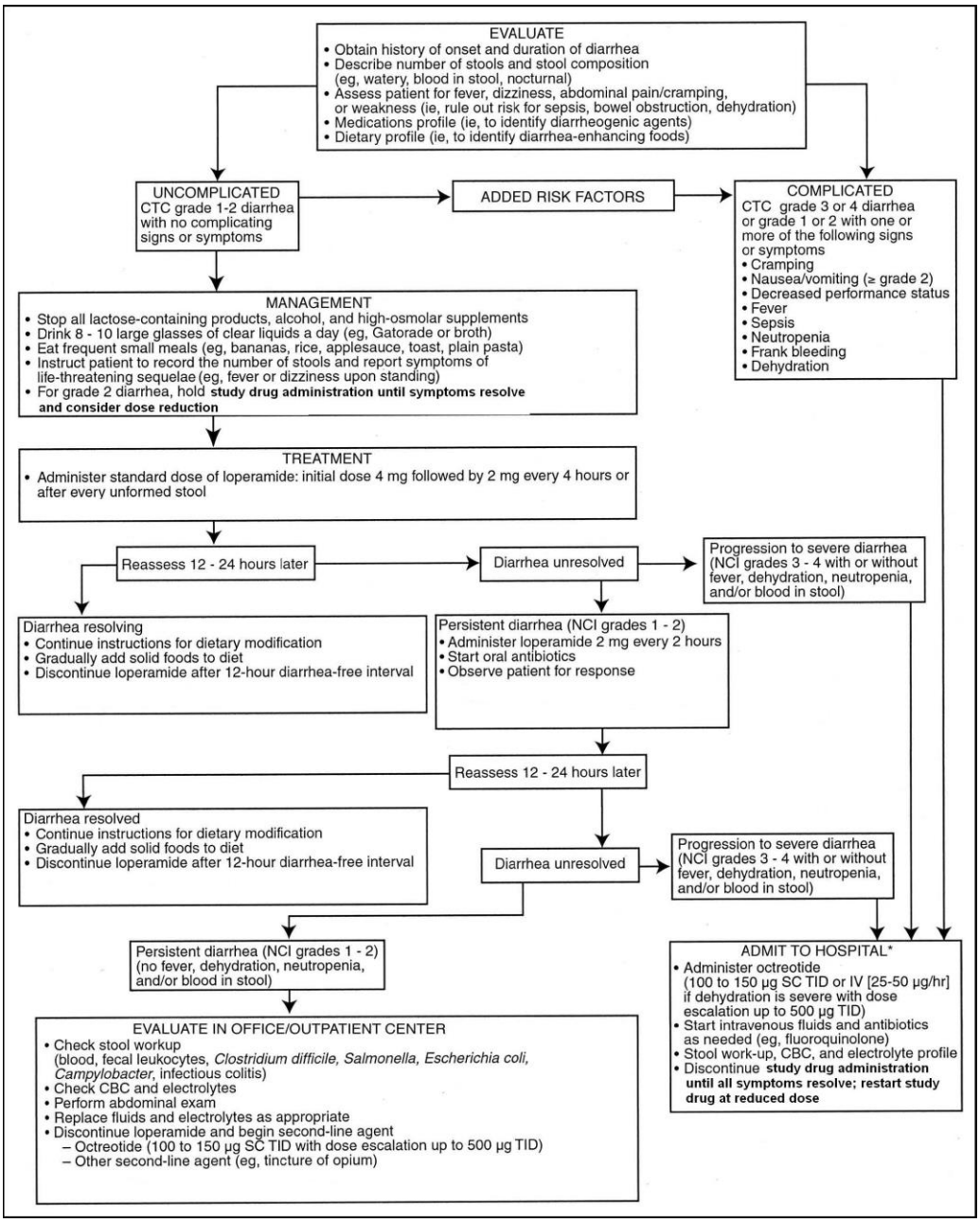
APPENDIX E. NCCN RISK CATEGORIZATION: GUIDELINES FOR AML, VERSION 2, 2016

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

AML = acute myeloid leukemia; NCCN = National Comprehensive Cancer Network

APPENDIX F. RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED DIARRHEA

The following published guidelines (Benson et al 2004) were modified to be consistent with the clinical study protocol.



Benson AB, Ajani JA, Catalano RB, et.al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. 2004. J Clin Oncol. 22(24):2918-26.

