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Protocol for Study M19-063

Acute Myeloid Leukemia: Venetoclax and Azacitidine

VERSION:	9.0	DATE:	08 April 2025
SPONSOR:	AbbVie*	NUMBER OF SITES:	Approximately 167
ABBVIE INVESTIGATIONAL PRODUCT:	Venetoclax (ABT-199)	EU CT:	2023-507222-17

FULL TITLE: A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T)

Incorporating Versions 1.0, 1.1 (VHP Countries Only), 1.2 (Canada Only), 1.1.1 (VHP Countries Only), 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0 and Administrative Changes 1, 2, 3, and 4

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1 SYNOPSIS

Title: A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T)	
Background and Rationale:	Allogeneic stem cell transplantation (SCT) plays an important role in treatment for many patients with AML; however, morbidity and mortality risks remain high in both the adult and adolescent population. The most serious unfavorable outcomes after allogeneic SCT are disease relapse and graft-versus-host-disease (GvHD). Up to 50% of adults allografted for AML will relapse and strategies with the potential to reduce the risk of disease recurrence are urgently required. Severe acute GvHD (aGvHD) occurs in 15 to 30% of patients transplanted using a sibling or matched unrelated donor while 30 to 60% of patients experience chronic GvHD (cGvHD) which is associated with significant morbidity. Venetoclax has demonstrated activity as monotherapy in relapsed/refractory AML, however, the response rate is higher when given in combination with azacitidine and the duration of remission is longer. Azacitidine is a hypomethylating agent, which synergizes with venetoclax in treatment of AML, and has various regulatory approvals for treatment of myelodysplastic syndromes and/or AML globally. Additionally, preclinical studies suggest venetoclax may also mitigate against GvHD. Therefore, venetoclax with azacitidine may reduce the risk of relapse post-transplant and reduce the frequency of GvHD. This study will evaluate the safety and efficacy of venetoclax and azacitidine compared to best supportive care (BSC), in subjects with AML after allogeneic SCT. Part 1 of the study focused on safety and establishing the dose and the RPTD was established to be venetoclax [redacted] mg for [redacted] days and azacitidine [redacted] mg/m^2 for [redacted] days. Part 2 of the study will focus on efficacy with Overall Survival (OS) as the primary endpoint.
Objective(s) and Endpoint(s):	**Part 1 Objectives** Primary Objective • To determine the recommended Phase 3 dose of venetoclax in combination with azacitidine in AML subjects when given as maintenance therapy following allogeneic SCT. **Part 2 Objectives** <u>Primary Objective:</u> • To determine the efficacy of venetoclax in combination with azacitidine to improve OS in AML subjects compared to BSC when given as maintenance therapy following allogeneic SCT. <u>Secondary Objectives:</u> • To confirm the safety of venetoclax in combination with azacitidine after allogeneic SCT in subjects diagnosed with AML. • To determine the efficacy of venetoclax in combination with azacitidine as measured by RFS.

	• To determine the effect of venetoclax in combination with azacitidine on the frequency and severity of GvHD. • To determine the effect of venetoclax in combination with azacitidine on Quality of Life (QoL). • To determine the effect of venetoclax in combination with azacitidine on measurable residual disease levels. Primary Endpoint: **Part 1** The primary endpoint is the frequency of dose-limiting toxicities (DLTs) of venetoclax in combination with azacitidine. **Part 2** The primary endpoint is Overall Survival (OS). Key Secondary Endpoints Part 2: • Independent Review Committee (IRC)-assessed morphologic RFS • Independent Review Committee-assessed composite relapse-free survival • GvHD-free, relapse free survival (GRFS) • The rate of subjects without higher grade GvHD at 90 days after randomization (Arm B) or initiation of treatment (Arm A) • Change from baseline at 6 months in physical functioning after randomization (Arm B) or initiation of study treatment (Arm A) in adult subjects • Fatigue Change from baseline at 6 months after randomization (Arm B) or initiation of study treatment (Arm A) in adult subjects • Measurable residual disease conversion rate • Time to deterioration in Global Health Status (GHS)/QoL in adult subjects Additional Secondary Endpoints Part 2: • Fatigue change at time points other than 6 months after randomization (Arm B) or initiation of treatment (Arm A). • Patient-Reported Outcomes: Change in subject reported signs, symptoms, and impact of AML.
Investigator(s):	Multi-center
Study Site(s):	Approximately 167 sites in 18 countries/territories: Australia, Brazil, Canada, China, Czechia, France, Germany, Greece, Hungary, Israel, Italy, Japan, South Korea, Spain, Switzerland, Taiwan, United Kingdom, and United States
Study Population and Number of Subjects to be Enrolled:	Approximately 424 total adolescent and adult subjects with AML post-transplant will be enrolled across Part 1 (Dose Confirmation with Safety Expansion) and Part 2 (Randomization) of this pivotal trial. Adolescent subjects will only be enrolled in Part 2.
Investigational Plan:	This is a Phase 3, open-label, randomized, two-arm study with an initial dose confirmation component evaluating the safety and efficacy of

	venetoclax and azacitidine compared to BSC, in subjects with AML after allogeneic SCT. Overall, approximately 424 total adult and adolescent (12 to 17 years of age) subjects with AML will be enrolled in this pivotal trial. This study will have 2 parts; Part 1 is for Dose Confirmation with Safety Expansion and Part 2 (Randomization) will directly compare the efficacy of venetoclax combined with azacitidine to BSC (current standard of care); subjects will be randomized 1:1. Adolescent subjects will be only enrolled in Part 2 of the study. Approximately 24 subjects will be enrolled in Part 1 of the study. Once the appropriate dose is identified using the Bayesian Optimal Interval Design (BOIN) method, an additional 12 subjects will be enrolled into a Safety Expansion cohort to confirm the venetoclax dose and azacitidine dose for Part 2. Approximately 400 subjects will be enrolled in Part 2 to collect 231 OS events. All subjects treated with venetoclax will receive mandatory anti-infective prophylaxis during Cycle 1. An external IDMC will periodically review unblinded data from the ongoing study and provide recommendations to the sponsor regarding ongoing trial conduct or modifications to the trial as described in a separate IDMC charter. Interim review of safety data from the ongoing study (Part 2) will be conducted at the following proposed time points: • The first analysis to review the safety data will occur when 20 subjects have been on study drug or BSC for 3 cycles in Part 2 of the study • The subsequent reviews of safety data will occur approximately every 6 months after the first review of safety data. In addition, an efficacy interim analysis will be performed once 173 OS events (75% of the total 231 events) are observed.
Key Eligibility Criteria:	Subjects must be ≥ 18 years old for Part 1 and at least 12 years old for Part 2. Subjects must be diagnosed with AML by World Health Organization Criteria (WHO; 2017) and either be planning for allogeneic SCT or have received allogeneic SCT within the past 60 days. All types and WHO categories of AML and any number of previous lines of therapy may be included. The key laboratory requirements are as follows: • Blast percentage in bone marrow prior to pre-transplant conditioning < 10% • Malignant blast percentage in bone marrow < 5% after transplant • Laboratory values meeting the following criteria prior to Cycle 1 Day 1 • Bilirubin ≤ 3 × ULN* within 7 days prior to Cycle 1 Day 1 (*Subjects with Gilbert's Syndrome may have a bilirubin concentration of > 3 × ULN per discussion between the investigator and AbbVie Therapeutic Area Medical Director [TA MD])

	• For Part 1: ANC ≥ 1,500/µL, measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have granulocyte-colony stimulating factor (G-CSF) treatment for 7 days before first ANC count. • For Part 2: ANC ≥ 1,000/µL, measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have granulocyte-colony stimulating factor (G-CSF) treatment for 7 days before first ANC count. • Part 1: Platelet count ≥ 80,000/µL measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have a platelet transfusion for 7 days before first platelet count. • Part 2: Platelet count ≥ 50,000/µL measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have a platelet transfusion for 7 days before first platelet count. • Adequate renal function as demonstrated by a creatinine clearance > 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection. • Subjects ≥ 17 years old must have a Karnofsky Performance Scale (KPS) score > 50 and Subjects 12 - 16 years old must have a Lansky Play-Performance Scale (LPPS) score > 40.
Study Drug and Duration of Treatment:	Part 1: Venetoclax once daily for each 28-day cycle up to 24 cycles + azacitidine once daily for 5 days (Days 1 to 5) of each 28-day cycle up to 6 cycles. Part 2: Venetoclax[redacted] mg once daily for each[redacted]-day cycle up to[redacted] cycles + azacitidine[redacted] mg/m^2 once daily for[redacted] days (Days[redacted] of each[redacted] day cycle up to[redacted] cycles.
Date of Protocol Synopsis:	08 April 2025

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Acute myeloid leukemia (AML) is one of the fastest proliferating malignancies,[1] the most common acute leukemia in adults, the second most common acute leukemia in children,[2] and occurs with an incidence of approximately 30 patients per million individuals per year.[3] Treatment guidelines are stratified by patient age and eligibility for intensive treatment,[4] and range from hospice care with no anticancer medication to intensive chemotherapy followed by stem cell transplantation (SCT). The treatment of younger and physically fit adults with AML includes intensive chemotherapy followed by allogeneic SCT, which is also common in the population.[5] In most patients, allogeneic SCT is not followed by any other anticancer therapy. Although outcomes have improved, the majority of adults still die as a result of AML, including those treated most intensively; consequently the prognosis of AML remains poor.[5-8]

The most serious unfavorable outcomes after allogeneic SCT for AML include disease relapse, graft-versus-host-disease (GvHD), and infections. Up to 50% of adults that have received allogeneic SCT for AML will relapse and strategies with the potential to reduce the risk of disease recurrence are urgently required.[9] Severe acute GvHD (aGvHD) occurs in 15 to 30% of patients transplanted using a sibling or matched unrelated donor while 30 to 60% of patients experience chronic GvHD (cGvHD) which is associated with significant morbidity. Thus, better treatments for prophylaxis and treatment of GvHD are needed.

Venetoclax is an oral small molecule inhibitor of B-cell lymphoma 2 (BCL-2)[10] which induces apoptosis in preclinical models of multiple hematological malignancies such as chronic lymphocytic leukemia (CLL), AML, and multiple myeloma (MM). Venetoclax has demonstrated efficacy as monotherapy in relapsed/refractory AML: The response rate in the setting of AML after morphological relapse was 19% as a monotherapy.[11,12] This effect may be greater in the post-transplant setting as cancer treatments are often more effective when administered at a time of lower disease burden.[13,14] Additionally, the largest clinical benefits with venetoclax have been observed in combination with other agents that are able to prime leukemic cells toward apoptosis.[11,12] Venetoclax in combination with azacitidine was recently approved by the US FDA for the treatment of patients with AML who are not eligible to receive intensive chemotherapy. When providing venetoclax after transplantation, the graft versus leukemia effect may contribute to the apoptotic priming effect in AML stem cells.

Azacitidine is a hypomethylating agent approved for the treatment of myelodysplastic syndrome (MDS)[15] and/or AML by some global regulatory agencies. Combined treatment with venetoclax and azacitidine has recently shown to be synergistic[16,17] and has established efficacy as an anti-leukemic regimen with the potential to reduce the risk of relapse.[16] Use of venetoclax with azacitidine received approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as first line therapy in AML subjects not eligible for intensive chemotherapy in 2020 and 2021, respectively. Azacitidine has not been approved in adolescent subjects. However, there is published experience in use of the drug in the adolescent population including experience after transplantation.[18-20] The drug is considered to be "safe and feasible" as far as can be determined in the absence of large multicenter prospective clinical trials.[20]

In addition to the potential anti-leukemia effects of venetoclax and azacitidine, the treatment may also mitigate GvHD post-SCT which results from a donor's immune cells recognizing and attacking host tissues. The activation of allogeneic T- and B-cells has been implicated in the pathophysiology of GvHD. Thus, modulating or killing these cells may mitigate GvHD. In a murine model of GvHD, treatment with ABT-737, a dual BCL-X_L and BCL-2 inhibitor, caused an enrichment of T-regulatory cells and demonstrated a significant improvement of GvHD[21] as measured by body weight retention, fur texture, and skin integrity. Additionally, recent data demonstrated that venetoclax can diminish the Nrf2 anti-oxidant pathway in AML cells.[22] Suppression of this pathway has been shown to improve GvHD while maintaining graft-versus-leukemia effects in a mouse model of GvHD.[23,24] Finally, in an analysis of more than 100 human transplant patients, T- and B-cells of patients with GvHD express elevated BCL-2 when compared to patients without GvHD; therefore, inhibiting BCL-2 in donor lymphocytes with venetoclax may serve to mitigate GvHD.[24] This prospective interventional study will also address the effect of the treatment on GvHD,[25,26] efficacy, and biomarkers as secondary and exploratory endpoints.

Based on this evidence, this study will evaluate venetoclax in combination with azacitidine in the setting of AML after allogeneic SCT. It is hypothesized that treatment with venetoclax in combination with azacitidine in a maintenance setting will improve relapse free survival (RFS) of AML subjects following allogeneic SCT. This study will evaluate the safety and efficacy of the drug combination compared to Best Supportive Care (BSC) in subjects with AML after allogeneic SCT.

Clinical Hypothesis

Venetoclax in combination with azacitidine and as monotherapy as a maintenance therapy following allogeneic SCT will improve overall survival (OS) for patients with AML.

2.2 Benefits and Risks to Subjects

The hypothesized benefits to subjects include decreased probability of AML relapse, reduced chance or severity of GvHD, and extended survival. These potential benefits are supported by recent studies using venetoclax and azacitidine in AML patients in various settings. Venetoclax has been evaluated as a single agent in patients with relapsed or refractory AML or first line in patients with AML who are unfit to receive intensive chemotherapy demonstrating clinical activity.[11,12] Azacitidine is a well-established component of AML treatment, in particular with older patients and those not eligible for intensive chemotherapy.[27]

The combination of venetoclax and azacitidine has demonstrated promising activity in preclinical studies of AML. Azacitidine has been shown to down-regulate MCL-1, supporting that this agent might act synergistically with BCL-2 inhibitors.[28] The BCL-2/BCL-X_L inhibitor ABT-737, a similar molecule to venetoclax and predecessor in the development process, has been shown to kill AML cells, including leukemia stem/progenitor cells, both as a single agent and in combination with azacitidine.[29] This synergism was shown to be particularly effective in leukemic stem cells.[30] The benefit of the combination has been demonstrated in patients.[17] Venetoclax in combination with azacitidine was highly active for newly diagnosed patients with AML who were unfit to receive intensive chemotherapy in a Sponsor clinical trial (Study M14-358; NCT 02203773). Responses were deep and durable, and outcomes were superior compared with historical controls. The reported complete remission (CR) + CR with incomplete blood count recovery (CRi) rate was 71.4%.[31] Median duration of response was 21.2 months.

The risk to subjects includes adverse events (AEs) from venetoclax, azacitidine, and the combination of both agents. The safety profiles of both drugs are well described. These are mainly nausea, diarrhea, and hematological risks, such as neutropenia and other low blood counts, as well as decreased appetite and fatigue.[17] Low neutrophil counts can lead to severe infections which can be fatal. Low platelet counts can lead to severe hemorrhages. Based on preclinical data, decreased spermatogenesis has been identified as a potential risk for venetoclax. In a Sponsor clinical trial (Study M14-358; NCT 02203773), the most common treatment-emergent adverse events were nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). No dose-limiting toxicities (DLTs) were reported in that trial. 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 and Study M14358 administered higher doses of -azacitidine than will be administered in the current study.

After transplantation, data from studies of azacitidine monotherapy are available.[32] The AEs include those previously listed above with the addition of dermatology/skin symptoms.

The protocol includes subjects aged 12 to 17. Current industry best clinical practices recommend including adolescents in adult oncology trials unless specific medical justifications support excluding adolescent patients.[33] Treatment of pediatric patients, including adolescents, with venetoclax is being studied and no specific precautions or treatment modifications are necessary in the adolescent population as compared to the adult population in studies to date.[34] The degree of burden and the risk threshold was thoroughly evaluated during the development of the protocol and it was determined that the degree of burden and foreseeable risks to the pediatric population is very small. The burden is further diminished by protocol modifications as compared to adult protocols. Pediatric transplantation patients have central lines and the protocol allows for the use of central lines for azacitidine administration as well as blood draws for pharmacokinetic samples. The risk of adverse events, such as infections, does not differ largely between the adult and the pediatric (adolescent) population. Typically, pediatric induction chemotherapy protocols for AML are of the same intensity (if not greater intensity) as they are for adults; suggesting that treatment with venetoclax and azacitidine does not need to be reduced in adolescent patients.

In addition to the aforementioned potential direct benefits of treatment upon the AML stem cells, venetoclax may prevent or improve GvHD. Refer to the Section 2.1 for details.

For further details, see findings from completed studies, including safety data, in the current venetoclax Investigator's Brochure[35] and the azacitidine package insert.[36]

Given the coronavirus disease – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Subjects receiving venetoclax in combination with azacitidine may be at an increased risk for COVID-19 infection 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

Primary

1. To determine the recommended Phase 3 dose of venetoclax in combination with azacitidine in AML subjects when given as maintenance therapy following allogeneic SCT.

Part 2 Objectives

Primary

1. To determine the efficacy of venetoclax in combination with azacitidine to improve OS in AML subjects compared to BSC when given as maintenance therapy following allogeneic SCT.

Secondary

2. To confirm the safety of venetoclax in combination with azacitidine after allogeneic SCT in subjects diagnosed with AML.
3. To determine the efficacy of venetoclax in combination with azacitidine as measured by RFS.
4. To determine the effect of venetoclax in combination with azacitidine on the frequency and severity of GvHD.
5. To determine the effect of venetoclax in combination with azacitidine on Quality of Life (QoL).
6. To determine the effect of venetoclax in combination with azacitidine on measurable residual disease levels.

3.1 Primary Endpoint

Part 1

The primary endpoint is the frequency of DLTs of venetoclax in combination with azacitidine.

Part 2

The primary endpoint is OS, defined as the time from randomization to death from any cause.

3.2 Secondary Endpoints

Key Secondary Endpoints Part 2

- Independent Review Committee (IRC)-assessed morphologic RFS defined as the time from randomization to either:
  - Morphologic relapse from AML defined as bone marrow blasts of ≥ 5% or reappearance of blasts in the peripheral blood not attributable to any other cause (e.g., bone marrow regeneration) in at least 2 peripheral blood samples at least one week apart or development of extramedullary disease after achieving a complete remission (CR) or complete remission with incomplete count recovery (CRi); or
  - Death from any cause
- Independent Review Committee (IRC) assessed composite relapse-free survival defined as the time from randomization to either:
  - Morphologic relapse from AML as defined above, or
  - Non-morphologic relapse from AML, which is defined as increase in disease burden determined by standard methods with reappearance or acquisition of new findings with or without change in anti-leukemic treatment per investigator decision due to any of the following:
    - Cytogenetic abnormalities, or
    - Change in molecular marker, or
    - Measurable residual disease (MRD) by multiparameter flow with sensitivity to at least 10^{-3}, or
  - Death from any cause.
- GvHD-free, relapse free survival (GRFS) defined as time from randomization to occurrence of a.) disease relapse, b.) incidence of GvHD, c.) death from any cause. In this context, incidence of GvHD is defined as grade III-IV aGVHD or cGVHD of any severity requiring systemic immunosuppressive therapy (IST)
- The rate of subjects without higher grade GvHD at 90 days after randomization (Arm B) or initiation of treatment (Arm A). "Higher grade GvHD" is defined as Grade 2 or higher for aGvHD and moderate or severe for cGvHD as defined by the investigator following National Institutes of Health (NIH) criteria
- Change from baseline at 6 months in physical functioning after randomization (Arm B) or initiation of study treatment (Arm A) in adult subjects, as measured by the EORTC QLQ-C30 physical functioning domain
- Fatigue Change from baseline at 6 months after randomization (Arm B) or initiation of study treatment (Arm A) in adult subjects – defined as Fatigue measured as Patient Reported Outcome (PRO) using Patient Reported Outcomes Measurement Information System (PROMIS) Cancer Fatigue SF 7a

- Measurable residual disease conversion rate – The rate will be calculated only among subjects with MRD ≥ 10^{-3} at baseline. The MRD conversion rate will be defined as proportion of subjects who convert to MRD < 10^{-3} after randomization (Arm B) or initiation of treatment (Arm A)
- Time to deterioration in Global Health Status (GHS)/QoL in adult subjects - defined as time from randomization to death from any cause, or the first-time deterioration of ≥ 10 points from baseline in GHS/QoL score as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Version 3, whichever occurs first[37]

Additional Secondary Endpoints Part 2

- Fatigue change at time points other than 6 months after randomization (Arm B) or initiation of treatment (Arm A).
- Patient-Reported Outcomes: Change in subject reported signs, symptoms and impact of AML as measured by the EORTC-QLQ-C30,[38-40] and European Quality-of-Life-5 dimensional-5-level (EQ-5D-5L).[41]

3.3 Exploratory Efficacy Endpoints

- Patient-reported outcomes for subjects with cGvHD.[42]
- Patient-reported outcomes for adolescent subjects: Pediatric Quality of Life Inventory (PedsQL)[43] (for Subjects 12 to 17 years old).
- Health Care Resource Utilization: Information will be collected on each hospitalization including reason for admission (e.g., disease relapse, AML-related illness, treatment-related AE) and days of hospitalization by treatment setting (e.g., inpatient unit, special care unit, etc.).
- Immunosuppressive therapy as a secondary indicator of GvHD severity.
- Frequency and type of infection-related morbidity and mortality, and anti-infective medications used.
- Further efficacy endpoints will be evaluated, including recurrence rate in AML.