APPENDIX G. RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED NAUSEA AND GASTROINTESTINAL EVENTS

The following guidance is provided for management of GI AEs in AML patients receiving oral AZA.[48]

1. Treatment of GI reflux with proton pump inhibitors or histamine H2-receptor antagonists (e.g., cimetidine, famotidine) may ameliorate dyspepsia, which can mimic nausea.
2. Taking oral AZA with food may alleviate nausea and vomiting by diluting the drug in the upper GI tract, improving motility, and slowing the rate of absorption.
3. Consensus clinical practice guidelines[49-51] emphasize the use of 3 drug classes for optimal treatment of chemotherapy-induced nausea and vomiting: 5-HT3 receptor antagonists, corticosteroids, and neurokinin-1 receptor antagonists.
4. Although higher-grade GI events are uncommon, oral AZA treatment should be interrupted for subjects who experience Grade 3 4 nausea, vomiting, or diarrhea, according to Appendix D.
5. Nonpharmacologic approaches to reducing nausea and vomiting are shown in the table below.
6. Note: When adding a new medication given concomitantly to venetoclax, make sure to check if venetoclax dose needs to be adjusted in case the new medication is a CYP3A inhibitor (as instructed in Table 4).

Practical tips for managing/preventing nausea and vomiting
Keep dry crackers near the bed for morning nausea
Try chamomile, peppermint, catnip, or ginger tea, and fresh, dried, or candied ginger
Sniff a cut lemon
Eat salty foods such as pretzels; carry a small packet of salt when leaving home
Avoid trigger foods known to cause nausea
Avoid strong odors
Avoid stomach irritants (e.g., tobacco, aspirin)
If there is a pattern to nausea, eat more during periods with less nausea
Do not eat and drink at the same time; drink liquids an hour before or after eating
Avoid lying down for at least an hour after eating; rest with your head higher than your feet
Keep the room temperature cool
Avoid eating in a room that is hot, stuffy, or filled with cooking odors
Dietary measures for relieving nausea, vomiting, and diarrhea
Drink clear beverages such as fruit juices, broth, ginger ale, energy drinks, or herbal teas
Eat small amounts of food every few hours rather than 2-3 large meals per day
Eat slowly and sip beverages slowly
Suck on popsicles or frozen fruit juice
Try the BRAT diet: bananas, white rice, applesauce, and white bread toast
Eat bland, soft foods (e.g., pasta, mashed potatoes, jello)
Eat dry foods such as unbuttered toast, saltine crackers, and dry cereal without milk
Avoid greasy foods, fried foods, margarine, butter, and oils
Avoid spicy foods
Avoid dairy products
Avoid caffeine (in coffee, tea, soft drinks, chocolate, some pain medications)
Avoid alcoholic beverages
Avoid acidic foods and juices (e.g., citrus fruits, tomatoes)
Eat foods high in soluble fiber and avoid foods high in insoluble fiber (e.g., nuts)
Adapted from Maceira E, Lesar TS, Smith HS. Medication related nausea and vomiting in palliative medicine. Ann Palliat Med. 2012;1(2):161-76.

APPENDIX H. ACTIVITY SCHEDULE

The following table shows the required activities across the 24 to 48 cycles each subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to a COVID-19 state of emergency are detailed within the Operations Manual (Appendix J).

Study Activities Tables

Part 1 (Dose Confirmation) Subjects treated with venetoclax + azacitidine Activity	Screen	Cycle 1			Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2 - 6 Days 2 - 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (odd cycles only)	Cycles 8 - 24 Day 1 (even cycles only)	Cycle 25 Day 1 and beyond	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up
		Day 1 (Baseline)	Days 2 - 5	Days 8, 15, and 22									
Visit Window (days)	28 to 1	No window							± 7	± 7	± 7	± 7	± 3
INTERVIEWS & QUESTIONNAIRES													
Subject information and informed consent	✓												
Eligibility criteria	✓												
Medical/oncology history	✓	✓											
ECOG performance status	✓	✓											
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS fatigue SF 7a		✓				✓			✓			✓	
EORTC QLQ C30		✓				✓			✓			✓	
EQ 5D 5L		✓				✓			✓			✓	
LOCAL LABORATORY VALUES & EXAMINATIONS													
Height (screening only) and weight	✓	✓			✓	✓			✓	✓	✓ (as SOC or as clinically indicated)	✓	✓

Part 1 (Dose Confirmation) Subjects treated with venetoclax + azacitidine **Activity**	Screen	Cycle 1			Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2 - 6 Days 2 - 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (odd cycles only)	Cycles 8 - 24 Day 1 (even cycles only)	Cycle 25 Day 1 and beyond	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up
		Day 1 (Baseline)	Days 2 - 5	Days 8, 15, and 22									
Visit Window (days)	28 to 1	No window							± 7	± 7	± 7	± 7	± 3
Physical examination	✓	✓			✓	✓			✓	✓	✓ (as SOC or as clinically indicated)	✓	✓
Vital signs	✓	✓	✓ (Day 5 only)		✓	✓	✓ (Day 5 only)		✓	✓	✓ (as SOC or as clinically indicated)	✓	✓
12 Lead electrocardiogram	✓											✓	
Serum pregnancy test	✓												
Urine pregnancy test, if applicable		✓			✓	✓			✓	✓	✓	✓	✓
Bone marrow aspirate and/or biopsy (disease assessment)	✓								✓ ± 14 days (Cycles 7 and 13 only)		✓ (as SOC or as clinically indicated)	✓ ± 14 day (Not required if completed within 4 weeks prior)	
Clinical chemistry and hematology	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓
Coagulation testing		✓											

Part 1 (Dose Confirmation) Subjects treated with venetoclax + azacitidine **Activity**	Screen	Cycle 1			Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2 - 6 Days 2 - 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (odd cycles only)	Cycles 8 - 24 Day 1 (even cycles only)	Cycle 25 Day 1 and beyond	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up
		Day 1 (Baseline)	Days 2 - 5	Days 8, 15, and 22									
Visit Window (days)	28 to 1	No window							± 7	± 7	± 7	± 7	± 3
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)	✓				✓ Cycle 6 only	✓ Cycle 3 only			✓ Cycle 9 and every 3 cycles thereafter		✓ Cycle 27 and every 3 cycles thereafter	✓	
CENTRAL LABORATORY													
Bone marrow aspirate (biomarker/MRD assessments)	✓								✓ ± 14 days (Cycles 7 and 13 only)			✓ ± 14 days (Not required if completed within 4 weeks prior)	
Peripheral blood (biomarker assessments)	✓	✓				✓			✓			✓	
Pharmacokinetic collection		✓	✓ (Day 5 only)				✓ Cycles 2, 4, 6 (Day 5 only)						
Optional biomarker sample: whole blood DNA/RNA		✓				✓ (Cycle 3, only)						✓	
TREATMENT													
Dispense venetoclax and subject diary		✓			✓	✓			✓	✓	✓		
Dosing with venetoclax		QD dosing on Days 1 to 21 or 28, depending on dose level, for each 28 day cycle up to 48 cycles.											

Part 1 (Dose Confirmation) Subjects treated with venetoclax + azacitidine Activity	Screen	Cycle 1			Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2 - 6 Days 2 - 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (odd cycles only)	Cycles 8 - 24 Day 1 (even cycles only)	Cycle 25 Day 1 and beyond	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up
		Day 1 (Baseline)	Days 2 - 5	Days 8, 15, and 22									
Visit Window (days)	28 to 1	No window							± 7	± 7	± 7	± 7	± 3
Collect venetoclax and review subject diary					✓	✓			✓	✓	✓	✓	
Dosing with azacitidine		QD dosing on Days 1 to 5 for each 28 day cycle up to 6 cycles.											

DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30-item; EQ-5D-5L = European Quality-of-Life-5 dimensions-5-level; HBV = hepatitis B virus; HCV = hepatitis C virus; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; RNA = ribonucleic acid; SF = short form

Study Activities Table

Part 3 (Dose Finding) Subjects treated with venetoclax + oral AZA Activity	Screen	Cycle 1				Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2, 4, and 6 Day 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (± 7 Days) (odd cycles only)	Cycles 8 - 24 Day 1 (± 7 Days)	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up	Post-Treatment Visits	Survival Follow-Up
		Cycle 1, Day 1 (Baseline)	Day 5	Days 8, 15, and 22	Days 14 & 21 (Dose Levels 1 & 2 only) in Dose Escalation only)										
Visit Window (days)	28 to 1	No window				Refer to the Operations Manual (Appendix J) for details.				± 7	± 7	± 7	± 3	± 28	± 28
INTERVIEWS & QUESTIONNAIRES															
Subject information and informed consent	✓														
Eligibility criteria	✓														
Medical/oncology history	✓	✓													
ECOG performance status	✓	✓													
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
PROMIS fatigue SF 7a		✓					✓			✓		✓			
EORTC QLQ C30		✓					✓			✓		✓			
EQ 5D 5L		✓					✓			✓		✓			
Survival follow up (including post treatment cancer therapies)															✓
LOCAL LABORATORY VALUES & EXAMINATIONS															
Height (screening only) and weight	✓	✓				✓	✓			✓	✓	✓	✓	✓	
Physical examination	✓ complete	✓ complete				✓	✓			✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	
12 Lead electrocardiogram	✓											✓			