3.4 Safety Endpoints

Safety and tolerability will be assessed by evaluating AEs, physical examinations, changes in laboratory data (hematology, chemistry and urinalysis), and vital signs for the entire study treatment duration.

3.5 Pharmacokinetic Endpoints

Sparse pharmacokinetic (PK) samples will be collected and analyzed for plasma concentrations of venetoclax and azacitidine. An analysis of venetoclax plasma concentrations may be performed using a nonlinear mixed effect population PK modeling approach.

3.6 Biomarker Exploratory Endpoints

Biospecimens (e.g., blood, plasma, serum, and bone marrow aspirate) will be collected at specified time points throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, peptides, 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 is exploratory in nature and the results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are described in the Operations Manual Section 3.18.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3, open-label, randomized, two-arm study with an initial dose confirmation component evaluating the safety and efficacy of venetoclax and azacitidine compared to BSC, in subjects with AML after allogeneic SCT. Overall, approximately 424 total adult and adolescent (12 to 17 years of age) subjects with AML will be enrolled post-transplant in this pivotal trial. This trial will have 2 parts; Part 1 is for Dose Confirmation with Safety Expansion and Part 2 (Randomization) directly compares the efficacy and safety of venetoclax with azacitidine compared to BSC, which is the current standard of care. Adolescent subjects will only be enrolled in Part 2. Approximately 24 subjects will be enrolled in the Part 1 Dose Confirmation portion of the study. Once the appropriate dose is identified using the Bayesian Optimal Interval Design (BOIN) method, an additional 12 subjects will be enrolled in a Safety Expansion cohort to confirm the Phase 3 dose for Part 2. Approximately 400 subjects will be enrolled in the Part 2 Randomized portion of the study to collect 231 OS events.

All subjects treated with venetoclax will receive mandatory anti-infective prophylaxis during Cycle 1 per the recommendations in Section 5.4 and Section 6.2.

Registration

Consent will be obtained at the registration visit prior to allogeneic SCT or within 60-days post-transplant. After appropriate information and documentation of the consent process, adult subjects legally entitled for their own decisions will sign and date a consent. A copy of the consent form will be given to them. For adolescent subjects, regulations and guidelines differ among countries/territories with participating principal investigators. In this study, all applicable local and global rules and regulations will be followed. This may include a similar consent process in an age-appropriate style and signing an assent form. The legal guardian will sign a separate consent form. Adolescent subjects who reach legal age (per local guidelines) to consent independent of legal guardians will be treated as adults, including new consent.

Screening

Once subjects have met the protocol defined post-transplant count recovery criteria, they may begin screening assessments. Count recovery requirements differ between Part 1 and Part 2, and are described in detail in the eligibility criteria (Section 5.1).

Screening assessments will occur within 14 days of Cycle 1 Day 1 to determine study eligibility (with the exception of peripheral blood and bone marrow aspirate or biopsy, which can be performed within 30 days of Cycle 1 Day 1 in Part 2). Once screening procedures are complete and eligibility is confirmed, subjects can be enrolled (i.e., start treatment in Part 1, be randomized in Part 2). Rescreening may be considered only once upon investigator discussion with the AbbVie Therapeutic Area Medical Director (TA MD) and subsequent agreement. Subjects with screen failure for COVID-19 will be allowed to rescreen after they meet SARS-CoV-2 infection viral clearance criteria defined in the eligibility criteria (Section 5.1).

Part 1 (Dose Confirmation)

The first part of the study follows a BOIN design[44] which will guide dose escalation and de-escalation based upon the cumulative number of dose limiting toxicities (DLTs) observed at the current dose level. Refer to Section 6.3 for events that meet DLT criteria. The initial starting dose (dose level 1) will be [redacted] mg/m^2 azacitidine daily subcutaneously or intravenously for 5 days in combination with [redacted] mg venetoclax once daily for 28 days of each 28-day cycle in addition to BSC.[17] The drug combination will be administered for a total of 6 cycles. Thereafter, venetoclax monotherapy will be administered for an additional 18 cycles. Venetoclax dose ramp up is not needed since the subjects will be in remission and the leukemic burden will be negligible.

Table 1 outlines the dose levels of venetoclax in combination with azacitidine to be explored. Subjects will be enrolled in cohorts of at least 3 subjects. The first cohort of subjects will receive dose level 1, with subsequent dose level escalation and de-escalation guided by the BOIN decision rules. At the conclusion of Part 1 (Dose Confirmation), the maximum tolerated dose (MTD) will be defined as the highest dose level for which the BOIN decision rule does not require de-escalation. The recommended Phase 3 dose (RPTD) will not exceed the MTD.

Table 1. BOIN Dose Levels for Venetoclax and Azacitidine

Dose Level	Venetoclax Dose (mg)	Venetoclax Duration/Cycle (days)	Azacitidine Dose (mg/m^2)	Azacitidine Duration (days/cycle)
–1[a]	[redacted]	14	[redacted]	5
1[b]		28		5
2		28		5
3		28		5

BOIN = Bayesian Optimal Interval Design

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

b. Starting dose.

Table 2 below gives the decision rules for the BOIN design with a target DLT rate of 20% and optimal interval of (15.7%, 23.8%).

Table 2. Dose Level Decision Rules for BOIN

	Number of Subjects Evaluable at Current Venetoclax Dose Level									
Action	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Escalate dose level if number of subjects with DLT ≤	0	0	0	0	1	1	1	1	1	1
Stay at current dose level if number of subjects with DLT =	-	-	1	1	-	-	2	2	2	2
De-escalate dose level if number of subjects with DLT ≥	1	1	2	2	2	2	3	3	3	3
Eliminate[a] if number of subjects with DLT ≥	2	3	3	3	4	4	4	5	5	5

BOIN = Bayesian Optimal Interval Design; DLT = dose limiting toxicity

a. Eliminate current and higher doses (i.e., venetoclax dose and azacitidine dose ≥ current dose level).

Part 1 (Safety Expansion)

Safety and efficacy will be evaluated after 12 subjects enrolled into the Safety Expansion Cohort complete at least 1 cycle of study treatment.

The subjects in Part 1 will continue to receive study treatment and be followed on study until confirmed disease relapse, intolerable AEs, or other reasons to terminate study participation. Those data may be included in exploratory analyses.

Part 2 (Randomization)

The randomized portion of the study (Part 2) will begin once the Phase 3 dose has been determined in Part 1 after review of all safety and efficacy data. Individual subject randomization will occur upon confirmation that the subject has met all eligibility requirements for the study.

Subjects will be randomized 1:1 to one of two arms:

- Arm A (venetoclax and azacitidine): 6 cycles of azacitidine treatment and up to 24 cycles of venetoclax treatment in addition to BSC (when required).
- Arm B (BSC): receive BSC only, without AML directed therapy, per the investigator and institutional guidelines.

Selection of Dose for Part 2 Arm A (Randomization)

Based on the MTD from Part 1 (Dose Confirmation and Safety Expansion), the RPTD for the Part 2 Arm A will be venetoclax [redacted] mg once daily for each [redacted]-day cycle and azacitidine [redacted] mg/m^2 once daily subcutaneously or intravenously for [redacted] days (Days [redacted]) of each [redacted]-day cycle (Dose Level 1) in addition to BSC. Similar to Part 1, the combination therapy will be administered for a total of [redacted] cycles. Thereafter, venetoclax [redacted] mg monotherapy will be administered for an additional 18 cycles. Similar to Part 1, venetoclax dose ramp up is not necessary for Part 2 Arm A.

Part 1 and Part 2 Arm A

Subjects will receive azacitidine for up to 6 cycles and venetoclax for up to 24 cycles or until subject meets study treatment discontinuation criteria (whichever is earlier). See Section 5.5 for discontinuation criteria.

Subjects in Part 2 Arm A who have been granted extended venetoclax treatment prior to communication with investigators regarding the change in continued treatment, will be allowed to receive continued study treatment (for up to 12 additional cycles beyond the 24 cycles of treatment, up to 36 cycles total). Subjects in Part 1 who have been receiving continued study treatment will end study treatment when they meet discontinuation criteria, as outlined in Section 5.5.

Subjects who discontinue study treatment for reasons other than a relapse event (morphologic or non-morphologic) will return for follow-up disease status assessment visits every 12 weeks until documented relapse. See Section 5.5 and Operations Manual Section 3.21 for Scheduled Follow-Up Visit requirements.

Part 2 Arm B (BSC)

Subjects will receive BSC (per institutional standards) for up to 24 cycles or until subject meets discontinuation criteria (whichever is earlier). See Section 5.5 for discontinuation criteria.

Subjects who discontinue BSC for reasons other than a relapse event (morphologic or non-morphologic) will return for follow-up disease status assessment visits every 12 weeks until documented relapse. See Section 5.5 and Operations Manual Section 3.21 for Scheduled Follow-Up Visit requirements.

Part 1 and Part 2 (All Subjects)

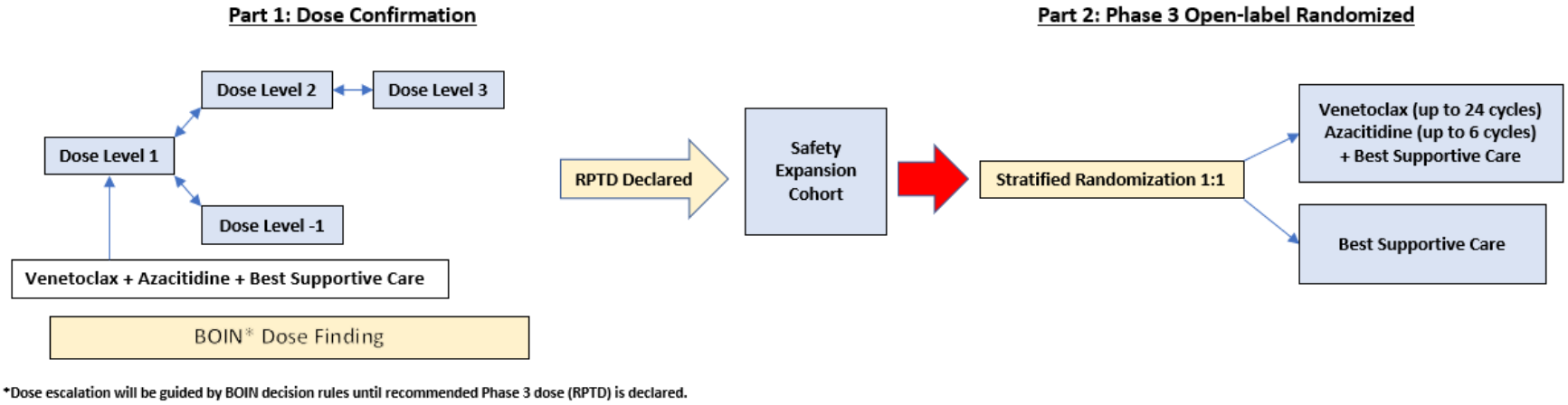
After documented relapse (morphologic or non-morphologic), subjects will be contacted (i.e., telephone calls) every 12 weeks (± 4 weeks) after the last study visit or relapse event (or as requested by the sponsor to support data analyses) to collect survival information. See Section 5.5 and Operations Manual Section 3.21 for survival follow-up requirements.

Bone marrow biopsy and/or aspirate samples are to be analyzed at the timepoints specified in the Operations Manual Section 2, and whenever clinically indicated as per standard care post-transplant, and whenever the suspicion of relapse occurs based upon blood counts or other indicators. All subjects will be monitored for potential evidence of AML disease relapse throughout the course of the study via scheduled study visit activities (e.g., physical examination, hematological laboratory review), and unscheduled visits -whenever clinically indicated-, where a bone marrow biopsy and/or aspirate analysis may be necessary to confirm disease relapse. A portion of the bone marrow samples drawn per the schedule of assessments and at times of suspected relapse will be submitted to central labs for biomarker analysis (prioritization of MRD assessment), if enough sample is collected. Details regarding disease assessment procedures are described in the Operations Manual Section 3.16 and Section 3.17. Collective disease assessment source data will be sent to an IRC when an AML relapse is detected by investigators, and at other time points as described in the Operations Manual Section 3.17. IRC interpreted disease assessments will not be shared with investigators.

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

A study schematic is shown in Figure 1.

Figure 1. Study M19-063: A Randomized, Open-Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in Combination with Azacitidine after Allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia



BOIN = Bayesian Optimal Interval Design; RPTD = recommended Phase 3 dose

Note: Dose escalation will be guided by BOIN decision rules until recommended Phase 3 Dose (RPTD) is declared.

4.2 Discussion of Study Design

Choice of Control Group

This study is open label as the route of azacitidine is subcutaneous (SC) or IV and causes local reactions and transient hematological changes that would distinguish potential sham injections from the experimental treatment. There are no standard additional anti-leukemia therapies after allogeneic SCT and no suitable sham therapy that would reliably blind investigators. Thus, unblinded BSC is an appropriate comparator for this study.

The planned study enrollment is approximately 424 subjects. Of those subjects, approximately 400 will be randomized to 1 of the 2 arms; either venetoclax in combination with azacitidine or BSC.

Appropriateness of Measurements

Standard statistical, 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.

Maintaining Quality of Life (QoL) and functioning in daily living is a relevant treatment goal in the setting of post SCT given the risk of relapse. Recent literature does not appear to support a bias in subject-centered outcome results from open-label studies based on subjects' awareness of their group assignment.[25,45] The FDA Oncology Center for Excellence has expressed increasing interest in understanding the subject's perspective in evaluating the efficacy of new oncology treatments and encourages sponsors to provide subject-centered outcomes data from clinical trials to support evidence of treatment efficacy.[46]

Suitability of Subject Population

There is an urgent medical need in this subject population: only half of the adult subjects receiving SCT will be cured from the disease.[47] Five-year survival rates in a retrospective study were reported from 25% to 79%.[47] Another study found the 2-year survival rates reported ranged from 24 to 34%.[48] This disease also affects the adolescent population, and large clinical trials took a similar approach as this study will: the adolescent AML-05 clinical trial[49] study includes Subjects 12 years and older, with a lower weight limit of 40 kg, consistent with the approach recommended by the FDA.[33]

To mitigate potential neutropenia and thrombocytopenia, subjects must have had at least 28 days to recover from their SCT and have ANC ≥ 1000/µL and platelets ≥ 50,000/µL to be eligible. Additionally, for Part 1, more strict eligibility criteria are defined (ANC ≥ 1500/µL and platelets ≥ 80,000/µL) and adolescent subjects are excluded as a safety precaution until preliminary data are generated.

Selection of Doses in the Study

For the treatment of newly diagnosed subjects with AML who are ineligible to receive intensive chemotherapy, venetoclax is dosed [redacted] mg per day when administered in combination with azacitidine. The initial dose level in Part 1 will evaluate [redacted] of venetoclax ([redacted] mg per day) given over 28 days. The highest dose tested in the Dose Confirmation portion of the study was [redacted] mg venetoclax for 28 days/cycle in combination with [redacted] mg/m^2 azacitidine for [redacted] days.

All subjects enrolled in Dose Confirmation of Part 1 were required to complete Cycle 1 with 80% dose compliance to be DLT-evaluable. Based on the data review of the subjects who completed DLT period, venetoclax [redacted] mg × 28 days and azacitidine [redacted] mg/m^2 × 5 days was determined to be the presumptive RPTD. Per protocol, 12 subjects in Safety Expansion were required to complete Cycle 1 while receiving the presumptive RPTD (venetoclax [redacted] × 28 days and azacitidine [redacted] mg/m^2 × 5 days). There were no new safety signals observed in this safety expansion cohort and therefore, this dose combination was declared to be the RPTD to be tested in Part 2 (randomized part) of the study.

Azacitidine is typically dosed [redacted] mg/m^2 daily for 7 days for the treatment of MDS. The same dose is recommended for the initial treatment of AML in combination with venetoclax[17] for subjects who are ineligible for intensive chemotherapy. However, in the post-transplant setting, a variety of azacitidine doses have been evaluated. Schroeder summarized the literature in 2018 noting azacitidine doses ranged from 16 mg/m^2 to 100 mg/m^2 and cycle treatment durations from 3 to 7 days.[50] Among the publications included in the review, two frequently referenced are De Lima 2010 and Craddock 2016. De Lima et al published a systematic dose finding study in the setting of AML after allogeneic SCT and recommended [redacted] mg/m^2 azacitidine for 5 days as monotherapy.[51] Craddock and colleagues reported on a 2016 prospective study with 37 subjects that recommended a dose of [redacted] mg/m^2 × 5 days with reduction to [redacted] mg/m^2 for hematological toxicity over 2 weeks as monotherapy.[32]

More recently, Platzbecker reported a study of [redacted] mg/m^2 × 7 days for subjects no longer in a clear remission but who had MRD recurrence.[52] Among 24 subjects treated after transplantation, 34% morphologically relapsed by 2 years.[52] Craddock et al 2019 reported "twenty-nine patients who had relapsed after allogeneic SCT for AML (n = 24) or MDS (n = 5) were treated with sequential azacitidine ([redacted] mg/m^2 for 7 days) followed by escalating doses of lenalidomide."[53] Karakulska-Prystupiuk reported that a study with 28 subjects treated up to [redacted] mg/m^2 for 7 days.[54] Lastly, Guillaume evaluated [redacted] mg/m^2 azacitidine for 5 days while providing donor lymphocyte infusions in 20 subjects.[55] The table in Appendix D provides an overview of the doses and adverse event frequencies reported. In review of these diverse approaches previously tested, additional variables such as subject age, number of days after transplantation chosen for treatment start, whether the treatment was given prophylactically or after detecting AML recurrence, and drug combinations play a role in the doses recommended by the authors, making a numeric comparison of adverse events difficult. In addition, the literature suggests the needs for dose modification guidelines.[32]

In the adolescent population, the literature is sparse; only case reports have been published with azacitidine treatment in adolescent subjects with AML after transplantation.[18,20] However, these case reports do support that the approach is possible in the adolescent population.

In summary, previous studies have safely administered azacitidine after transplantation. Initial starting doses vary from [redacted] mg/m^2 × 5 days[51] to [redacted] mg/m^2 for 7 days[54] and some studies have implemented dose reductions down to [redacted] mg/m^2. The initial dose level in Part 1 will conservatively evaluate a starting azacitidine dose of [redacted] mg/m^2 × 5 days and, if tolerated, subsequent cohorts may escalate up to a maximal dose of [redacted] mg/m^2 × 5 days.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all the following criteria during the registration visit and screening period in order to be included in the study.

Registration Visit:

Consent

- 1. Subjects and/or their legally authorized representative (where permitted per local regulations) must voluntarily sign and date an informed consent form (and assent form for minors if required by applicable regulations), 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 male or female ≥ 18 years old; and, for Part 2 only, male or female at least 12 years old.

Disease Activity

- 3. Subject must be diagnosed with AML by World Health Organization (WHO) criteria (2017) and either be planning for allogeneic SCT or have received allogeneic SCT within the past 60 days. All types and WHO categories of AML[56] and any number of previous lines of therapy may be included.

Subject History

- 4. Subjects with favorable cytogenetic risk per NCCN 2016 criteria (Appendix F) and in first complete remission prior to transplant are not eligible to enroll in this study.
- 5. Subjects that have previously been treated with venetoclax, can only be included if there was no history of disease progression during venetoclax treatment.
- 6. Blast percentage in bone marrow prior to pre-transplant conditioning < 10%.
- 7. Pre-transplant conditioning protocols must be as follows: Both myeloablative and reduced intensity transplantation conditioning or non-myeloablative protocols are allowed.
- 8. Grafts must be from one of the following sources: Bone marrow or peripheral blood stem cells or cord blood cells irrespective of degree of matching.
- 9. If graft failure occurs during the registration period and a subsequent transplant is planned, the subject can be reconsented for the study. (Notes a - b):
    - a) C1D1 must occur within 28 to 100 days of this subsequent transplant date.

- b) If there is a subsequent (second) graft failure after reconsent during the registration period, the subject will not be permitted to enroll into the study.

Screening Period

Demographic and Laboratory Assessments

- 10. **For the Dose Escalation part of Part 1 Only:** There is a backup graft identified and ready to be used in case of graft failure (Notes a - d):
  - a.) Institution guidelines should be followed for backup graft collection/procurement.
  - b.) given differences in standard procedures, the back-up graft does not need to be collected at the time of the Screening visit, however, at a minimum the investigator must be able to confirm and document at the Screening Visit that the infrastructure and either a suitable donor or back-up graft are available in case of graft failure.
  - c.) Investigator must be able to confirm and document that the product will be available for use ≤ 7 days from identifying the need for a back-up graft and when the actual infusion occurs.
  - d.) The backup graft does not need to be from the original donor.
- 11. Body weight ≥ 40 kg.
- 12. **Laboratory values** meeting the following criteria prior to Cycle 1 Day 1:
  - Bilirubin ≤ 3 × ULN* within 7 days prior to Cycle 1 Day 1

    (*Subjects with Gilbert's Syndrome may have a bilirubin concentration of > 3 × ULN per discussion between the investigator and AbbVie TA MD).
  - For Part 1: ANC ≥ 1,500/µL, measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have granulocyte-colony stimulating factor (G-CSF) treatment for 7 days before first ANC count.
  - For Part 2: ANC ≥ 1,000/µL, measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1 or prior to dosing on Cycle 1 Day 1. Subjects should not have granulocyte-colony stimulating factor (G-CSF) treatment for 7 days before first ANC count.
  - Part 1: Platelet count ≥ 80,000/µL measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1. Subjects should not have supportive treatment (e.g., transfusions and/or growth factors) for 7 days before first platelet count.
  - Part 2: Platelet count ≥ 50,000/µL measured twice at least 2 days apart (approximately 48 hours) and within 1 week prior to Cycle 1 Day 1 or prior to dosing on Cycle 1 Day 1. Subjects should not have supportive treatment (e.g., transfusions and/or growth factors) for 7 days before first platelet count.
  - Adequate renal function as demonstrated by a creatinine clearance > 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection.
- 13. Are willing and able to comply with procedures required in this protocol.

- 14. Subjects ≥ 17 years old must have a Karnofsky Performance Scale (KPS)[57,58] score > 50 and Subjects 12 to 16 years old must have a Lansky Play-Performance Scale (LPPS) score > 40.[59]
  - Part 2: If a subject is 12 to 16 at the time of screening and turns 17 during the study, the subject will continue with the LPPS.

Disease Activity

- 15. Blast count of zero in peripheral blood, within 7 days prior to Cycle 1 Day 1.
- 16. Malignant blast percentage in bone marrow < 5% after transplant.
- 17. Subject has no known evidence indicating leukemia relapse, which may include immunophenotype, cytogenetic or molecular methods after transplant and prior to Cycle 1 Day 1.

Subject History

- 18. No malabsorption syndrome or other condition that precludes oral route of administration.
- 19. No history of any other malignancy within 2 years prior to study entry, with the exception of:
  - Adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast;
  - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
  - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent;
  - Myelodysplastic Syndrome (MDS);
  - Myeloproliferative neoplasm (only allowed if it transformed to AML and AML should be the indication for marrow transplantation).
- 20. In situations where SCT is delayed from the original scheduled date, transplantation must occur within ≤ 90 days of the Registration Visit.
- 21. Cycle 1 Day 1 administration of 1st dose of the study drug(s) must occur within 28 to 100 days after transplant. Subjects may enter into Screening upon the first instance of meeting the count recovery criteria without the need for supportive care (e.g., growth factors and/or platelet transfusions) for at least 7 days prior. Upon entering screening, subjects must maintain count thresholds on at least 2 occasions (approximately 48 hours apart) in the absence of supportive care (platelet transfusion/G-CSF within 7 days).
- 22. No psychiatric illness/social situation that would limit compliance with the study.
- 23. 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.
- 24. No known human immunodeficiency virus (HIV) infection. HIV testing will be performed at screening, if required per local guidelines or institutional standards.

- 25. 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 (non-exclusionary medications) are eligible. Low viral hepatitis titer is defined per institutional guidelines.
- 26. No evidence of other clinically significant uncontrolled systemic infection.
- 27. No clinical or laboratory symptoms or signs for extramedullary myeloid malignancy. No history of central nervous system (CNS) involvement.
- 28. No known hypersensitivity to the active substance or to any of the excipients of venetoclax and azacitidine.
- 29. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test result. Note: SARSCoV-2 diagnostic tests should be applied following local requirements/recommendations.
    - Subjects with confirmed SARS-CoV-2 infection 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 COVID 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.
        - Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Contraception

- 30. For all females of child-bearing potential; a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline (predose) on Cycle 1 Day 1 is required.
- 31. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Cycle 1 Day 1 through at least 30 days after the last dose of venetoclax and at least 180 days after the last dose of azacitidine (whatever occurs later). Female subjects of non-childbearing potential do not need to use birth control.
- 32. Female subjects of child-bearing potential are eligible if they commit to contraception listed in Section 5.2, and if they are not pregnant, breastfeeding, nor considering becoming pregnant during the study or for at least 30 days after the last dose of venetoclax and at least 180 days after the last dose of azacitidine (whatever occurs later).
- 33. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, to practice the protocol-specified contraception from Cycle 1 Day 1 through at least 90 days after the last dose of azacitidine or per local label (whichever is longer) and at least 30 days after the last dose of venetoclax, whenever the last dose of drug occurs (either azacitidine or venetoclax).
- 34. Males who are not sexually active and are not considering becoming sexually active and are not considering fathering a child or donating sperm during the study, are not required to practice contraception for study participation.

Concomitant Medications

- 35. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is shorter) prior to Cycle 1 Day 1 or is currently enrolled in another clinical study or was previously enrolled in this study.
- 36. Cytochrome P450 (CYP)3A inducers and grapefruit/grapefruit products:
  - Subject must not have received a known strong or moderate CYP3A inducer for at least 7 days prior to Cycle 1 Day 1. Subject must not have known medical conditions requiring chronic therapy of moderate CYP3A inducers.
  - Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit for at least 3 days prior to Cycle 1 Day 1
- 37. Subject must not have received any live vaccine within 4 weeks prior to Cycle 1 Day 1. The subject must not be expected to need a live vaccination throughout study participation. The subject must not be expected to need a live vaccine if any of the following 6 conditions are applicable:
  - Active GvHD
  - Lymphocyte count < 1,500/µL
  - Less than 12 months in remission
  - Less than 3 months after the last dose of oncological therapy
  - Less than 4 weeks after the most recent infusion of immunoglobulins
  - Less than 4 weeks after the most recent immunosuppressive therapy
- 38. No intrathecal (IT) prophylaxis during study treatment period in both treatment and BSC arms.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects should follow the below contraception guidelines for both Part 1 and Part 2 of the study. See eligibility criteria above for contraception before and after venetoclax and azacitidine treatment. The study does not require contraception for the BSC arm. However, standard medical care and individual conditions may make contraception advisable. Therefore, contraception methods for subjects in the BSC Arm or the decision that these are not needed should be provided by the treating physician.

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential:

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause

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

- Females, of Childbearing Potential:

  Females who have experienced menarche (at least one menstrual period) prior to or during the study.

  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 180 days after the last dose of azacitidine and at least 30 days after the last dose of venetoclax (whatever occurs later). Those females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to Cycle 1 Day 1
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Cycle 1 Day 1
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject)
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject are acceptable. (Note: In contrast, periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label. 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 Cycle 1 Day 1
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method)

Contraception Requirements for Males

- Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use condoms, even if the male subject has undergone a successful vasectomy**, from Cycle 1 Day 1 through at least 90 days after the last dose of azacitidine or per local label (whichever is longer) and at least 30 days after the last dose of venetoclax, whenever the last dose of drug occurs (either azacitidine or venetoclax). The female partner(s) of the male subject must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Cycle 1 Day 1 [predose])
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study baseline (Cycle 1 Day 1 [predose])
  - bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
  - IUD
  - IUS
  - Female partners of vasectomized male subjects do not need to use birth control, provided the male subject 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 medications or therapies are not allowed after randomization, unless an RFS event was documented:

- Donor lymphocytic infusion (DLI; considered a subsequent line of therapy resulting in treatment discontinuation). DLI not allowed anytime after transplant.
- AML-directed therapy, approved or investigational, such as (but not limited to): acalabrutinib, alisertib, alemtuzumab, arsenic, atezolizumab, avelumab, bendamustine, bosutinib, busulfan, chlorambucil, cemiplimab, cytarabine, CAR T-cells, carboplatin, cladribine, crenolamib, dasatenib, durvalumab, duvelisib, etoposide, daunorubicin, doxorubicine, decitabine, enasidenib, fludarabine, glasdegib, guadecitabine, gemtuzumab ozogamicin, gilteritinib, hydroxyurea, idarubicin, imatinib, interferon-alpha, ipilimumab, ivosidenib, lauromustine, 6-mercaptopurine, mechlorethamine, midostaurin, mitoxantrone, moxetumomab, nilotinib, nivolumab, obinutuzumab, omacetaxine, panobinostat, pembrolizumab, ponatinib, sapacitabine, sorafenib, radiation, retinoic acid, tagraxofusp-erzs, 6-thioguanine, tyrosine kinase inhibitors, vorinostat, vincristine, other anthracyclines, DNA-binding agents, or experimental anti-AML agents. Cyclophosphamide is not allowed with the intention antileukemia therapy, as indicated by leukemia specific dose and schedule. However, cyclophosphamide is allowed as anti-GvHD drug as indicated by dose and schedule typical for GvHD and described by applicable

guidelines and local pre-described treatment conventions. Similar, drugs used with the intention to prevent or treat GvHD listed below in Section 5.4 (Prior and Concomitant Therapy) are allowed even when they may also be classified as chemotherapy. Any questions regarding anti-AML therapies not listed here should be raised to the AbbVie TA MD.

For subjects in Part 1 and Arm A of Part 2 receiving venetoclax treatment, the following is not allowed during the study:

- Strong cytochrome P450 3A (CYP3A) inducers (consider alternative treatments with less CYP3A induction)
- Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) and star fruit 3 days before starting venetoclax treatment in each cycle and while taking venetoclax.

Subjects must be able to safely discontinue any prohibited medications within 5 half-lives or 30 days (whichever is shorter) prior to Cycle 1 Day 1. 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 (including GvHD prophylaxis), beginning with the screening visit through 30 days after the last dose of the study drug (Part 1 and Part 2 Arm A) and through 30 days after the End Visit (Part 2 Arm B), 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 interactions.

Concomitant medications are to be noted on the dosing diary (see Section 5.11 for description of dosing diaries) and will be reviewed by study personnel.

Live attenuated vaccines should not be administered within 4 weeks prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Although subjects should be advised that vaccinations may be less effective, all other vaccinations per local guidelines, such as the pneumococcus vaccine, are recommended.

For subjects receiving venetoclax in Part 1 or Part 2 of the study, the following therapies are allowed:

- Herbal supplements should be discouraged unless known not to be CYP3A active
- If a P-glycoprotein (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

- Co-administration of a strong or moderate CYP3A inhibitor requires a specified venetoclax dose reduction as presented in Table 3
- Concomitant use of a moderate CYP3A inducer should be avoided. Alternative treatments with less CYP3A induction should be considered
- Live attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs

Table 3. Dose Modifications for Venetoclax: Moderate and Strong CYP3A Inhibitor Use

Assigned Venetoclax Dose	Venetoclax Dose if Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose if Co-Administered with a Strong CYP3A Inhibitor
[redacted] mg	[redacted] mg	[redacted] mg[a] or [redacted] mg[b,c] as defined in the local label
[redacted] mg	[redacted] mg	[redacted] mg as defined in the local label

CYP3A = cytochrome P450 3A

a. United States, China, Israel, Japan, and Taiwan will reduce venetoclax dose to [redacted] mg when co-administered with posaconazole.

b. All other countries will reduce venetoclax dose to [redacted] mg when co-administered with posaconazole.

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

Note: Venetoclax dose adjustments should not be added or combined. If dosing more than one medication in combination with Venetoclax, use the highest recommended dose reduction.

Dose modifications may lead to target doses of venetoclax other than [redacted] or [redacted] mg. If venetoclax dosing needs to be modified (e.g., adjusting for CYP3A inhibitors), then dose modification should be followed according to Table 3, rounding down to the target dose based on available tablet doses. 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. If the subject began venetoclax treatment at a modified dose due to concomitant use of a strong or moderate CYP3A inhibitor and subsequently discontinues the inhibitor, venetoclax dose should resume at the previously assigned target dose 2 to 3 days after discontinuation of the inhibitor.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie TA MD. Information regarding potential drug interactions with venetoclax and azacitidine can be located in the venetoclax Investigator's Brochure[35] and the azacitidine package insert.[36]

Breast cancer resistance protein (BCRP) inhibitors are not expected to result in clinically relevant effects on venetoclax exposure.[60] When coadministered with a BCRP inhibitor, no dose adjustment for venetoclax is 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.[60] When coadministered with an OATP inhibitor, no dose adjustment for venetoclax is 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.

Antibiotic Prophylaxis

All subjects treated with venetoclax will receive mandatory antibiotic prophylaxis during Cycle 1. Subjects with ≥ grade 3 neutropenia (ANC less than 1000/mm^3), and those subjects expected to become neutropenic, in the investigator's opinion, will also receive mandatory antibiotic prophylaxis. Recommendations for antibiotic prophylaxis include Sulfamethoxazole (800 mg)/Trimethoprim (160 mg) or other therapy, and Amoxicillin clavulanate or levofloxacin or other antibiotic therapy per institutional guidelines or at physician's discretion, unless the subject has hypersensitivity to these agents. After Cycle 1, the duration of antibiotic prophylaxis should be determined by the investigator.

Supportive Care (G-CSF and Platelet Transfusions)

Transfusion of blood and blood products (other than DLIs, and CAR-T cells), antibiotics, anti-fungals, anti-virals, anti-emetics, intravenous immunoglobulin, and other standard supportive care medications should be considered and are permitted as needed, per institutional practices (with appropriate dose reductions for drug-drug interaction [DDI] as listed). In addition, the use of G-CSF is permitted and should be considered per institutional practices. Filgrastim and other cytokines aiming to increase blood counts may be administered, per clinical practice.

Prophylaxis for GvHD

GvHD prophylaxis and treatment is allowed during the study and will follow institutional guidelines but should follow published regimens. This includes the following drugs typically considered GvHD prophylaxis medications (not AML treatment):

- Alpha 1 antitrypsin
- Antithymocyte globulin (ATG)
- Bortezomib
- Beclomethasone
- Budesonide
- Cyclosporine (venetoclax dose needs to be reduced by 50%)
    - Should be administered at least 6 hours before venetoclax, and if twice a day dosing, the second dose of the day should be administered at least 6 hours after venetoclax.
- Etanercept
- Ibrutinib
- Immune globulin
- Maraviroc
- Methotrexate
- Methylprednisolone and other glucocorticoids
- Mycophenolate Mofetil
- Octreotide
- Prednisone

- Pentostatin
- Post-transplant cyclophosphamide
- Ruxolitinib
- Rituximab
- Sirolimus
  - Should be administered at least 6 hours before venetoclax.
- Tacrolimus
  - Should be administered at least 6 hours before venetoclax, and if twice a day dosing, the second dose of the day should be administered at least 6 hours after venetoclax.

COVID-19 Pandemic-Related Vaccination Guidance

Selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

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) venetoclax, 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 patients 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 adverse events associated with the COVID-19 vaccine.

5.5 Subject Treatment Discontinuation, Withdrawal of Subjects, and Study Discontinuation

Subject Treatment Discontinuation

Part 1 and Part 2 Arm A (treatment with venetoclax and azacitidine):

At any time, a subject may be discontinued from study treatment. *Reasons for discontinuation of treatment include, but are not limited to, the following*:

- The investigator believes discontinuation of study drug is in the best interest of the subject.

- The subject requests withdrawal (e.g., withdrawn consent) from study treatment (Part 1 or Part 2 Arm A)
- Subject experiences clinically significant abnormal laboratory results or AEs which indicate continuation of the study drug could put the subject at undue risk as determined by the investigator or the Sponsor.
- Any reasons, including drug-related toxicities, that lead to dose interruption of > 12 weeks for all study drugs, unless the investigator determines that the subject is deriving clinical benefit from the study drugs and has consulted with the AbbVie Medical Director.
- The subject becomes pregnant.
- Morphologic or non-morphologic relapse as described in the Operations Manual Section 3.17.
- Introduction of prohibited medication(s), putting the subject at undue risk as determined by the investigator or the Sponsor.
- Eligibility criteria violation noted after the subject enrolled and continuation on the study would place the subject at risk as determined by the investigator or the Sponsor.
- The subject is significantly noncompliant with study procedures as determined by the investigator or the Sponsor.
- Subject starts a new anti-AML treatment.
- Graft failure

Part 2 Arm B (BSC):

- The subject requests withdrawal (e.g., withdrawn consent) from BSC and/or study participation
- Morphologic or non-morphologic relapse as described in the Operations Manual Section 3.17.
- Eligibility criteria violation noted after the subject enrolled and continuation on study would place the subject at risk as determined by the investigator or the Sponsor.
- The subject is significantly noncompliant with study procedures as determined by the investigator or the Sponsor.
- Subject starts an anti-AML treatment
- Graft failure

End of Treatment/End Visit and Safety Follow-Up:

If a subject is discontinued from study treatment (Part 1 or Arm A of Part 2) or BSC without antileukemia drugs (Arm B of Part 2) for any reason, then the procedures outlined for the End of Treatment Visit (Part 1 or Part 2 Arm A) or End Visit (Part 2 Arm B) should be completed as soon as possible, preferably within 2 weeks. Subjects in Part 1 or Arm A of Part 2 should have a safety follow-up visit completed approximately 30 days after the last dose of study drug to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved. If the investigator deems that an on-site 30-day safety follow-up visit is not required, a safety follow-up phone call may be completed approximately 30 days after the last dose of study drug.

In addition, for subjects in Arm B of Part 2, a safety follow-up phone call approximately 30 days after withdrawal may be completed to ensure all ongoing AEs/serious adverse events (SAEs) have been resolved. An on-site 30-day safety follow-up visit for subjects in Arm B of Part 2 is not required.

Scheduled Follow-Up:

The 1st scheduled follow-up visit should occur 12 weeks (± 1 week) after the last dose of study treatment. Subjects who discontinue study treatment for reasons other than disease relapse (morphological or non-morphologic) will return for follow-up disease status assessment visits every 12 weeks until documented relapse. See Operations Manual Section 3.21 for Scheduled Follow-Up Visit requirements.

To minimize missing data for efficacy and safety assessments, subjects who discontinue study treatment or BSC early should be advised on the scientific importance of the collection of their data after stopping treatment. Subjects should continue study and be monitored through follow-up visits, and survival follow-up until death (per the Operations Manual Section 2), subject withdrawal from study participation (i.e., withdrawal of informed consent), or study end; whichever occurs first.

Survival Follow-Up

All subjects will be followed for overall survival. Subjects who have documented disease relapse (morphological or non-morphologic) will enter the survival follow-up phase. Survival information will be collected, including subsequent anti-cancer therapies (dates and responses), survival status and the date and cause of death (via telephone calls, clinical visits, public database searches) every 12 weeks (± 4 weeks) (or as requested by the sponsor to support data analyses) for up to 5 years after the last subject has been enrolled (provided informed consent has not been withdrawn for collection of such information).