Part 3 (Dose Finding) Subjects treated with venetoclax + oral AZA Activity	Screen	Cycle 1				Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2, 4, and 6 Day 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (± 7 Days) (odd cycles only)	Cycles 8 - 24 Day 1 (± 7 Days)	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up	Post-Treatment Visits	Survival Follow-Up
		Cycle 1, Day 1 (Baseline)	Day 5	Days 8, 15, and 22	Days 14 & 21 (Dose Levels 1 & 2 only) in Dose Escalation only)										
Visit Window (days)	28 to 1	No window				Refer to the Operations Manual (Appendix) for details.				± 7	± 7	± 7	± 3	± 28	± 28
Serum pregnancy test	✓														
Urine pregnancy test, if applicable		✓				✓	✓			✓	✓	✓	✓		
Bone marrow aspirate and/or biopsy (disease assessment) (± 14 days except screening)	✓					✓ Cycle 6 only	✓ Cycle 3 only			✓ Cycle 9 and every 3 cycles thereafter		✓ (Not required if completed within 4 weeks prior)		✓ (as SOC or as clinically indicated)	
Clinical chemistry and hematology (3 days at Cycle 1 Day 1 only)	✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓ (as SOC or as clinically indicated)	
Coagulation testing (3 days at Cycle 1 Day 1 only)		✓													
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)	✓					✓ Cycle 6 only	✓ Cycle 3 only			✓ Cycle 9 and every 3 cycles thereafter		✓			

Part 3 (Dose Finding) Subjects treated with venetoclax + oral AZA Activity	Screen	Cycle 1				Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2, 4, and 6 Day 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (± 7 Days) (odd cycles only)	Cycles 8 - 24 Day 1 (± 7 Days)	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up	Post-Treatment Visits	Survival Follow-Up
		Cycle 1, Day 1 (Baseline)	Day 5	Days 8, 15, and 22	Days 14 & 21 (Dose Levels 1 & 2 only) in Dose Escalation only)										
Visit Window (days)	28 to 1	No window				Refer to the Operations Manual (Appendix) for details.				± 7	± 7	± 7	± 3	± 28	± 28
CENTRAL LABORATORY															
Bone marrow aspirate (biomarker/MRD assessments) (± 14 days except screening)	✓					✓ Cycle 6 only	✓ Cycle 3 only			✓ Cycle 9 and every 3 cycles thereafter		✓ (Not required if completed within 4 weeks prior)			
Peripheral blood (biomarker assessments)	✓	✓				✓ Cycle 6 only	✓ Cycle 3 only			✓ Cycle 9 and every 3 cycles thereafter		✓			
Pharmacokinetic collection		✓	✓		✓			✓							
Optional biomarker sample: whole blood DNA/RNA		✓					✓ (Cycle 3, only)					✓			
TREATMENT															
Drug assignment (up to 3 days before study drug administration)		✓													
Part 3 (Dose Finding): Dispense venetoclax and oral AZA and subject diary		✓				✓	✓			✓	✓				

Part 3 (Dose Finding) Subjects treated with venetoclax + oral AZA Activity	Screen	Cycle 1				Cycle 2, 4, 6 Day 1	Cycle 3 and 5 Day 1	Cycles 2, 4, and 6 Day 5	Cycle 2, Days 8, 15, and 22	Cycles 7 - 23 Day 1 (± 7 Days) (odd cycles only)	Cycles 8 - 24 Day 1 (± 7 Days)	Final Visit (study drug discontinuation, relapse, or early discontinuation)	30-Day Safety Follow-Up	Post-Treatment Visits	Survival Follow-Up
		Cycle 1, Day 1 (Baseline)	Day 5	Days 8, 15, and 22	Days 14 & 21 (Dose Levels 1 & 2 only) in Dose Escalation only)										
Visit Window (days)	28 to 1	No window				Refer to the Operations Manual (Appendix) for details.				± 7	± 7	± 7	± 3	± 28	± 28
Part 3 (Dose Finding): Dosing with venetoclax		QD dosing on Days 1 to 14, 21, or 28, depending on dose level, for each 28 day cycle up to 24 cycles.													
Part 3 (Dose Finding): Collect venetoclax and oral AZA and review subject diary						✓	✓			✓	✓	✓			
Part 3 (Dose Finding): Dosing with oral AZA		QD dosing on Days 1 to 14 for each 28 day cycle up to 24 cycles.													

DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30-item; EQ-5D-5L = European Quality-of-Life-5 dimensions-5-level; HBV = hepatitis B virus; HCV = hepatitis C virus; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; RNA = ribonucleic acid; SF = short form

APPENDIX I. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	20 August 2019
Version 1.1 (VHP Countries Only)	31 October 2019
Version 1.1.1 (VHP Countries Only)	26 November 2019
Version 2.0	18 December 2019
Version 2.1 (Canada Only)	17 February 2020
Version 3.0	01 December 2020
Version 4.0	29 December 2020
Version 5.0	18 August 2021
Version 6.0	05 June 2023
Version 7.0	01 August 2023

The purpose of this amendment is to correct minor clerical errors for consistency and other administrative changes throughout the protocol and the following:

- **Rationale:** To update EudraCT number with EU CT number.
  - Updated throughout
- **Rationale:** To update the sponsor/emergency medical contact.
  - Updated throughout
- **Rationale:** The study title was updated to reflect that the Part 3 randomization portion from the study had been previously removed and to reflect both IV/SC AZA and oral AZA are being studied.
  - Updated throughout
- **Rationale:** CC-486 was changed to oral AZA.
  - Updated throughout
- **Rationale:** To remove Austria, Poland, Israel, and Portugal from the country site list.
  - Updated Protocol SYNOPSIS
- **Rationale:** To update references for prescribing information of drugs used in the study.
  - Updated Section 2.2 and Section 5.4
- **Rationale:** To clarify that that completion of the study treatment for Part 1 subjects is considered to be 24 cycles of venetoclax although subjects can go up to 48 cycles.
  - Updated Section 4.1 and throughout the Operations Manual

- **Rationale:** To streamline Study Design and Plan wording.
  - Updated Section 4.1
- **Rationale:** To clarify that contraceptive recommendations apply to both AZA and oral AZA.
  - Updated Section 5.2
- **Rationale:** There are procedures that need to be done in-person for the 30-day follow-up visit.
  - Updated Section 5.5
- **Rationale:** Edited follow-up visit timing for Part 3 subjects that have discontinued study drug prior to Cycle 24 or who have completed 24 cycles for consistency with the rest of the protocol.
  - Updated Section 5.6
- **Rationale:** Updated to align with current AbbVie template
  - Updated Section 5.9, Section 5.10, Section 8.2, Section 8.3, Section 9, Section 10, and the Operations Manual
- **Rationale:** Bone Marrow Aspirate/Biopsy samples are not required for Part 1 and Part 3 Final Visits if the sample had been collected within 4 weeks prior to the Final Visit.
  - Updated Appendix H and the Operations Manual
  - Operations Manual.
- **Rationale:** Clarified that survival follow up includes follow-up on post-treatment cancer therapies as specified in Section 3.18 in the Operations Manual.
  - Updated Appendix H and the Operations Manual.
- **Rationale:** Clarify that Bone Marrow Aspirate/Biopsy samples and clinical chemistry and hematology labs will be collected as standard of care or as clinically indicated during Post Treatment Follow-up Visits for Part 3 subjects.
  - Updated Appendix H and the Operations Manual
- **Rationale:** Peripheral Blood samples and a bone marrow biopsy are not required to be drawn same day same time at the Part 3 Post Treatment Visit.
  - Edited sentence to read "A peripheral blood smear should also be evaluated from the same day and same time that the bone marrow aspirate and/or bone marrow biopsy is collected for disease assessment." from the Operations Manual
- **Rationale:** To clarify whether subjects have prematurely discontinued from the study.
  - Added Section 8 and Section 8.1 to the Operations Manual and added references to Section 8.1 in Operations Manual Section 2.2, Section 2.4, and Section 3.18.