Subject Withdrawal from Study

A subject may voluntarily withdraw consent from all study participation at any time, including withdrawal of consent to provide any further data.

Biomarker samples (Mandatory or Optional): A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. 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 subject has withdrawn consent and no longer wishes biomarker research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). Data generated from clinical study and/or biomarker research (mandatory or optional) before subject withdrawal of consent will remain part of the study results.

If a 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.

Subject Lost to Follow-Up

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.

Early Termination or 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 his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it 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 I.

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 I 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 14 days since first PCR test result have passed in asymptomatic patients or 14 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 medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow the above guidance in this protocol section (Section 5.5) for subjects who discontinued study drug. Study drug interruption may be allowed at the local investigator discretion on a case-by-case basis after carefully reviewing the benefits and risks of continuing the study drugs.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix I.

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

Interruption/Discontinuation of Study Drug Due to Geo-Political Conflict in Israel

Delays in study drug dosing for subjects must be discussed with the AbbVie TA MD, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug.

5.6 Study Drug

Venetoclax will be administered orally beginning on Cycle 1 Day 1, for 24 cycles. Azacitidine will be administered SC or IV, daily on Days 1 to 5 of each 28-day cycle for 6 cycles. Blood count starting criteria for Day 1 of each cycle in Part 1 is ANC ≥ 1500/µL and platelets ≥ 80,000/µL and in Part 2 is ANC ≥ 1000/µL and platelets ≥ 50,000/µL. Details regarding venetoclax and azacitidine administration, packaging, dispensation, and storage/disposal are provided in the Operations Manual Section 6.

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.

5.7 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the interactive response technology (IRT) at the Registration Visit that will be used throughout the study. Randomization/IRT transaction may occur up to 3 days prior to Cycle 1 Day 1. For subjects who rescreen, the subject number assigned by the IRT at the initial Registration Visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Randomization will be stratified by:

- < 18 years of age – no further stratification in this group.
- ≥ 18 years of age, stratified further by:
  - Previous treatment with either venetoclax or azacitidine (yes/no)
  - High risk of recurrence (yes/no), where high risk is defined as:
    - MRD positive (≥ 10^{-3}), per investigator prior to transplantation, or
    - High-risk AML as described in Appendix F, or
    - Previous recurrence (CR2 or later), or
    - Previous refractory disease at end of induction, i.e., failure to achieve CR or CRi
  - Geographic region (North and South America + Australia + Europe versus China versus Japan versus Other Asian Countries/territories).

5.8 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the geo-political conflict in Israel and surrounding impacted regions), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.9 Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will periodically review unblinded data from the ongoing study. The IDMC is responsible for safeguarding the interests of trial subjects, assessing the safety and the efficacy of the interventions during the trial, as well as for monitoring the integrity and interpretability of the trial. The IDMC will provide recommendations to the sponsor regarding ongoing trial conduct or modifications to the trial as described in a separate IDMC charter.

The details of the interim analyses of efficacy are included in Section 7.6. In order to maintain the integrity of the study conduct, an external statistical data analysis center is responsible for performing the analyses described in the IDMC charter as well as additional analyses requested by the IDMC and facilitating interpretation and answering questions that arise before, during, or after IDMC review.

A separate IDMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the IDMC members, frequency and scope of the data reviews, and expectations for blinded communications.

5.10 Publication Policy

AbbVie is committed to fostering the highest standard of conduct related to Scientific Publications and transparency, while at the same time, protecting its confidential information. Authorship related to scientific publications shall be determined in accordance with and governed by the criteria defined by the International Committee of Medical Journal Editors ("ICMJE") "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals." AbbVie's role in support of the Study should be appropriately disclosed in any scientific publications.

5.11 Dosing Diary

For all subjects, a dosing diary will be provided at Day 1 of each cycle and EOT visit. Subjects will be trained on how to complete the dosing diary by site staff during the Cycle 1 Day 1 visit. If subjects require re-training during the study, the site staff will accommodate this requirement.

All subjects should complete their dosing diary throughout the entire study. Subjects will be instructed to bring their dosing diary back to the site to be reviewed and collected at Day 1 of each cycle. If COVID-19 circumstances warrant a virtual visit on Day 1 of a cycle, the dosing diary should be reviewed

virtually with the subject and site should collect the dosing diary at the next on-site visit. Subjects treated with investigator product (Arm A) will be instructed to record the date and time each dose of venetoclax is taken (indicating if any doses of study drug are missed), dosage of venetoclax taken, and if taken within 30 minutes after the completion of a meal (preferably breakfast).

All subjects will also be instructed to record adverse events symptoms and concomitant medications in the dosing diary. At Day 1 of each cycle, the dosing diary are to be reviewed by the study staff, assessed for any updates needed, and collected from the subject by study staff. Relevant information will be recorded in existing drug administration and concomitant medication forms in the eCRF as applicable. Additionally, AEs considered clinically significant by the investigator will be followed as appropriate and recorded in the source documents and on the adverse event eCRF, through 30 days after the last dose of study drug or End Visit for Arm B subjects (as specified in Section 6.1). At Day 1 of every subsequent cycle after Day 1 of Cycle 1, including the EOT visit and 30-day safety follow-up visit, the dosing diary is to be returned to the site and appropriately filed with the subject's source documents for this study. At Day 1 of each cycle after the dosing diary is initially dispensed (including the EOT visit), the subject will be provided a new dosing diary.

In case of missing dosing diary information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes to data in site records and eCRF forms, if applicable. The need for completion of the dosing diary will be reinforced with the subject during study visits, as necessary, by the site personnel.

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 adverse events 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 adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be clinically significant.

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 pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

Admission to the hospital for an extended infusion will not be considered an SAE if the hospitalization is due to a pre-planned infusion or other medical intervention or procedure. However, it will be considered an SAE, if the subject's hospital stay is prolonged for any reason after completion of the infusion or other medical intervention or procedure.

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 a SAE within 24 hours of the site being made aware of the SAE (refer to 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.

Study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent until study drug is started for subjects in Part 1 and Part 2 Arm A, or from the time the subject signs the study-specific informed consent until study enrollment for subjects in Part 2 Arm B.

For subjects in Part 1 and Part 2 Arm A: All 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.

For subjects in Arm B of Part 2: All AEs reported from the time of enrollment until 30 days after the end of Cycle 24, or relapse, or early discontinuation (whichever is earliest) will be collected, whether solicited or spontaneously reported by the subject.

After the 30 days and throughout the scheduled follow-up period, only spontaneously reported SAEs will be collected for subjects in Part 1, Arm A of Part 2, and Arm B of Part 2.

In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific ICF.

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

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	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 unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions reporting for the Investigational Medicinal Product 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.

Recording of Adverse Events Symptoms on the Subject Paper Diary Cards

AE symptoms should be noted on dosing diary (see Section 5.11 for description of dosing diary) and are to be reviewed by study personnel as applicable.

Adverse Events of Special Interest

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

- TLS

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. If a reported AE increases in severity, the initial AE should be given, and an end date. The increased severity will be reported in a new AE entry with a different onset date than the end date of the previous AE. 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 discontinue treatment (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 at least 90 days after the last dose of azacitidine or per local label (whichever is longer) and at least 30 days after the last dose of venetoclax, whenever the last dose of drug occurs (either azacitidine or 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 Study Drug Related Toxicity Management

The management of study drug-related specific AEs and laboratory parameters is described below. This includes AEs of neutropenia for venetoclax and known potential risks associated with azacitidine. Subjects will be monitored for these events throughout the study and study drug may be discontinued or adjusted as appropriate. This section does not apply to the BSC arm (Part 2 Arm B). If an intra-cycle treatment is interrupted for ≥ 14 days or the start of the next cycle is delayed by > 21 days, a discussion with the TA MD should occur.

Management of Treatment-Related Neutropenia

Venetoclax may cause neutropenia. Subjects will be managed for neutropenia as detailed below.

Complete blood counts should be monitored throughout the treatment period. Supportive measures including prophylactic antimicrobials will be mandatory for subjects treated with venetoclax, with Grade 3 neutropenia, or if expected to become neutropenic. Prophylactic and therapeutic use of growth factors (e.g., G-CSF) are recommended. Dose interruptions and dose modifications are described Appendix E.

Management of Treatment-Related Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Complete diagnostics including bone marrow aspiration and biopsy, and analysis of potential infectious reasons (e.g., Parvovirus B19), and of potential autoimmune cytopenia are highly encouraged. Transfusions, cytokine medication, and supplementation of vitamin B12, folic acid, iron, and other supplemental treatments if deficiencies are noted are encouraged. Dose interruptions, and dose modification of venetoclax and azacitidine are described in Appendix E.

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 Dose Modification for Nonhematologic Toxicities Table (Appendix E) should be followed when resuming study drug following resolution. Additional dose reductions may occur at the discretion of the investigator. Supportive measures for Grade ≥ 3 diarrhea that includes hydration and anti-diarrheal medications (ex: loperamide) should be considered.

Management of Infection

For subjects treated with venetoclax, antibiotic prophylaxis for bacterial infections is mandatory for the following subjects:

- for all subjects during Cycle 1,
- for subjects with ANC of < 1000/mm^3 in any cycle, and for all subjects expected to become neutropenic by the decision of the investigator.

Prophylaxis for viral and fungal infections is recommended as long as the subject receives glucocorticoids (steroids) or is leukopenic. For the choice of the agents, the institutional frequency of

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. Refer to Section 5.4 for a list of concomitant medications recommended for antibiotic prophylaxis.

Treatment of fever and neutropenia should occur without delay, include immediate broad-spectrum antibiotics, and fluids if necessary. Details should follow local guidelines. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs, and potentially adjust the local standard guidelines and instructions to subjects accordingly. Some medications may require dose adjustments due to the potential for drug-drug interactions.

Treatment of specific infections such as pneumonia should follow the guidelines of the transplant center, considering potential DDI. Refer to Section 5.4 for a list of concomitant medications recommended for antibiotic prophylaxis.

Dose interruptions, and dose modification of venetoclax and azacitidine are described in Appendix E.

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.

Dose Modifications Based on Toxicities

Subjects who discontinue one study drug because of study drug-related toxicities may continue to receive the other planned study drug at the discretion of the investigator.

Dose Modifications for Venetoclax and Azacitidine

The guidelines to modify doses venetoclax and azacitidine are described in Appendix E.

6.3 Other Safety Data Collection: Dose Limiting Toxicity Criteria

For subjects in the dose escalation component of Part 1, the DLT observation period is defined as the first treatment cycle (Cycle 1; 28 days). However, adverse events and laboratory data occurring after the DLT observation period will also be reviewed and may be taken into consideration for dose escalation and de-escalation decisions. To be considered evaluable for DLT assessment, subjects must have completed Cycle 1 (28 days); received at least 80% of the originally prescribed dose over the course of the cycle; or have experienced a DLT as defined below.

Any of the following events will be considered a DLT, unless the Investigator can attribute the event to a clearly identifiable cause such as underlying illness, disease progression/relapse, other concurrent illness, or from concomitant medication.

Non-Hematological Toxicity:

- Any grade 3 AEs lasting ≥ 72 hours
- 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.

Hematological Toxicity:

- Any grade ≥ 3 neutropenia (< 1000/mm^3) that is ≥ 14 days duration
- Grade ≥ 4 thrombocytopenia (< 25000/mm^3) associated with clinically significant bleeding that requires transfusion of platelets
- Graft failure

In addition, AEs not meeting above criteria but lead to omitting > 20% of the scheduled dose within the first cycle will be considered DLTs.

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 of Part 2. 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 efficacy interim database lock. The statistical analyses will be performed using Statistical Analysis Software (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Intent-To-Treat (ITT) population includes all randomized subjects in Part 2. Subjects will be analyzed in the group to which they are randomized. Unless otherwise noted, the ITT population will be used for all efficacy and baseline analyses.

The Safety Analysis Set (SAS) consists of all subjects who received at least 1 dose of study drug in Part 1 or Arm A of Part 2 and all subjects in Arm B of Part 2.

7.3 Handling Potential Intercurrent Events

Primary and Key Secondary Endpoints

Refer to Section 3 and Section 7.4 for the definitions of the primary and key secondary endpoints. Refer to Table 4 for the handling of intercurrent events for the primary and key secondary endpoints.

7.4 Statistical Analyses for Efficacy

General Considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05.

When 231 OS events in the ITT population occur, there will be a final review of the eCRF data. After the data collection is completed and reviewed for completeness and all data management quality assurance and quality control procedures are performed, the clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data.

Unless otherwise specified, the analysis of all relapse related endpoints (e.g., morphologic RFS, composite RFS, GRFS) will be based on IRC assessment. Sensitivity analyses will be performed based on the investigator assessment.

Sensitivity analyses will also be performed by defining AML risk groups using European Leukemia Net (ELN) criteria, upon availability of data.

Primary Efficacy Analysis

The primary efficacy endpoint is OS. OS is defined as time from randomization 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 arm using Kaplan-Meier methodology and compared between 2 arms using the log-rank test, stratified by age (< 18, ≥ 18) and further stratified for age ≥ 18 by previous treatment with either venetoclax or azacitidine (yes, no) and high risk of AML recurrence (yes, no).

Key Secondary Efficacy Analysis

Key secondary efficacy endpoints include morphologic RFS, composite RFS, GRFS, time to deterioration in GHS/QoL in adult subjects, rate of subjects without higher grade GvHD at 90 days after randomization, change in physical functioning from baseline in adult subjects at 6 months after treatment or randomization, change in fatigue from baseline in adult subjects at 6 months after treatment or randomization, and MRD conversion rate.

Morphologic RFS is defined as time from randomization to death from any cause or morphologic relapse, whichever occurs first. Morphologic RFS data from subjects without any of the specified morphologic RFS events will be censored at the date of the last disease assessment or the date of randomization if the subject does not have any post-baseline disease assessment. The distribution of morphologic RFS will be estimated for each arm using Kaplan-Meier methodology and compared between 2 arms using the log-rank test, stratified by age (< 18, ≥ 18) and further stratified for age ≥ 18 by previous treatment with either venetoclax or azacitidine (Yes, No) and high risk of AML recurrence (Yes, No).

Composite RFS is defined as time from randomization to death from any cause, morphologic relapse, or non-morphologic relapse, whichever occurs first. Composite RFS data from subjects without any of the specified composite RFS events will be censored at the date of the last disease assessment or the date of

randomization if the subject does not have any post-baseline disease assessment. The distribution of composite RFS will be estimated for each arm using Kaplan-Meier methodology and compared between 2 arms using the log-rank test, stratified by age (< 18, ≥ 18) and further stratified for age ≥ 18 by previous treatment with either venetoclax or azacitidine (Yes, No) and high risk of AML recurrence (Yes, No).

GRFS is defined as time from randomization to disease relapse (morphologic or non-morphologic), or occurrence of grade III-IV aGVHD or cGVHD of any severity requiring systemic immunosuppressive therapy, or death from any cause. GRFS data from subjects without any of the specified GRFS events will be censored at the date of the last disease assessment or the date of the last GvHD assessment, whichever occurs earlier. The distribution of GRFS will be estimated for each arm using Kaplan-Meier methodology and compared between the study arms using the log-rank test, stratified by age (< 18, ≥ 18) and further stratified for age ≥ 18 by previous treatment with either venetoclax or azacitidine (yes, no), high risk of recurrence (yes, no), and type of donor (matched related, other).

Time to deterioration in GHS/QoL for adult subjects is defined as time from randomization to death from any cause, or the first-time deterioration of ≥ 10 points from baseline in GHS/QoL score as measured by EORTC QLQ-C30, whichever occurs first. Data from subjects without any of the specified events will be censored at the date of last assessment. Time to deterioration in GHS/QoL will be analyzed in the same way as RFS and OS.

Higher grade GvHD is defined as Grade 2 or higher aGvHD and moderate or severe cGvHD at 90 days after randomization (Arm B) or initiation of treatment (Arm A). The rate of subjects without higher grade GvHD will be compared between the study arms using Cochran-Mantel-Haenszel (CMH) test stratified by type of donor (matched related, other). Subjects who do not have GvHD assessment at 90 days will be included in the denominator in the analysis.

Physical functioning will be assessed using the physical functioning score as measured by EORTC QLQ-C30 for adult subjects. Scores will be computed according to the EORTC QLQ-C30 scoring manual. A linear mixed effects regression model with an appropriate covariance structure will be used to fit the longitudinal data. In the linear mixed effects regression model, previous treatment with either venetoclax or azacitidine (Yes, No), high risk of recurrence (Yes, No), baseline score, time, study arm and study arm by time interaction will be included as fixed factors. Change from baseline scores at 6 months after randomization (Arm B) or initiation of treatment (Arm A) will be compared between the study arms based on the linear mixed effects model.

Fatigue will be assessed using the global fatigue score as measured by PROMIS Fatigue SF 7a for adult subjects. Scores will be computed according to the PROMIS Fatigue scoring manual. A linear mixed effects regression model with an appropriate covariance structure will be used to fit the longitudinal data. In the linear mixed effects regression model, previous treatment with either venetoclax or azacitidine (Yes, No), high risk of recurrence (Yes, No), baseline score, time, study arm and study arm by time interaction will be included as fixed factors. Change from baseline scores at 6 months after randomization (Arm B) or initiation of treatment (Arm A) will be compared between the study arms based on the linear mixed effects model.

MRD conversion rate is defined as percentage of subjects with MRD $\geq 10^{-3}$ at baseline who convert to MRD $< 10^{-3}$ after randomization (Arm B) or initiation of treatment (Arm A). Subjects who have MRD $\geq 10^{-3}$ at randomization but do not have any MRD assessment after randomization will be assumed to be

MRD positive. Subjects whose MRD is < 10^{-3} or unknown at baseline will be excluded from the analysis. The MRD conversion rates will be compared between study arms using Fisher's exact test.

Additional Efficacy Analyses

Details on other efficacy analyses will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the impact of demographics and baseline characteristics on efficacy, subgroup analyses will be performed on efficacy endpoints including, but not limited to, RFS, OS, and GRFS and will be performed for subgroups including, but not limited to, those defined below:

- Age (< 18, ≥ 18, ≥ 18 - < 65, ≥ 65)
- Gender (male, female)
- Previous treatment with venetoclax (yes, no)
- Previous treatment with azacitidine (yes, no)
- Subjects with MRD < 10^{-3} prior to transplant (yes, no)
- Remission status prior to transplant (first CR, second CR, non-CR)
- Subjects with MRD < 10^{-3} after transplant at time of randomization (yes/no)
- Baseline remission status (CR, CRi)
- Reduced intensity induction or non-myeloablative versus myeloablative conditioning
- Match related donor versus other donors
- AML risk category (favorable, intermediate, poor) as defined in Appendix F
- AML risk category (favorable, intermediate, adverse) as defined by ELN criteria[4]
- By geographic region
- Dose modifications during Cycles 1 or 2 (yes, no)
- Acute GvHD subgroups: grade 0, grade 1, grade 2, grade 3, grade 4 at baseline
- Other influencing factors of GvHD including stem cell graft source (bone marrow, cord blood stem cell, peripheral blood stem cell), HLA match (10/10 match and other matches) and use of ex-vivo T-cell depletion (yes, no)

Estimands for Primary and Key Secondary Efficacy Endpoints

The 5 key components of estimands are summarized in Table 4 below for the primary endpoint and key secondary endpoints.

Table 4. Estimands for Primary and Key Secondary Endpoints

Endpoint	Treatment	Population	Intercurrent events	Population-level Summary
OS	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects	Initiation of new anti-leukemic therapy • Treatment Policy Strategy: this intercurrent event is irrelevant; OS data will be used in the analysis regardless of whether the subject is on new treatment or not Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; OS data will be used in the analysis regardless of whether the subject is on study drug or not	Hazard ratio
Morphologic RFS	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects	Initiation of new anti-leukemic therapy • Treatment Policy Strategy: this intercurrent event is irrelevant; morphologic RFS data will be used in the analysis regardless of whether the subject is on new treatment or not Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; morphologic RFS data will be used in the analysis regardless of whether the subject is on study drug or not	Hazard ratio

Endpoint	Treatment	Population	Intercurrent events	Population-level Summary
Composite RFS	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects	Initiation of new anti-leukemic therapy • Treatment Policy Strategy: this intercurrent event is irrelevant; composite RFS data will be used in the analysis regardless of whether the subject is on new treatment or not Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; composite RFS data will be used in the analysis regardless of whether the subject is on study drug or not	Hazard ratio
GRFS	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects	Initiation of new anti-leukemic therapy • Treatment Policy Strategy: this intercurrent event is irrelevant; GRFS data will be used in the analysis regardless of whether the subject is on new treatment or not Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; GRFS data will be used in the analysis regardless of whether the subject is on study drug or not	Hazard ratio
Time to deterioration in QoL	Best supportive care with and without venetoclax plus azacitidine	All randomized adult subjects (≥ 18 years old)	Initiation of new anti-leukemic therapy • While On Treatment Strategy: data after the initiation of the new anti-leukemic therapy will not be included in the analysis Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; data will be used in the analysis regardless of whether the subject is on study drug or not	Hazard ratio

Endpoint	Treatment	Population	Intercurrent events	Population-level Summary
Subjects without higher grade GvHD	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects	Initiation of new anti-leukemic therapy • While On Treatment Strategy: data after the initiation of new therapy will not be used in the analysis Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; data will be used in the analysis regardless of whether the subject is on study drug or not	Difference in proportions of subjects without higher grade GvHD
Physical functioning	Best supportive care with and without venetoclax plus azacitidine	All randomized adult subjects (≥ 18 years old)	Initiation of new anti-leukemic therapy • While On Treatment Strategy: data after the initiation of the new anti-leukemic therapy will not be included in the analysis Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; data will be used in the analysis regardless of whether the subject is on study drug or not	Difference in change from baseline in physical functioning score
PROMIS Cancer Fatigue SF 7a	Best supportive care with and without venetoclax plus azacitidine	All randomized adult subjects (≥ 18 years old)	Initiation of new anti-leukemic therapy • While On Treatment Strategy: data after the initiation of the new anti-leukemic therapy will not be included in the analysis Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • Treatment Policy Strategy: this intercurrent event is irrelevant; data will be used in the analysis regardless of whether the subject is on study drug or not	Difference in change from baseline in fatigue score

Endpoint	Treatment	Population	Intercurrent events	Population-level Summary
MRD Conversion	Best supportive care with and without venetoclax plus azacitidine	All randomized subjects with MRD ≥ 10^{-3} at baseline	Initiation of new anti-leukemic therapy • While On Treatment Strategy: data after the initiation of new therapy will not be used in the analysis Discontinuation (either premature discontinuation or completion of protocol-specified treatment duration) of study drug • While On Treatment Strategy: data collected after discontinuation of study drug or completion of protocol-specified treatment duration will not be used in the analysis	Difference in proportions of subjects who convert to MRD < 10^{-3}

GRFS = GvHD-free, relapse free survival; GvHD = graft-versus-host disease; MRD = measurable residual disease; OS = overall survival; PROMIS = Patient Reported Outcomes Measurement Information System; QoL = Quality of Life; RFS = relapse free survival; SF = short form

7.5 Statistical Analyses for Safety

General Considerations

Safety analyses will only include subjects in the Safety Analysis Set as defined in Section 7.2. Safety summaries will be presented separately for Part 1 and Part 2 based on the assigned treatment.

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. Further details will be provided in the SAP.

Analysis of Laboratory Data

Change from baseline will be analyzed for each scheduled post-baseline visit for blood chemistry and hematology parameters.

Where applicable, blood chemistry and hematology laboratory determinations will be categorized according to NCI CTCAE (version 5.0) grades and shifts from baseline NCI CTCAE grades to maximum post-baseline grades will be assessed. The baseline grade will be defined as the grade of the last measurement collected prior to the first dose of study drug for subjects in Part 1 or Part 2 Arm A and prior to randomization for subjects in Part 2 Arm B.

Analysis of Vital Signs

Change from baseline will be analyzed for each scheduled post-baseline visit for the vital sign parameters.

Other Safety Analysis

Details of other safety analyses will be provided in the SAP.

7.6 Interim Analysis

Interim review of safety data from the ongoing study (Part 2) will be conducted at the following proposed time points:

- The first analysis to review the safety data will occur when 20 subjects have been on study drug or BSC for 3 cycles in Part 2 of the study
- The subsequent reviews of safety data will occur approximately every 6 months after the first review of safety data.

In addition, an efficacy interim analysis will be performed once 173 OS events (75% of the total 231 events) are observed. The planned stopping boundaries for OS at each interim and final analysis are described in Table 5 below.

Table 5. Planned Stopping Boundaries at the Interim Analysis and Final Analysis of OS

		Stopping Boundaries
Analysis	**# of Events**	**P-Value (two-sided)**
IA (75%)	173	0.0192
FA	231	0.0443

FA = final analysis; IA = interim analysis; OS = overall survival

At the 75% OS efficacy interim, the probability of declaring success is 70% assuming a true HR of 0.65 and is 85% assuming a true HR of 0.6.

The interim analyses will be performed by an independent Statistical Data Analysis Center. An independent data monitoring committee (IDMC) composed of persons independent of AbbVie and with relevant expertise in their field will review the above interim analyses.

A separate IDMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency of data reviews, and relevant safety data to be assessed.

7.7 Multiplicity Adjustment and Overall Type I Error Control

The fixed sequence testing procedure will be performed with a significance level of 0.05 (two-sided) for the primary efficacy endpoint and key secondary efficacy endpoints sequentially. The ranking and alpha spending of the key secondary efficacy endpoints are described in Table 6. If the statistical test is not significant for the primary efficacy endpoint, then statistical significance will not to be declared for any of the key secondary endpoints. The Lan-DeMets alpha spending function with O'Brien-Fleming boundary will be used at the interim analysis to ensure that the false positive rate for OS the primary efficacy endpoint is controlled at the two-sided 0.05 level.

Table 6. Testing Sequence and Alpha-Spending Boundaries (Two-Sided P-value) for Primary and Secondary Endpoints

Testing Sequence	Endpoint	Timing of Analysis	
		OS IA	OS FA
1	OS	As specified in Table 5	As specified in Table 5
2	Morphologic RFS	As specified in Table 5	As specified in Table 5[a]
3	Composite RFS	As specified in Table 5	As specified in Table 5[a]
4	GRFS	As specified in Table 5	As specified in Table 5[a]
5	Rate of subjects without higher grade GvHD[b]	0.05	NA
6	MRD[b]	0.05	NA
7	Physical functioning[b]	0.05	NA
8	PROMIS Cancer Fatigue SF 7a[b]	0.05	NA
9	Time to deterioration in QoL[b]	0.05	NA

FA = final analysis; GRFS = GvHD-free, relapse free survival; GvHD = graft-versus-host disease; IA = interim analysis; MRD = measurable residual disease; NA = not applicable; OBF = O'Brien-Fleming; OS = overall survival; PROMIS = Patient Reported Outcomes Measurement Information System; QoL = quality of life; RFS = relapse-free survival; SF = short form

a. The actual stopping boundary will be recalibrated based on the actual number of observed events.

b. Will be tested one time using the data at 75% OS interim (IA).

7.8 Sample Size Determination

This study has two parts. Part 1 is a dose confirmation study and Part 2 is a randomized study. The assumed hazard ratio of 0.65 describes a relevant and clinically meaningful improvement over BSC. In Study M14-358, a CR + CRi rate of 71% was observed for venetoclax [redacted] mg in combination with azacitidine[61] as compared to a 28% CR + CRi rate in azacitidine alone.[62] The observed median OS for venetoclax [redacted] mg in combination with azacitidine in Study M14-358 was 16.9 months[61] as compared to 10.4 months for azacitidine monotherapy.[62] The projected hazard ratio below appears to be reasonable based on what was observed in the treatment effect of venetoclax [redacted] mg in combination with azacitidine in Study M14-358.

The sample size for Part 1 is dependent upon the dose levels utilized. The sample size calculation for Part 2 is based on the following assumptions:

- 2-year OS for the BSC arm is 50%.
- Hazard ratio (venetoclax in combination with azacitidine versus BSC) is 0.65
- An efficacy interim analysis of OS at 75% of total OS events with O'Brien-Fleming boundary
- 1:1 randomization ratio to venetoclax in combination with azacitidine arm and the BSC arm

With the above assumptions, a total of 231 OS events will provide 90% overall power to detect a statistically significant difference between treatment arms at two-sided alpha level of 0.05 using the log-rank test.

Approximately 400 subjects will be randomized into the study to obtain the 231 OS events.

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 of Technical Requirement for Pharmaceuticals for Human Use (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 KG acting as sponsor of the submitted study ("AbbVie Deutschland") 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 Deutschland has a data protection impact assessment (DPIA) 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 Deutschland 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. Due to the geo-political conflict in Israel and surrounding impacted regions, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

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

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
aGvHD	Acute graft-versus-host disease
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCL-2	B-cell lymphoma 2
BCRP	Breast cancer resistance protein
BMI	Body mass index
BOIN	Bayesian Optimal Interval Design
BSC	Best Supportive Care
cGvHD	Chronic graft-versus-host-disease
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
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
CYP3A	cytochrome P450 3A
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLI	Donor lymphocytic infusion
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid
DTP	Direct-to-patient
eCRF	Electronic case report form
EDC	Electronic data capture (system)
EFS	Event-free survival
ELN	European Leukemia Net

EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality-of-Life-5 dimensional-5-level
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating fact*or*
GHS	Global Health Status
GRFS	GvHD-free, relapse free survival
GvHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICH	International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional review board
IRC	Independent Review Committee
IRT	Interactive response technology
IT	Intrathecal
ITT	Intent-To Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

IV	Intravenous
IWG	International Working Group
KPS	Karnofsky Performance Scale
LPPS	Lansky Play-Performance Scale
MD	Medical director
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRD	Measurable residual disease
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
OATP	Organic anion transporting polypeptide
OS	Overall survival
PedsQL	Pediatric Quality of Life Inventory
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcomes Measurement Information System
QoL	Quality of Life
RFS	Relapse free survival
RFS2	Relapse free survival 2
RNA	Ribonucleic acid
RPTD	Recommended Phase 3 dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCT	Stem cell transplant or transplantation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TLS	tumor lysis syndrome

ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WHO	World Health Organization

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-063: A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T)

Protocol Date: 08 April 2025

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP), as well as and 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 law or regulation 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 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]		Clinical Development
		Clinical Study Leadership
		Statistics
		Statistics

APPENDIX D. PUBLISHED STUDIES EVALUATING AZACITIDINE POST-TRANSPLANT WITH REPORTED ADVERSE EVENT RATES

Reference	Azacitidine and Combination Therapy Dose and Schedule	Total Enrolled Subjects	Subjects having at least 1 AE Grade ≥ 3	Select Adverse Events					Comments
				Diarrhea	Infections	Nausea	Neutropenia	Vomiting	
Oshikawa 2015[63]	Gemtuzumab ozogamicin + Aza [redacted] mg/m^2 × 7days q 28 days[a]	10	NR	NR	50%	NR	NR	NR	AML post-transplant prophylactic
El-Cheikh 2017[64]	Start Day 6, Aza [redacted] mg/m^2 × 5 days monthly	18	NR	5%	17%	NR	5%	NR	AML and MDS post-transplant prophylaxis,
Guillaume 2019[55]	Donor lymphocyte Infusions + Aza [redacted] mg/m^2 daily × 5 every 28 days[a]	15	NR	NR	7%	NR	NR	NR	AML or MDS post-transplant
Craddock 2016[32]	Start Day 54, Aza [redacted] mg/m^2 daily × 5 every 28 days, reduction to [redacted] mg/m^2 for grade 3 or 4 AE > 2 weeks	37	NR	NR	54 occurrences	NR	27%	NR	AML post-SCT, prophylactic, Multicenter,
Karakulska-Prystupiuk 2018[65]	Aza [redacted] mg/m^2 × 7 days[a]	28	NR	NR	36%	NR	71%	NR	AML post-transplant
Platzbecker 2018[52]	Aza [redacted] mg/m^2 daily × 7 every 29 days 24 cycles[a]	53	NR	8%	30%	13%	92%	NR	MDS or AML in CR, after chemo or transplant 1-year RFS among MRD+ at enrollment, and 46%, MRD–: 88%
Craddock 2019[53]	Lenalidomide + Aza [redacted] mg/m^2 × 7 days[a]	29	NR	NR	NR	NR	NR	NR	AML + MDS after allo SCT prophylactic

Reference	Azacitidine and Combination Therapy Dose and Schedule	Total Enrolled Subjects	Subjects having at least 1 AE Grade ≥ 3	Select Adverse Events					Comments
				Diarrhea	Infections	Nausea	Neutropenia	Vomiting	
Czibere 2009[66]	Aza [redacted] mg/m^2 daily × 5 days × 2 - 5 cycles[a]	22	32%	NR	31% (due to neutropenia)	NR	NR	NR	Relapse after allo-SCT. Retrospective mOS 144 days having leukocyte count reductions was predictor of survival
Steinmann 2015[67]	DLI + Aza [redacted] mg × 3 days q 21 days[a]	72	NR	NR	38.9% admissions for infections, 2 Grade 5	NR	NR	NR	Retrospective analysis including AML, MDS, or CMML.
Schroeder 2013[68]	DLI + Aza [redacted] mg/m^2/day × 5 days q 28 days[a]	28	NR	32%	50%	54%	Grade ≥ 3: 65%	29%	Subjects with AML + MDS relapse post-transplant relapse

Allo-SCT = allogeneic stem cell transplant; AML = acute myeloid leukemia; Aza = azacitidine; CMML = chronic myelomonocytic leukemia; CR = complete remission; DLI = donor lymphocyte infusion; MDS = myelodysplastic syndrome; mOS = median overall survival; MRD = measurable residual disease; NR = not reported; RFS = Relapse free survival; SCT = stem cell transplant

a. No treatment start date provided.

APPENDIX E. DOSE MODIFICATION GUIDELINES

The dose modification guidelines include 1) changes initiated for subject safety (described here) and 2) change initiated due to drug-drug interaction (DDI) (described in Section 5.4). Those two dose modifications should be applied separately. Dose modifications initiated for safety purposes should be calculated first (assuming no DDI), then the DDI modifications should be applied to the altered dose as applicable.

Expert medical judgment of the investigator is necessary to account for the clinical presentation of the individual subject when determining if the dose and/or schedule of study drugs should be modified. Below guidelines describe how the investigator may modify the dose when necessary. Guidelines for starting day and doses for Cycles 2 and beyond depend upon events experienced during prior treatment cycles and therefore may vary from cycle to cycle – as outlined in the Table 7 below. If a subject's medical findings may warrant dose modifications outside of these guidelines, investigators must first discuss with the AbbVie TA MD or appropriate delegate.

Overall Guidance:

- Blood count starting criteria for Day 1 of each cycle in Part 1 is ANC ≥ 1500/µL and platelets ≥ 80,000/µL and in Part 2 is ANC ≥ 1000/µL and platelets ≥ 50,000/µL. In Part 2, the criteria only apply to subjects in Arm A.
- If study drugs are interrupted mid-cycle (≥ Day 14), they should not be restarted until Day 1 of the subsequent cycle and not prior to meeting blood count recovery criteria.
- Missed doses of both drugs due to treatment interruptions should not be added or administered retrospectively.
- Changes of both duration and dose should be avoided, and require communication between investigator and AbbVie TA MD or appropriate delegate.
- Venetoclax dose reductions to as low as 100 mg and azacitidine dose reductions to as low as 10 mg/m^2 x 5 days are permitted. These reductions do not require TA MD approval if reductions follow the stated guidelines.
- Part 1 dose confirmation only: If an investigator feels that a subject may benefit from a higher dose of study drug, individual dose escalations above the starting dose of an assigned cohort are permitted after the completion of Cycle 2 and may only occur if the dose being escalated to has been tested and approved in a previous cohort. No dose escalations are permitted during Cycles 1 or 2.
- Dosing delays for up to 21 days will be at the discretion of the investigator. Longer delays may be appropriate after discussion and agreement between the investigator and the AbbVie TA MD (or appropriate delegate).
- Subjects should complete all 6 cycles of combination treatment before starting Cycle 7 (venetoclax monotherapy). Subjects will begin Cycle 7 once all 6 cycles of combination treatment have been completed, regardless of the length of any treatment delays during the combination treatment phase. Subjects must meet the clinical and laboratory requirements for dosing before starting Cycle 7. In cases when subjects are not able to complete all 6 cycles of

combination treatment, they may still continue to receive venetoclax monotherapy at Cycle 7, if the investigator feels it is appropriate after discussion and agreement between the Investigator and the AbbVie TA MD and the subject meets the clinical and laboratory requirements for dosing.

- If the treatment start count criteria are not met within 6 weeks after the start of Cycle 1, then a bone marrow evaluation is recommended. If performed, this bone marrow aspirate and/or biopsy will be documented as an unscheduled visit for disease assessment and the peripheral blood and bone marrow aspirate biomarker samples (not peripheral blood DNA/RNA) should be sent to the central lab.
- If disease relapse is identified, then the subject must discontinue treatment and enter the survival phase. If other causes for low blood counts are identified (e.g., infections, GvHD, bone marrow suppression from drugs other than the study drugs), then these causes should be addressed, the subject should be treated accordingly if possible. In that case resuming treatment with venetoclax and azacitidine may be indicated as soon as blood counts have recovered to treatment starting criteria. If there is prolonged bone marrow toxicity attributed to the study drugs, then supportive care for cytopenia, and further monitoring of CBCs without restarting the study medication is indicated.
- Any dose modifications outside of those described specifically in this guideline should be discussed with the AbbVie TA MD or appropriate delegate.

Table 7. Dose Modifications (Reductions, Interruptions, and Modifications)

Event	Occurrence	Action
Grade 3 neutropenia and/or thrombocytopenia if lasts greater than 7 days; 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 + azacitidine. 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 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 + azacitidine after resolution. Please also refer to Inter-Cycle Delays below.
	2nd Occurrence and subsequent occurrences	Interrupt venetoclax + azacitidine. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax + azacitidine after resolution (resolved to ≤ Grade 1 or returned to 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 [redacted] mg for more. Please also refer to Inter-Cycle Delays below.

MD = Medical Director; TA = Therapeutic Area

Inter-Cycle Delays:

If the start of the next cycle is delayed by > 14 days but ≤ 21 days, dose reduction of azacitidine should be considered. Azacitidine should be reduced from [redacted] mg/m^2 x 5 days to [redacted] mg/m^2 x 5 days, if possible. Please consult TA MD if any other dose reductions are being considered.

If the start of the next cycle is delayed by > 21 days, venetoclax dose reduction by 50% and/or duration should be considered. Please consult TA MD if delay is longer than 21 days.

Table 8. Dose Reduction for venetoclax + azacitidine for Subjects with Cytopenia

If current dose level is:		Then dose reduction level should be:	
Venetoclax	**Azacitidine**	**Venetoclax**	**Azacitidine**
[redacted] mg x 28 days	[redacted] mg/m^2 x 5 days	[redacted] mg x 21 days	[redacted] mg/m^2 x 5 days
[redacted] mg x 21 days	[redacted] mg/m^2 x 5 days	[redacted] mg x 14 days	[redacted] mg/m^2 x 5 days
[redacted] mg x 14 days	[redacted] mg/m^2 x 5 days	[redacted] mg x 14 days	[redacted] mg/m^2 x 5 days
[redacted] mg x 14 days	[redacted] mg/m^2 x 5 days	[redacted] mg x 14 days	[redacted] mg/m^2 x 5 days

Recommended Dose Modifications for Nonhematologic Toxicities

Event	Occurrence	Action
Nonhematologic Adverse Events[a,b]		
≥ Grade 3 nonhematologic toxicities	1st occurrence	Interrupt venetoclax and/or azacitidine. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax and/or azacitidine may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax and/or azacitidine. Dose reduction consistent with dose modification for hematological toxicity. The azacitidine dose may be reduced from [redacted] mg/m^2 to [redacted] mg/m^2, with the lowest allowable dose being [redacted] mg/m^2. However, if previous dose reduction has occurred, then the venetoclax dose might be reduced, as well.

a. If a toxicity is attributed to 1 study drug (venetoclax or azacitidine), only the 1 study drug may be interrupted or reduced after consultation with the TA MD.

b. If the Investigator assesses that the ≥ Grade 3 nonhematologic AE is not a toxicity of either study drug, both study drugs may potentially be continued upon consensus of the Investigator and TA MD.

Cumulative Delay and End of Treatment

The planned treatment duration is up to 24 cycles after treatment start regardless of cumulative delays.

Treatment Continuation beyond 24 cycles:

Subjects in Part 2 Arm A who have been granted extended venetoclax treatment prior to communication with investigators regarding the change in continued treatment will be allowed to

receive continued study treatment (for up to 12 additional cycles beyond the 24 cycles of treatment, up to 36 cycles total). Subjects in Part 1 who have been receiving continued study treatment may end treatment when they meet discontinuation criteria, as outlined in Section 5.5.

APPENDIX F. HIGH-RISK AML CRITERIA

NCCN Risk Categorization: Guidelines for AML, Version 2.2016

Risk Category	**Cytogenetic**
Not High Risk (Favorable Risk)	Core binding factor: inv(16) or t(16;16) or t(8;21) t(15;17)
Not High Risk (Intermediate Risk)	Normal cytogenetics +8 alone t(9;11) Other non-defined
High Risk (Poor Risk)	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5,5q-,-7,7q- 11q23-non t(9;11) inv(3),t(3;3) t(6;9) t(9;22)

APPENDIX G. ACTIVITY SCHEDULE

The following table shows the required activities across the 24 cycles each subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to the geo-political conflict in Israel and surrounding impacted regions are detailed within the Operations Manual (Appendix I).

Study Activities Table

Part 1 (Dose Confirmation) Registration through Cycle 4 **Activity**	Registration	Screening	Baseline	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day s 2 - 4	Day 5	Day 15
INTERVIEWS & QUESTIONNAIRES																		
Informed consent	✓																	
Eligibility criteria	✓	✓																
Medical history	✓																	
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense/Collect subject dosing diary and review for adverse event, concomitant therapy, and venetoclax administration as applicable			✓				✓				✓				✓			
EQ-5D-5L and EORTC-QLQ-C30			✓				✓				✓				✓			
PROMIS fatigue			✓				✓				✓				✓			
cGvHD PRO			✓				✓				✓				✓			

Part 1 (Dose Confirmation) Registration through Cycle 4 Activity	Registration	Screening	Baseline	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
KPS assessment		✓	✓				✓				✓				✓			
Survival follow-up																		
LOCAL LABS & EXAMS																		
Height (Screening only) and Weight		✓	✓				✓				✓				✓			
Vital signs		✓	✓				✓				✓				✓			
Physical examination		✓	✓			✓	✓			✓	✓			✓	✓			
Urinalysis			✓															
Hematology		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓			✓
Chemistry		✓	✓		✓	✓	✓		✓	✓	✓				✓			
Coagulation (after Baseline, only when relapse suspected)		✓	✓															
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)		✓									✓							
Serum pregnancy test		✓																
Urine pregnancy test			✓				✓				✓				✓			
Bone marrow biopsy and/or aspirate (disease assessment) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1.)		✓																
Clinical GvHD assessment			✓				✓				✓				✓			

Part 1 (Dose Confirmation) Registration through Cycle 4 Activity	Registration	Screening	Baseline	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
CENTRAL LABS																		
Bone marrow aspirate (biomarker assessment) (and when relapse suspected) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1.)		✓																
Peripheral blood (biomarker assessments) – (and when relapse suspected) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1. Additionally, only 1 specimen is needed at either screening or Cycle 1 Day 1.)		✓	✓								✓							
Pharmacokinetic samples			✓		✓				✓								✓	
Optional biomarker sample: whole blood DNA/RNA			✓								✓							
TREATMENT																		
Dispense venetoclax			✓				✓				✓				✓			
Venetoclax QD (Cycle 1 - 4, Days 1 - 28)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Azacitidine QD			✓	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓	

cGvHD = chronic graft-versus-host-disease; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; GvHD = graft-versus-host-disease; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; KPS = Karnofsky Performance Scale; PRO = Patient Reported Outcome; PROMIS = Patient Reported Outcomes Measurement Information System; QD = once a day; RNA = ribonucleic acid

Part 1 (Dose Confirmation) Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14-18	Cycle 19	Cycles 20-24	Cycles ≥ 25 (if additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
INTERVIEWS & QUESTIONNAIRES																						
Informed consent																						
Eligibility criteria																						
Medical history																						
Adverse event assessment (Note: only spontaneously reported SAEs collected at scheduled follow-up)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Dispense/Collect subject dosing diary and review for adverse event, concomitant therapy, and venetoclax administration as applicable	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Part 1 (Dose Confirmation) Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14-18	Cycle 19	Cycles 20-24	Cycles ≥ 25 (if additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
EQ-5D-5L and EORTC-QLQ-C30				✓				✓				✓		✓		✓	✓	✓ (≤ C50)	✓		✓ (only at first follow-up visit after last study treatment)	
PROMIS fatigue				✓				✓				✓		✓		✓	✓	✓ (≤ C50)	✓		✓ (only at first follow-up visit after last study treatment)	
cGvHD PRO								✓						✓		✓	✓ C24 only		✓			
KPS assessment	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
Survival follow-up																						✓
LOCAL LABS & EXAMS																						
Weight	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Vital signs	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓			✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Part 1 (Dose Confirmation) Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14-18	Cycle 19	Cycles 20-24	Cycles ≥ 25 (if additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
Urinalysis																			✓			
Hematology	✓		✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Chemistry	✓			✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Coagulation (after Baseline, only when relapse suspected)																			✓		✓	
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)				✓							✓		✓ Cycle 12 and every 3 cycles thereafter						✓			
Serum pregnancy test																						
Urine pregnancy test	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Bone marrow biopsy and/or aspirate (disease assessment)								✓						✓				✓ (only when relapse suspected)	✓		✓ (only when relapse suspected)	
Clinical GvHD assessment								✓						✓		✓	✓ C24 only		✓			

Part 1 (Dose Confirmation) Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14-18	Cycle 19	Cycles 20-24	Cycles ≥ 25 (if additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
CENTRAL LABS																						
Bone marrow aspirate (biomarker assessment)								✓						✓				✓ (only when relapse suspected)	✓		✓ (only when relapse suspected)	
Peripheral blood (biomarker assessments)	✓							✓			✓			✓		✓		✓ (only when relapse suspected)	✓		✓ (only when relapse suspected)	
Pharmacokinetic samples						✓																
Optional biomarker sample: whole blood DNA/RNA																			✓			

Part 1 (Dose Confirmation) Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14-18	Cycle 19	Cycles 20-24	Cycles ≥ 25 (if additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
℞ TREATMENT																						
Dispense venetoclax	✓			✓				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓				
Venetoclax QD (Cycles 1 - 24, Days 1 - 28; optional Cycle ≥ 25)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Azacitidine QD	✓	✓		✓	✓	✓																

cGvHD = chronic graft-versus-host-disease; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; GvHD = graft-versus-host-disease; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; KPS = Karnofsky Performance Scale; PRO = Patient Reported Outcome; PROMIS = Patient Reported Outcomes Measurement Information System; QD = once a day; RNA = ribonucleic acid

Study Activities Table

Part 2 (Venetoclax/Azacitidine Arm) Arm A Registration through Cycle 4 Activity	Registration	Screening	Randomization (Baseline)	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
INTERVIEWS & QUESTIONNAIRES																		
Informed consent	✓																	
Eligibility criteria	✓	✓																
Medical history	✓																	
Token information (US adult subjects only)	✓																	
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense/Collect subject dosing diary and review for adverse event, concomitant therapy, and venetoclax administration as applicable			✓				✓				✓				✓			
EQ-5D-5L and EORTC			✓				✓				✓				✓			
PedsQL (if applicable)			✓				✓				✓				✓			
PROMIS fatigue			✓				✓				✓				✓			
cGvHD PRO			✓				✓				✓				✓			

Part 2 (Venetoclax/Azacitidine Arm) Arm A Registration through Cycle 4 Activity	Registration	Screening	Randomization (Baseline)	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
KPS assessment/LPPS		✓	✓				✓				✓				✓			
Survival follow-up																		
LOCAL LABS & EXAMS																		
Weight and Height (Note: Adult height measurement is only required at screening; adolescents' height should be measured at screening and on Day 1 of Cycles 1-6)		✓	✓				✓				✓				✓			
Vital signs		✓	✓				✓				✓				✓			
Physical examination		✓	✓			✓	✓			✓	✓			✓	✓			
Urinalysis			✓															
Hematology		✓	✓		✓	✓	✓		✓	✓	✓		✓	✓	✓			✓
Chemistry		✓	✓		✓		✓		✓		✓				✓			
Coagulation (after Baseline, only when relapse suspected)		✓	✓															
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)		✓									✓							
Serum pregnancy test		✓																

Part 2 (Venetoclax/Azacitidine Arm) Arm A Registration through Cycle 4 Activity	Registration	Screening	Randomization (Baseline)	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
Urine pregnancy test			✓				✓				✓				✓			
Bone marrow biopsy and/or aspirate (disease assessment) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1)		✓																
Clinical GvHD assessment			✓				✓				✓				✓			
CENTRAL LABS																		
Bone marrow aspirate (biomarker assessment) (and when relapse suspected) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1)		✓																
Peripheral blood (biomarker assessments) – (and when relapse suspected) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1, preferably on the same day as the screening bone marrow aspirate collection. Additionally, only 1 specimen is needed at either screening or Cycle 1 Day 1.)		✓	✓								✓							
Pharmacokinetic sample			✓		✓				✓								✓	
Optional biomarker sample: whole blood DNA/RNA			✓								✓							

Part 2 (Venetoclax/Azacitidine Arm) Arm A Registration through Cycle 4 Activity	Registration	Screening	Randomization (Baseline)	Cycle 1	Cycle 1	Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycle 3	Cycle 3	Cycle 3	Cycle 3	Cycle 4	Cycle 4	Cycle 4	Cycle 4
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Days 8, 15, 22	Day 1	Days 2 - 4	Day 5	Day 15	Day 1	Days 2 - 4	Day 5	Day 15
℞ TREATMENT																		
[redacted]																		

cGvHD = chronic graft-versus-host-disease; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; GvHD = graft-versus-host-disease; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; LPPS = Lansky Play-Performance Scale; KPS = Karnofsky Performance Scale; PedsQL = Pediatric Quality of Life Inventory; PRO = Patient Reported Outcome; PROMIS = Patient Reported Outcomes Measurement Information System; QD = once a day; RNA = ribonucleic acid

Part 2 (Venetoclax/Azacitidine Arm) Arm A Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14 - 18	Cycle 19	Cycles 20 - 24	≥ Cycles 25 (if ≤ 12 additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 1	Days 2 - 4	Day 5	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
INTERVIEWS & QUESTIONNAIRES																				
Informed consent																				
Eligibility criteria																				
Medical history																				
Adverse event assessment (Note: only spontaneously reported SAEs collected at scheduled follow-up)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Dispense/Collect subject dosing diary and review for adverse event, concomitant therapy, and venetoclax administration as applicable	✓		✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
EQ-5D-5L and EORTC-QLQ-C30			✓			✓				✓		✓		✓	✓	✓	✓		✓ (only at first follow-up visit after last study treatment)	

Part 2 (Venetoclax/Azacitidine Arm) Arm A Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14 - 18	Cycle 19	Cycles 20 - 24	≥ Cycles 25 (if ≤ 12 additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 1	Days 2 - 4	Day 5	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
PedsQL (if applicable)			✓			✓				✓		✓		✓	✓	✓	✓		✓ (only at first follow-up visit after last study treatment)	
PROMIS fatigue			✓			✓				✓		✓		✓	✓	✓	✓		✓ (only at first follow-up visit after last study treatment)	
cGvHD PRO						✓						✓		✓	✓ C24 only		✓			
KPS assessment/LPPS	✓		✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	
Survival follow-up																				✓

Part 2 (Venetoclax/Azacitidine Arm) Arm A Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14 - 18	Cycle 19	Cycles 20 - 24	≥ Cycles 25 (if ≤ 12 additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 1	Days 2 - 4	Day 5	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
LOCAL LABS & EXAMS																				
Height (Day 1 of Cycles 1-6 for adolescents) and Weight	✓		✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Vital signs	✓		✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urinalysis																	✓			
Hematology	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Chemistry	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Coagulation (at EOT and when relapse suspected)																	✓		✓	
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)			✓						✓		✓ Cycle 12 and every 3 cycles thereafter						✓			
Serum pregnancy test																				
Urine pregnancy test	✓		✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Bone marrow biopsy and/or aspirate (disease assessment)						✓						✓				✓ (only when relapse suspected)	✓		✓ (only when relapse suspected)	

Part 2 (Venetoclax/Azacitidine Arm) Arm A Cycle 5 through Survival Follow-up Activity	Cycle 5	Cycle 5	Cycle 6	Cycle 6	Cycle 6	Cycle 7	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycles 11 and 12	Cycle 13	Cycles 14 - 18	Cycle 19	Cycles 20 - 24	≥ Cycles 25 (if ≤ 12 additional cycles approved)	End of Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Day 1	Days 2 - 5	Day 1	Days 2 - 4	Day 5	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1				
Clinical GvHD assessment						✓						✓		✓	✓ C24 only		✓			
CENTRAL LABS																				
Bone marrow aspirate (biomarker assessment)						✓						✓				✓ (only when relapse suspected)	✓		✓ (only when relapse suspected)	
Peripheral blood (biomarker assessments) (and when relapse is suspected)	✓					✓			✓			✓		✓		✓ (only when relapse suspected)	✓		✓	
Pharmacokinetic sample					✓															
Optional biomarker sample: whole blood DNA/RNA																	✓			
TREATMENT																				
[redacted]																				

cGvHD = chronic graft-versus-host-disease; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; GvHD = graft-versus-host-disease; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; LPPS = Lansky

Play-Performance Scale; KPS = Karnofsky Performance Scale; PedsQL = Pediatric Quality of Life Inventory; PRO = Patient Reported Outcome; PROMIS = Patient Reported Outcomes Measurement Information System; QD = once a day; RNA = ribonucleic acid

Study Activities Table

Part 2 (Best Supportive Care Arm) Arm B Activity	Registration	Screening	Randomization (Baseline)	Cycle 2	Cycles 3 - 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 13	Cycles 16 and 22	Cycle 19	Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1			
INTERVIEWS & QUESTIONNAIRES																
Informed consent	✓															
Eligibility criteria	✓	✓														
Medical history	✓															
Token information (US adult subjects only)	✓															
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Dispense/Collect subject dosing diary and review for adverse event, and concomitant therapy			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Part 2 (Best Supportive Care Arm) Arm B Activity	Registration	Screening	Randomization (Baseline)	Cycle 2	Cycles 3 - 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 13	Cycles 16 and 22	Cycle 19	Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1			
EQ-5D-5L and EORTC QLQ-C30 (including Cycles 20 to 24)			✓	✓	✓ C3, C4, and C6 only	✓			✓	✓	✓ C22 only	✓	✓ C20, C21, C23, and C24 only	✓	✓ (only at first follow-up visit after last study treatment)	
PedsQL (if applicable) (including Cycles 20 to 24)			✓	✓	✓ C3, C4, and C6 only	✓			✓	✓	✓ C22 only	✓	✓ C20, C21, C23, and C24 only	✓	✓ (only at first follow-up visit after last study treatment)	
PROMIS fatigue (including Cycles 20 to 24)			✓	✓	✓ C3, C4, and C6 only	✓			✓	✓	✓ C22 only	✓	✓ C20, C21, C23, and C24 only	✓	✓ (only at first follow-up visit after last study treatment)	
cGvHD PRO			✓	✓	✓ C3 & C4 only	✓				✓		✓	✓ C24 only	✓		

Part 2 (Best Supportive Care Arm) Arm B Activity	Registration	Screening	Randomization (Baseline)	Cycle 2	Cycles 3 - 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 13	Cycles 16 and 22	Cycle 19	Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
KPS assessment/LPPS		✓	✓	✓	✓ C3, C4, and C6 only	✓			✓	✓		✓		✓	✓	
Survival follow-up																✓
LOCAL LABS & EXAMS																
Weight and Height (Note: Adult height measurement is only required at screening; adolescents' height should be measured at screening and on Day 1 of Cycles 1-6)		✓	✓	✓	✓	✓			✓	✓		✓	✓	✓		
Vital signs		✓	✓	✓	✓	✓			✓	✓		✓		✓	✓	
Physical examination		✓	✓	✓	✓	✓			✓	✓	✓	✓		✓	✓	
Urinalysis			✓											✓		
Hematology		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Chemistry		✓	✓	✓	✓	✓			✓	✓				✓		
Coagulation (at EOT and when relapse suspected)		✓	✓											✓	✓	
HBV and/or HCV testing (only subjects diagnosed with HBV and/or HCV prior to enrollment)		✓			✓ C3 & C6 only			✓		✓ Cycle 12 and every 3 cycles thereafter				✓		

Part 2 (Best Supportive Care Arm) Arm B Activity	Registration	Screening	Randomization (Baseline)	Cycle 2	Cycles 3 - 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 13	Cycles 16 and 22	Cycle 19	Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	**Up to 60 days post-transplant**	**Day –14 to Day -1**	**Cycle 1 Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**			
Serum pregnancy test		✓														
Urine pregnancy test			✓													
Bone marrow biopsy and/or aspirate (disease assessment)		✓				✓				✓				✓	✓ (only when relapse suspected)	
Clinical GvHD assessment			✓	✓	✓ **C3 & C4 only**	✓				✓		✓	✓ **C24 only**	✓		

Part 2 (Best Supportive Care Arm) Arm B Activity	Registration	Screening	Randomization (Baseline)	Cycle 2	Cycles 3 - 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 13	Cycles 16 and 22	Cycle 19	Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24	End Visit	Scheduled Follow-Up Visits (Every 12 Weeks [± 1 weeks] Until Documented Relapse)	Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)
Day	Up to 60 days post-transplant	Day –14 to Day -1	Cycle 1 Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1			
CENTRAL LABS																
Bone marrow aspirate (biomarker assessment) (Note: Screening assessment may be performed within 30 days of Cycle 1 Day 1)		✓				✓				✓				✓	✓ (only when relapse suspected)	
Peripheral blood (biomarker assessments) (and when relapse suspected) (Note: Only 1 specimen is needed at either screening or Cycle 1 Day 1.)		✓	✓		✓ C3 & C5 only	✓		✓		✓		✓		✓	✓	
Optional biomarker sample: whole blood DNA/RNA			✓		✓ C3 only									✓		

cGvHD = chronic graft-versus-host-disease; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; GvHD = graft-versus-host-disease; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; LPPS = Lasky Play-Performance Scale; KPS = Karnofsky Performance Scale; PedsQL = Pediatric Quality of Life Inventory; PRO = Patient Reported Outcome; PROMIS = Patient Reported Outcomes Measurement Information System; RNA = ribonucleic acid

APPENDIX H. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	16 August 2019
Version 1.1 (VHP Countries Only)	31 October 2019
Version 1.2 (Canada Only)	11 November 2019
Version 1.1.1 (VHP Countries Only)	26 November 2019
Version 2.0	19 December 2019
Administrative Change 1	20 February 2020
Administrative Change 2	08 May 2020
Version 3.0	04 November 2020
Version 4.0	05 October 2021
Version 5.0	07 February 2022
Administrative Change 3	01 June 2022
Version 6.0	30 August 2022
Administrative Change 4	13 October 2022
Version 7.0	09 June 2023
Version 8.0	25 June 2024

The purpose of this amendment for Protocol and Operations Manual version 8.0 is to include administration changes, correct minor clerical errors for consistency, and the following:

- **Rationale**: To not allow additional subjects to continue study treatment past Cycle 24.
  - In Protocol Section 4.1, Appendix E, Appendix G, Operations Manual Section 2.1, Operations Manual Section 2.4, and Operations Manual Section 3.22, to harmonize the duration of study treatment to 24 cycles, removed text regarding additional venetoclax treatment beyond 24-cycle treatment period, limited the duration of previously approved extended study treatment for Part 2 Arm A subjects to 12 additional cycles (total of 36 cycles), and specified that Part 1 subjects receiving additional study treatment may continue until meeting discontinuation criteria.
- **Rationale**: To update the sponsor/emergency medical contact.
  - In Protocol Title Page, Operations Manual Section 1, and Operations Manual Section 4.3, updated contact information.
- **Rationale**: To harmonize PRO collection.
  - In Protocol Appendix G, Operations Manual Section 2.1, Operations Manual Section 2.6, specified PRO collection timelines.

- **Rationale**: To not require clinical chemistry at scheduled follow-up visits.
  - In Protocol Appendix G, Operations Manual Section 2.3, Operations Manual Section 2.6, and Operations Manual Section 2.9, removed clinical chemistry from scheduled follow-up visits.
- **Rationale**: To not require adverse event assessment at scheduled follow-up visits in Part A.
  - In Protocol Appendix G, Operations Manual Section 2.3, removed adverse event assessment from scheduled follow-up visits.
- **Rationale**: To update study personnel contacts.
  - In Operations Manual Section 1, updated contact information for protocol deviations and product complaints and PG biomarker sample lab.

APPENDIX I. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-063

Acute Myeloid Leukemia: Venetoclax and Azacitidine

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

FULL TITLE: A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T)

1 CONTACTS

Emergency Contact	[redacted] MD AbbVie 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Mobile: Email: [redacted]
Safety Concerns	Oncology Safety Team AbbVie Bldg. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (833) 942-2226 Email: SafetyManagement_Oncology@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 806-2062 Backup: +1 (847) 935-2844
Protocol Deviations and Product Complaints	[redacted] AbbVie 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: [redacted]
Bioanalytical Lab	Bioanalysis AbbVie Dept. [redacted] Bldg. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (847) 937-1919 Fax: +1 (847) 938-9898 Email: Sample.Receiving@abbvie.com
	Pharmaceutical Product Development (PPD) Attn: [redacted] Specimen Management 3230 Deming Way Middleton, WI 53562	Phone: +1 (608) 662-7706 Fax: +1 (608) 662-9025 Email: DemingWaySampleMgmnt@ppdi.com
PG Biomarker Sample Lab	[redacted] AbbVie Dept [redacted], [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: [redacted]

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2 INVESTIGATION PLAN

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

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed for routine visits (routine visits do not include the screening visit, Day 1, the end of treatment visit/end visit, and any visit that requires a bone marrow aspirate or biopsy sample):

- If permitted by local regulations, the independent ethics committee (IEC)/institutional review board (IRB), and the subject, routine visits may be conducted in the subject's home residence.
- Routine study visits and/or activities may be performed by phone/virtually
- Routine study visits and/or activities may be performed by a local clinic/hospital/laboratory.
- Routine study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
    - For routine visits, reschedule the visit within ± 7 days.

If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained ± 3 days from the scheduled visit.

2.1 Treatment Period - Visit Activities (Part 1 [Dose Confirmation])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 1 - REGISTRATION (Before Transplantation, Up to 60 Days Post-Transplant):

INTERVIEW & QUESTIONAIRES	• Informed consent • Eligibility criteria	• Medical history

NOTES: Subjects must have AML as assessed by World Health Organization (WHO 2017) criteria.[1]
Refer to Registration eligibility criteria (Protocol Section 5.1, Criteria 1 - 7).
Obtain blast counts from medical history. Pre-transplant blast count should be taken from the most recent bone marrow aspirate or biopsy and hematology labs (for peripheral blood blast count) performed prior to pre-transplant conditioning. Blasts must be less than 10% in bone marrow or peripheral blood.

Part 1 - SCREENING (Day –14 to Day –1):

INTERVIEW & QUESTIONAIRES	• Eligibility criteria • Adverse event assessment	• Prior/concomitant therapy • KPS Assessment
EXAMINATIONS	• Vital Signs • Height and Weight	• Complete (or full) physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry • Bone marrow aspirate and/or biopsy (disease assessment)[a]	• Coagulation • Serum pregnancy test • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)[c]

NOTES: All screening procedures must be performed onsite.
Refer to Screening eligibility criteria (Protocol Section 5.1, Criteria 8 - 31).
Screening bone marrow will serve as the baseline disease assessment.
Clinical laboratory tests (hematology and chemistry) will be performed within 7 days of Cycle 1 Day 1. Neutrophils and platelet count must be measured twice, at least 2 days apart (approximately 48 hours) within 1 week prior to Cycle 1 Day 1 or prior to dosing on Cycle 1 Day 1.

a. Bone marrow aspirate and/or biopsy may be performed within 30 days of Cycle 1 Day 1. If a bone marrow aspirate sample is collected, it should be split for biomarker analysis. Additional details are provided in Section 3.16.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

c. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 1 - Cycle 1, Day 1 (Baseline):

INTERVIEW & QUESTIONAIRES	• Adverse event Assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD assessment(s)	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Urinalysis • Hematology • Chemistry	• Coagulation • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)[a] • Pharmacokinetic samples	• Optional biomarker whole blood sample (DNA/RNA)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

NOTES: All Day 1 procedures must be performed onsite.

Procedures performed on Cycle 1 Day 1 should be performed predose and will serve as baseline.

Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

a. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 1 - Cycle 1, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 1, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 1 - Cycle 1, Days 8, 15, and 22:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 2, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event Assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

Part 1 - Cycle 2, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 2, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 1 - Cycle 2, Days 8, 15, and 22:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 3, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	• Optional biomarker whole blood sample (DNA/RNA)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycle 3, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 3, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 3, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 4, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

Part 1 - Cycle 4, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 4, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 1 - Cycle 4, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 5, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

Part 1 - Cycle 5, Days 2 - 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 5, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 6, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • KPS Assessment
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycle 6, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 1 - Cycle 6, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 1 - Cycle 6, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 7, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. If a bone marrow aspirate sample is collected, it should be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 1 - Cycle 7, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
TREATMENT	• Venetoclax QD (PO)	

Part 1 - Cycle 8, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

Part 1 - Cycle 9, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycle 10, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • Prior/concomitant therapy • EQ-5D-5L and EORTC • PROMIS fatigue
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

Part 1 - Cycles 11 and 12, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• KPS Assessment • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

a. Cycle 12: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycle 13, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. If a bone marrow aspirate sample is collected, it should be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 1 - Cycles 14 - 18, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

a. Cycles 15 and 18: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycle 19, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• cGvHD PRO • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • KPS Assessment
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax • Venetoclax QD (PO)	

Part 1 - Cycles 20 - 24, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration KPS Assessment	• EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • Prior/concomitant therapy • cGvHD PRO[a]
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment[a]	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[b]
TREATMENT	• Venetoclax QD (PO)	• Dispense venetoclax

a. Cycle 24 only.

b. Cycles 21 and 24: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 1 - Cycles ≥ 25 (if additional cycles approved), Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment[a] • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration[a] • KPS Assessment	• Prior/concomitant therapy • EQ-5D-5L and EORTC QLQ-C30 (≤ Cycle 50) • PROMIS fatigue (≤ Cycle 50)
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments) –only when relapse suspected	• Bone marrow aspirate (biomarker assessment) – only when relapse suspected
TREATMENT	• Venetoclax QD (PO) (if applicable)	• Dispense venetoclax (if applicable)

NOTE: Subjects in Part 1 who have been receiving continued study treatment will end treatment when they meet discontinuation criteria, as outlined in Protocol Section 5.5.

a. Adverse event data and dosing diaries for Cycles ≥ 25 will only be collected and reviewed if venetoclax is continued.

b. Day 1 of every 3rd cycle after Cycle 24 (i.e., Cycles 27, 30, 33, etc.): Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.2 End of Treatment - Visit Activities (Part 1 [Dose Confirmation])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 1 - End of Treatment:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration Prior/concomitant therapy	• KPS Assessment • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Complete (or full) physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urinalysis • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Coagulation (only when relapse suspected) • Urine pregnancy test • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)[a] • Optional biomarker whole blood sample (DNA/RNA)

NOTE: The End of Treatment Visit is defined as the visit in which the subject has had documented relapse, the subject meets other criteria for treatment discontinuation, or at the end of Cycle 24. The End of Treatment Visit must be performed onsite.

a. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Subjects who do not have previously confirmed disease relapse require bone marrow biopsy and/or aspirate for disease assessment. Bone marrow aspirate should be split for biomarker analysis.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.3 Follow-Up Period - Visit Activities (Part 1 [Dose Confirmation])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 1 - 30-DAY SAFETY FOLLOW-UP

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATION	• Complete (or full) physical examination	• Vital signs
LOCAL LABORATORY TESTS & ASSESSMENTS	• Chemistry • Hematology	• Urine pregnancy test

Part 1 - Scheduled Follow-Up Visits (Every 12 Weeks [± 1 week] Until Documented Relapse)

INTERVIEW & QUESTIONAIRES	• EQ-5D-5L and EORTC (only at first follow-up visit after last study treatment)	• KPS Assessment • PROMIS fatigue (only at first follow-up visit after last study treatment)
EXAMINATIONS	• Targeted physical examination	• Vital signs
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment; only when relapse suspected)	• Coagulation (only when relapse suspected)
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment; only when relapse suspected)	• Peripheral blood (biomarker assessments; only when relapse suspected)

NOTE: Refer to Section 3.21 for additional details.

Part 1 - Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)

INTERVIEW & QUESTIONAIRES	• Survival follow-up

NOTE: After relapse, a subject will be followed every 12 weeks (± 4 weeks) for survival. No on-site visits required. Refer to Section 3.21 for additional details.

2.4 Treatment Period - Visit Activities (Part 2 Arm A [Venetoclax/Azacitidine])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm A – REGISTRATION (Before Transplantation, Up to 60 Days Post-Transplant):

INTERVIEW & QUESTIONAIRES	• Informed consent • Eligibility criteria • Medical history	• Token information (US adult subjects only) • Adverse event assessment

NOTES: Subjects must have AML as assessed by World Health Organization (WHO 2017) criteria.[1] Refer to Registration eligibility criteria (Protocol Section 5.1, Criteria 1 - 7). Obtain blast counts from medical history. Pre-transplant blast count should be taken from the most recent bone marrow aspirate or biopsy and hematology labs (for peripheral blood blast count) performed prior to pre-transplant conditioning. Blasts must be less than 10% in bone marrow or peripheral blood.

Part 2 Arm A - SCREENING (Day –14 to Day –1):

INTERVIEW & QUESTIONAIRES	• Eligibility criteria • Adverse event assessment	• Prior/concomitant therapy • KPS Assessment/LPPS
EXAMINATIONS	• Vital Signs • Height and Weight	• Complete (or full) physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Coagulation • Serum pregnancy test • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)[c]

NOTES: All screening procedures must be performed onsite.
Refer to Screening eligibility criteria (Protocol Section 5.1, Criteria 8 - 31).
Clinical laboratory tests (hematology and chemistry) may be performed within 7 days of Cycle 1 Day 1. Neutrophils and platelet count must be measured twice at least 2 days apart (approximately 48 hours) within 1 week prior to Cycle 1 Day 1 or prior to dosing on Cycle 1 Day 1. Measurement of neutrophil and platelet counts should occur at least 7 days after G-CSF and transfusion.

a. Bone marrow aspirate and biopsy may be performed within 30 days of Cycle 1 Day 1. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

c. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 2 Arm A – Cycle 1, Day 1 (Randomization [Baseline]):

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • KPS Assessment/LPPS	• PedsQL (if applicable) • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Urinalysis • Hematology • Chemistry	• Coagulation • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)[a]	• Pharmacokinetic samples • Optional biomarker whole blood sample (DNA/RNA)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

NOTES: All Day 1 procedures must be performed onsite.

Procedures performed on Cycle 1 Day 1 must be performed predose and will serve as baseline.

Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

a. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 2 Arm A – Cycle 1, Days 2-4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 1, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 2 Arm A – Cycle 1, Days 8, 15, and 22:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 2 Arm A – Cycle 2, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

NOTE: Day 1 of all cycles after Cycle 1 (starting from Cycle 2) should be calculated based on the last day of previous cycle, not C1D1.

Part 2 Arm A – Cycle 2, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 2, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 2 Arm A – Cycle 2, Days 8, 15, and 22:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 2 Arm A – Cycle 3, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	• Optional biomarker whole blood sample (DNA/RNA)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycle 3, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 3, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 3, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Targeted physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 2 Arm A – Cycle 4, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

Part 2 Arm A – Cycle 4, Days 2 - 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 4, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 2 Arm A – Cycle 4, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	
TREATMENT	• Venetoclax QD (PO)	

Part 2 Arm A – Cycle 5, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• Prior/concomitant therapy • KPS Assessment/LPPS
EXAMINATIONS	• Vital Signs • Targeted physical examination	• Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

Part 2 Arm A – Cycle 5, Days 2 - 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 6, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration Prior/concomitant therapy	• PROMIS fatigue • EQ-5D-5L and EORTC QLQ-C30 • PedsQL • KPS Assessment/LPPS
EXAMINATIONS	• Vital Signs • Targeted physical examination	• Height (adolescents only) and Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO) • Azacitidine QD (SC or IV)

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycle 6, Days 2, 3, and 4:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 6, Day 5:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
CENTRAL LABORATORY TESTS	• Pharmacokinetic samples	
TREATMENT	• Azacitidine QD (SC or IV)	• Venetoclax QD (PO)

NOTE: Pharmacokinetic samples: Blood samples for assay of venetoclax and possible metabolite(s) are best collected by venipuncture. In subjects in whom venipunctures are not ethically appropriate, the blood may be drawn from the central line. In this case, sufficient blood volume must be drawn before the PK sample is taken as to not draw previous content of the line into the PK sample tube.

Part 2 Arm A – Cycle 7, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • PedsQL • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 2 Arm A – Cycle 7, Day 15:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Physical examination	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry
TREATMENT	• Venetoclax QD (PO)	

Part 2 Arm A – Cycle 8, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

Part 2 Arm A – Cycle 9, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycle 10, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • KPS Assessment/LPPS • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• PROMIS fatigue • Prior/concomitant therapy • EQ-5D-5L and EORTC QLQ-C30 • PedsQL
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

Part 2 Arm A – Cycles 11 and 12, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. Cycle 12: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycle 13, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Urine pregnancy test
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 2 Arm A – Cycles 14 - 18, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • Prior/concomitant therapy
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[a]
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. Cycles 15 and 18: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycle 19, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • KPS Assessment/LPPS • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• PROMIS fatigue • Prior/concomitant therapy • EQ-5D-5L and EORTC QLQ-C30 • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

Part 2 Arm A – Cycles 20 - 24, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • KPS Assessment/LPPS • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• PROMIS fatigue • PedsQL • Prior/concomitant therapy • EQ-5D-5L and EORTC QLQ-C30 • cGvHD PRO[a]
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment[a]	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[b]
TREATMENT	• Dispense venetoclax	• Venetoclax QD (PO)

a. Cycle 24 only.

b. Cycles 21 and 24: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm A – Cycles ≥ 25 (if ≤ 12 additional cycles approved), Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • KPS Assessment/LPPS • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration [a]	• PROMIS fatigue • PedsQL • Prior/concomitant therapy • EQ-5D-5L and EORTC QLQ-C30
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urine pregnancy test	• Chemistry • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments) – only when relapse suspected	• Bone marrow aspirate (biomarker assessment) - only when relapse suspected
TREATMENT	• Dispense venetoclax (if applicable)	• Venetoclax QD (PO) (if applicable)

NOTE: Subjects in Part 2 Arm A who have been granted extended venetoclax treatment prior to communication with investigators regarding the change in continued treatment will be allowed to receive continued study treatment (for up to 12 additional cycles beyond the 24 cycles of treatment, (up to 36 cycles total).

a. Adverse event data and dosing diaries for Cycles ≥ 25 will only be collected and reviewed if venetoclax is continued.

b. Day 1 of every 3rd cycle after Cycle 24 (i.e., Cycles 27, 30, 33, etc.): Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.5 End of Treatment - Visit Activities (Part 2 Arm A [Venetoclax/Azacitidine])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm A - End of Treatment:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, concomitant therapy, and venetoclax administration	• KPS Assessment/LPPS • PedsQL • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Complete (or full) physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urinalysis • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Coagulation • Urine pregnancy test • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments) • Optional biomarker whole blood sample (DNA/RNA)

NOTE: The End of Treatment Visit is defined as the visit in which the subject has had documented relapse or at which the subject meets other criteria for treatment discontinuation or at the end of Cycle 24. The End of Treatment Visit must be performed onsite.

a. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Subjects who do not have previously confirmed disease relapse require bone marrow biopsy and/or aspirate and/or other exams if needed for disease assessment. Bone marrow aspirate should also be split for biomarker analysis.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.6 Follow-Up Period - Visit Activities (Part 2 Arm A [Venetoclax/Azacitidine])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm A - 30-DAY SAFETY FOLLOW-UP

INTERVIEW & QUESTIONAIRES	• Adverse event assessment	• Prior/concomitant therapy
EXAMINATIONS	• Complete (or full) physical examination	• Vital signs
LOCAL LABORATORY TESTS & ASSESSMENTS	• Chemistry • Hematology	• Urine pregnancy test

Part 2 Arm A - Scheduled Follow-Up Visits (Every 12 Weeks [± 1 week] Until Documented Relapse)

INTERVIEW & QUESTIONAIRES	• EQ-5D-5L and EORTC QLQ-C30 (only at first follow-up visit after last study treatment) • PedsQL (only at first follow-up visit after last study treatment)	• KPS Assessment/LPPS • PROMIS fatigue (only at first follow-up visit after last study treatment)
EXAMINATIONS	• Targeted physical examination	• Vital signs
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Coagulation (only when relapse suspected)	• Bone marrow biopsy and/or aspirate (disease assessment; only when relapse suspected)
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment; only when relapse suspected)	• Peripheral blood (biomarker assessments)

NOTE: Refer to Section 3.21 for additional details.

Part 2 Arm A - Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)

INTERVIEW & QUESTIONAIRES	• Survival follow-up

NOTE: After relapse, a subject will be followed every 12 weeks (± 4 weeks) for survival. No on-site visits required. Refer to Section 3.21 for additional details.

2.7 Supportive Care - Visit Activities (Part 2 Arm B [Best Supportive Care])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm B – REGISTRATION (Before Transplantation, Up to 60 Days Post-Transplant):

INTERVIEW & QUESTIONAIRES	• Informed consent • Eligibility criteria • Medical history	• Token information (US adult subjects only) • Adverse event assessment

NOTES: Subjects must have AML as assessed by World Health Organization (WHO 2017) criteria.[1]
Refer to Registration eligibility criteria (Protocol Section 5.1, Criteria 1 - 7).
Obtain blast counts from medical history. Pre-transplant blast count should be taken from the most recent bone marrow aspirate or biopsy and hematology labs (for peripheral blood blast count) performed prior to pre-transplant conditioning. Blasts must be less than 10% in bone marrow or peripheral blood.

Part 2 Arm B - SCREENING (Day –14 to Day –1):

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Eligibility criteria	• Prior/concomitant therapy • KPS Assessment/LPPS
EXAMINATIONS	• Vital Signs • Complete (or full) physical examination • Height and Weight	• Bone marrow biopsy and/or aspirate (disease assessment)[a]
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry • Coagulation	• Serum pregnancy test • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)[c]

NOTES: All screening procedures must be performed onsite.

Refer to Screening eligibility criteria (Protocol Section 5.1, Criteria 8 - 31).

Clinical laboratory tests (hematology and chemistry) will be performed within 7 days of Cycle 1 Day 1. Neutrophils and platelet count must be measured twice at least 2 days apart (approximately 48 hours) within 1 week prior to Cycle 1 Day 1 or prior to dosing on Cycle 1 Day 1. Measurement of neutrophil and platelet counts should occur at least 7 days after G-CSF and platelet transfusion.

a. Bone marrow aspirate and biopsy may be performed within 30 days of Cycle 1 Day 1. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

c. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 2 Arm B – Cycle 1, Day 1
(Randomization [Baseline]):

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • KPS Assessment/LPPS	• EQ-5D-5L and EORTC QLQ-C30 • PedsQL • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry • Coagulation	• Urine pregnancy test • Urinalysis
CENTRAL LABORATORY TESTS	• Peripheral blood[a] (biomarker assessments)	• Optional biomarker whole blood sample (DNA/RNA)

NOTES: All Day 1 procedures must be performed onsite.
Procedures performed on Cycle 1 Day 1 will serve as baseline. All following visits should be calculated from C1D1, not last cycle.

a. Only 1 peripheral blood specimen is needed at either screening or Cycle 1 Day 1.

Part 2 Arm B – Cycle 2, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms, and concomitant therapy • KPS Assessment/LPPS	• EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry

Part 2 Arm B – Cycles 3 - 6, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • KPS Assessment/LPPS (Cycles 3, 4, and 6 only)	• EQ-5D-5L and EORTC QLQ-C30 (Cycles 3, 4, and 6 only) • PROMIS fatigue (Cycles 3, 4, and 6 only) • PedsQL (Cycles 3, 4, and 6 only) • cGvHD PRO (Cycles 3 and 4 only)
EXAMINATIONS	• Vital Signs • Targeted physical examination • Weight	• Clinical GvHD assessment (Cycles 3 and 4 only)
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry	• HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments) (Cycles 3 and 5 only)	• Optional biomarker whole blood sample (DNA/RNA) (Cycle 3 only)

a. Cycles 3 and 6: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm B – Cycle 7, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • KPS Assessment/LPPS	• EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry	• Bone marrow biopsy and/or aspirate (disease assessment)[a]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 2 Arm B – Cycle 8, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy	• Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	

Part 2 Arm B – Cycle 9, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy	• Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• HBV and/or HCV testing[a]
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	

a. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

Part 2 Arm B – Cycle 10, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • KPS Assessment/LPPS • PROMIS fatigue	• Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • EQ-5D-5L and EORTC QLQ-C30 • PedsQL
EXAMINATIONS	• Vital Signs • Weight	• Targeted physical examination
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• Chemistry

Part 2 Arm B – Cycle 13, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • KPS Assessment/LPPS	• EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • PedsQL • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Chemistry	• Bone marrow biopsy and/or aspirate (disease assessment)[a]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)

a. All visits with bone marrow biopsy and/or aspirate collection must be done onsite. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Bone marrow aspirate sample must be split for biomarker analysis. Additional details are provided in Section 3.16.

Part 2 Arm B – Cycles 16 and 22, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • EQ-5D-5L and EORTC (Cycle 22 only) • PedsQL (Cycle 22 only)	• Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • PROMIS fatigue (Cycle 22 only)
EXAMINATIONS	• Targeted physical examination • Weight	
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	

Part 2 Arm B – Cycle 19, Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • PROMIS fatigue	• EQ-5D-5L and EORTC QLQ-C30 • PedsQL • cGvHD PRO • KPS Assessment/LPPS
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Targeted physical examination • Weight
CENTRAL LABORATORY TESTS	• Peripheral blood (biomarker assessments)	

Part 2 Arm B – Cycles 11, 12, 14, 15, 17, 18, 20, 21, 23, and 24; Day 1:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Dispense/Collect dosing diary and review for adverse event symptoms and concomitant therapy • cGvHD PRO[a]	• EQ-5D-5L and EORTC QLQ-C30[b] • PedsQL[b] • PROMIS fatigue[b]
EXAMINATIONS	• Clinical GvHD Assessment[a]	• Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology	• HBV and/or HCV testing[c]

a. Cycle 24 only.

b. EQ-5D-5L and EORTC QLQ-C30, PedsQL, and PROMIS fatigue to be performed Cycles 20 to 24.

c. Cycles 12, 15, 18, 21, and 24: Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.8 End Visit Activities (Part 2 Arm B [Best Supportive Care])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm B - End Visit:

INTERVIEW & QUESTIONAIRES	• Adverse event assessment • Prior/concomitant therapy • Collect dosing diary and review for adverse event symptoms and concomitant therapy • KPS Assessment/LPPS	• PedsQL • EQ-5D-5L and EORTC QLQ-C30 • PROMIS fatigue • cGvHD PRO
EXAMINATIONS	• Vital Signs • Clinical GvHD Assessment	• Complete (or full) physical examination • Weight
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Urinalysis • Bone marrow biopsy and/or aspirate (disease assessment)[a]	• Chemistry • Coagulation • HBV and/or HCV testing[b]
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment)[a]	• Peripheral blood (biomarker assessments)[a] • Optional biomarker whole blood sample (DNA/RNA)

NOTE: The End Visit is defined as the visit in which the subject has had documented relapse or at which the subject meets other criteria for study discontinuation or at the end of Cycle 24. The End Visit must be performed onsite.

a. Bone marrow aspirate and biopsy may be performed up to 7 days prior to a scheduled visit. Subjects who do not have previously confirmed disease relapse require bone marrow biopsy and/or aspirate and/or other exams as needed for disease assessment. Bone marrow aspirate should also be split for biomarker analysis.

b. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) testing will be performed only on subjects who are diagnosed with HBV and/or HCV prior to enrollment.

2.9 Follow-Up Period - Visit Activities (Part 2 Arm B [Best Supportive Care])

This section presents a list of activities performed during each visit, organized by visit.

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

Part 2 Arm B - Scheduled Follow-Up Visits (Every 12 Weeks [± 1 week] Until Documented Relapse)

INTERVIEW & QUESTIONAIRES	• EQ-5D-5L and EORTC QLQ-C30 (only at first follow-up visit after last study treatment) • PedsQL (only at first follow-up visit after last study treatment)	• KPS Assessment/LPPS • PROMIS fatigue (only at first follow-up visit after last study treatment)
EXAMINATIONS	• Targeted physical examination	• Vital signs
LOCAL LABORATORY TESTS & ASSESSMENTS	• Hematology • Bone marrow biopsy and/or aspirate (disease assessment; only when relapse suspected)	• Coagulation (only when relapse suspected)
CENTRAL LABORATORY TESTS	• Bone marrow aspirate (biomarker assessment; only when relapse suspected)	• Peripheral blood (biomarker assessments)

NOTE: Refer to Section 3.21 for additional details.

Part 2 Arm B - Survival Follow-Up (Every 12 weeks [± 4 weeks] After the Last Study Visit or RFS Event)

INTERVIEW & QUESTIONAIRES	• Survival follow-up

NOTE: After relapse, a subject will be followed every 12 weeks (± 4 weeks) for survival. No on-site visits required. Refer to Section 3.21 for additional details.

3 STUDY PROCEDURES

Study procedures (except administration of study drug) may be performed within ± 1 day for all scheduled timepoints. Clinical laboratory tests may be performed up to 3 days prior to Day 1 of each Cycle and within ± 1 day for all other scheduled timepoints. All laboratory tests must be reviewed prior to dosing. Screening laboratory tests should be performed per required eligibility criteria timelines. Peripheral blood, bone marrow aspirate, and biopsy may be performed up to 7 days prior to a scheduled visit and within 30 days of Cycle 1 Day 1. Procedures performed on Cycle 1 Day 1 should be performed predose and will serve as baseline.

3.1 Study Information and Informed Consent

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

Rules and regulations for the consent or assent process of minors differ among countries with participating principal investigators. It remains in the responsibility of the investigators to assure compliance with *all* applicable rules. In general, a subject who is a minor should be informed within the limits of his/her understanding and with age appropriate words. When deemed necessary by the IRB/Independent Ethics Committee (IEC), the documented assent for subjects who are minors must be obtained.

Where assent is required for adolescent subjects, the investigator or his/her representative will explain the nature of the study to the subject and the subject's parent/legal guardian and answer all questions regarding this study. Adolescent subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-specific screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB/IEC requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. A copy of the informed consent form and the assent form will be given to the subject and the subject's parent/legal guardian and the original will be placed in the subject's medical record. If a subject becomes of legal age (per local regulations) during the course of the study, the consent procedure needs to be repeated.

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

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

Due to the geo-political conflict in Israel and surrounding impacted regions, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

3.2 Token Information (US Subjects Only)

For Part 2 only: For all US subjects aged ≥18 who signed the informed consent form, the site personnel will enter the following required patient identifiers into a secured web portal: first name, last name, gender, date of birth, and zip code. Insurance ID and state code will also be included in the portal as optional fields. This information will be used to generate a unique, encrypted token identifier for each patient. All the personal information (personally identifiable information and protected health information) will be removed after the token has been generated and the token identifier will be sent to a third-party vendor who may link the identifier to other sources of de-identified data, including, medical claims, pharmacy claims, hospital charge master records, behavioral and demographic information, electronic medical records, long-term care pharmacy, and laboratory data. AbbVie will not have access to the token identifiers. The aggregate study-level analytics based on the real-world data will be shared with AbbVie.

Subjects under the age of 18 will not have the patient identifiers entered into the secure web portal and a token will not be created. Once the subject turns 18 and when they consent with the adult consent form, their patient identifiers will be entered into the secure web portal for a token to be generated.

3.3 Medical History

A complete medical history including demographics (which includes full date of birth for subjects age 12 to 17), history of tobacco, alcohol, and drug use will be taken at registration. The subject's medical history will be updated before Cycle 1 Day 1. This updated medical history will serve as the baseline for clinical assessment. A detailed oncology history will also be collected including AML clinical and prognostic features such as cytogenetic and molecular findings, date of diagnosis of acute myeloid leukemia (AML), any surgical procedures, and treatments administered (including dates and type of treatment).

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

3.4 Concomitant Medication

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. Groups of drugs affected by drug-drug interactions are described in the Protocol Section 5.4. The start of a new anticancer drug with laboratory evidence of an imminent relapse is considered equivalent to morphologic relapse and should be recorded as a subsequent line of treatment and not as a concomitant medication. The start of an anticancer drug or cellular product (such as donor lymphocyte infusion [DLI]) without laboratory evidence of an imminent relapse is prohibited as outlined in Protocol Section 5.3. In contrast, standard GvHD drugs are allowed: refer to Protocol Section 5.4 for listing of medications generally recognized as treatment and prophylaxis for GvHD.

Within the limits of allowed medication, subjects should receive full supportive care during study participation including transfusion of red blood cells, or platelets, fluid and electrolyte replacement, as well as antibiotics antifungals and antivirals when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Further details are provided in the Protocol Section 5.4.

General guidelines regarding prohibited and cautionary concomitant medications and dietary restrictions are provided in Protocol Section 5.1, Section 5.3, and Section 5.4. Although cautionary, use of strong or moderate cytochrome P450 3A isoform subfamily (CYP3A) inhibitors or moderate inducers are allowed if no appropriate therapeutic alternative exists (Protocol Section 5.4). Dose reductions of venetoclax are required with concomitant administration of a strong or moderate CYP3A inhibitor (refer to the Protocol Section 5.4 and Protocol Appendix E). Alternative treatments with less CYP3A induction or inhibition should be considered.

For guidance regarding medications for neutropenia, refer to the Protocol Section 6.2.

Examples of clinical CYP3A inhibitors or inducers, or clinical substrates or inhibitors of transporters are provided on the Food and Drug Administration (FDA)'s website for Drug Development and Drug Interactions: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

The AbbVie Therapeutic Area Medical Director (TA MD) identified in Section 1 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

3.5 Height and Weight

For subjects ≥ 18 years of age, height will be measured at the Screening Visit only (with shoes off). For subjects < 18 years of age, where locally permitted, height will be measured at the Screening Visit (with shoes off), and for adolescents in Part 2 Arm A, height will be measured at Day 1 of the 6 cycles of azacitidine dosing (with shoes off). Body weight will be measured at scheduled visits as specified in Section 2. The subject will wear lightweight clothing and no shoes during weighing.

3.6 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. In addition, vital signs will be measured as clinically indicated.

Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Cycle 1 Day 1will serve as baseline.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

3.7 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2. The physical examination performed on Cycle 1 Day 1 (predose) will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the baseline visit before the first dose of study drug should be recorded in the subject's medical history. Any significant physical examination findings occurring after the first dose will be recorded as adverse events (AEs). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate electronic case report form (eCRF) page.

Targeted, symptom-directed physical examinations will be performed at the visits specified in Section 2 and may be performed at any visit as deemed necessary by the investigator. The targeted physical examination includes an assessment of heart, lung, and abdomen, as well as any body system, guided by the examiner's observations or subject complaints on new or changed conditions, symptoms, or concerns. Targeted examinations can be performed by the PI or delegated to qualified medical staff (e.g., a sub-Investigator, nurse, etc.).

Physical examinations after Cycle 3 may be performed within 3 days before or after the scheduled visit. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as AEs.

Height and weight will be measured in order to calculate body mass index (BMI). Height will be measured at screening only; body weight may be measured at additional timepoints throughout the study. The subject will wear lightweight clothing and no shoes during height measurement and weighing.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, subject visits may be conducted via phone or video conference. In these situations, weight measurements may be reported by the subject or caregiver.

3.8 GvHD Assessments

Clinical GvHD Assessments (acute and chronic)

In support of the study endpoints for GvHD and related statistical analyses, GvHD assessments have been strategically scheduled to occur at certain time points. The study-specific GvHD assessments must be performed per the table of activities (Section 2) and the assessment worksheets must be completed by the PI or sub-I at the time of visit.

Per standard of clinical care, it is expected that subjects having active GvHD will be seen and assessed for GvHD symptoms more frequently than the protocol-required assessments. It is also critical to collect the data for these assessments, especially when there is new onset of GvHD or changes in GvHD severity occur, to support the secondary endpoint of GRFS for this study.

Clinical assessment of GvHD may include physical exam, routine blood hematology and chemistry, diagnostic tests, and review of other lab values related to GvHD. The Investigator should continually monitor subjects for the presence or onset of acute and/or chronic GvHD. The study-specific clinical GvHD assessments should be performed to diagnose and score the severity of GvHD (if present).

At Baseline (Cycle 1 Day 1 [predose]), the acute GvHD (aGvHD) assessment must be performed for all subjects. If a subject displays symptoms of chronic GvHD at the C1D1 visit, the chronic GvHD (cGvHD) assessment should also be performed. Scheduled post-baseline clinical GvHD assessments will be performed per protocol and as outlined in Section 2. For subjects without prior onset of GvHD, acute or chronic, study-specific assessments should still be performed at visits where GvHD assessments are required; the acute assessment should be performed if the visit occurs < 100 days post-transplant, otherwise the cGvHD assessment should be performed. If there is a clinical impression of worsening GvHD or the appearance of new GvHD signs or symptoms, the study-specific GvHD assessments should be performed as unscheduled. If either acute or chronic GvHD is diagnosed at any point during the study, the corresponding clinical assessments should be performed at all subsequent GvHD assessments. Subjects beyond 100 days post-transplant having signs and symptoms consistent with late onset aGvHD the investigator should also perform the aGvHD assessment. Refer to the GvHD study training materials for further details on performing clinical GvHD assessments.

Entry of Adverse Events related to GvHD

If signs or symptoms of GvHD are considered "possibly related to GvHD," then the event (e.g., nausea) will be entered as an AE, but "events related to GvHD" will not be checked on the AE page. If a sign or symptom of GvHD is confirmed or probable, then the event will be entered as an AE and "event related to GvHD" must be checked on the AE page.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, subject visits may be conducted via phone or video conference.

For subjects with no signs or symptoms of GvHD: GvHD assessments do not need to be completed.

For subjects with existing GvHD or for subjects who develop new signs/symptoms of GvHD: GvHD assessments are to be done as clinically indicated and as possible given the circumstances. Treatment of

GvHD should follow local guidelines adopted to the situation of the pandemic as appropriate. Complete formal GvHD assessments for acute and chronic GvHD require a physical exam. Those are to be conducted whenever a) indicated by the study, and b) not against the best interest of the subject, and c) feasible with available resources; but they are not to be conducted if condition b or c is missing. If an assessment cannot be conducted, the next assessment should be completed as soon as possible, and further following later assessments should follow the time points described in Section 2.

Subject Rated cGvHD Assessments (cGvHD ePRO)

At each timepoint where a clinical cGvHD assessment is performed as outlined in Section 2, cGvHD related symptoms and overall patient ratings will also be assessed using Form B from Lee 2015 for chronic GvHD.[2] Subjects rate their symptoms on an 11-point scale using the electronic tablets (electronic PRO [ePRO] devices) supplied by the sponsor. The 11-point scale is measured from "0" (not present) to "10" (as bad as you can imagine) when symptoms are at their worst. Subjects rate their overall cGvHD- as 1-mild, 2-moderate, or 3-severe. Subjects rate their overall cGvHD severity on a 11-point scale as 0 (cGvHD symptoms not severe at all) through 10 (most severe cGvHD symptoms possible). Subjects rate change in cGvHD over the past month using a 7-point scale as +3 (very much better) through –3 (very much worse). All subjects, regardless of whether they have been diagnosed with cGvHD, must complete the PRO as per the activities schedule.

3.9 Clinical Laboratory Tests

Hematology and chemistry will be analyzed by certified laboratories during visits described in Section 2. Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate subject medical management. Local laboratory values will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges and certification for the laboratory that is used will be provided to the AbbVie clinical team. Required tests are listed below in Table 1.

Clinical laboratory tests may be performed up to 3 days prior to Day 1 of each Cycle and within ± 1 day for all other scheduled timepoints. All laboratory tests must be reviewed prior to dosing. Screening laboratory tests should be performed per required eligibility criteria timelines. All lab tests performed during screening should be reported. Lab tests collected in addition to those required by the protocol during screening will be recorded on the unscheduled lab eCRF. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement before the initial dose of study drug in Part 1 and Part 2 Arm A or the initial measurement on Cycle 1 Day 1 in Part 2 Arm B.

For cycles with bone marrow assessments, hematology laboratory tests should be performed ± 3 days of the bone marrow assessment.

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

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue or modify study treatment, and or provide additional supportive care treatment. in these cases, the laboratory result will be recorded as AEs

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin White blood cell (WBC) count Absolute neutrophils Absolute lymphocytes Absolute monocytes Platelet count (estimate not acceptable) Blasts[e]	Blood urea nitrogen (BUN) and/or urea[f] Creatinine Total bilirubin Direct bilirubin (if total bilirubin is not within normal range) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Glucose Albumin Bicarbonate and/or carbon dioxide[f] Creatinine clearance (Cockcroft-Gault formula) Uric Acid Lactate dehydrogenase	Microscopy (if reported) Protein Glucose
Coagulation		**Other Tests**
Prothrombin time (PT) and/or INR Activated partial thromboplastin time (aPTT)		Urine and serum pregnancy Human chorionic gonadotropin[a,b,c] Follicle-stimulating hormone[a,b,d] Hepatitis viral tests[g] • Hepatitis B virus (HBV) DNA[h] Hepatitis B core antibody (anti-HBc)[h] • Hepatitis B surface antigen (HBsAg)[h] • Hepatitis B surface antibody (anti-HBs)[h] • Hepatitis C virus (HCV) RNA[i]

DNA = deoxyribonucleic acid; INR = international normalized ration; RNA = ribonucleic acid

a. Performed only at screening.

b. Females only.

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

d. If needed to determine postmenopausal status.

e. Blasts may be reported in a peripheral blood smear.

f. As per local standards.

g. Performed only at screening and subsequently as indicated in Section 2.

h. Only subjects who have HBV carrier status prior to enrollment.

i. Only subjects who have HCV with low viral titers prior to enrollment.

Hepatitis Viral Tests

Subjects who have HBV inactive carrier status and/or subjects who have HCV with low viral titers (as defined per institution guidelines) prior to enrollment will have a serial HBV and/or HCV assessments performed, respectively, as specified in Section 2.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

If the geo-political conflict in Israel and surrounding impacted regions prevents the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. Local laboratory results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided that, at a minimum, the complete blood count (CBC) laboratory sample are obtained, and the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current laboratory assessments. The subject should be scheduled for laboratory draws as soon as feasible within 3 days from the scheduled visit.

Bone marrow aspirates can be delayed up to 1 month. The subject should be scheduled for bone marrow biopsies and/or aspirates as soon as feasible within 1 month from the scheduled visit.

3.10 Pregnancy Test (Serum/Urine)

Pregnancy testing should only be performed for adolescents and women of childbearing potential. Determination of postmenopausal status will be made during the screening period based on the subject's history (refer to definition provided in the Protocol Section 5.2).

A qualitative serum pregnancy test will be performed at screening and a urine pregnancy test will be performed at baseline (Cycle 1 Day 1 [predose]). Subsequent urine pregnancy testing will be performed on Day 1 of each Cycle (prior to dosing), at the End of Treatment Visit and 30-day Safety Follow-up Visit (when applicable) for all female subjects of childbearing potential participating in either Part 1 or Arm A of Part 2. Serum pregnancy testing may be performed at Day 1 of each cycle if required per institutional guidelines.

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

If the repeat serum pregnancy test is:

- positive, the subject is considered a screen failure;
- negative, the subject can be enrolled into the trial;
- still borderline ≥ 3 days later will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements; subjects in Canada will be considered a screen failure) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Urine pregnancy tests will be performed locally at visits indicated in Section 2. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the baseline urine pregnancy test is negative, then dosing with study drug may begin
- If the baseline or postbaseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above)

3.11 Adverse Event Assessment

Refer to Section 4.

3.12 Karnofsky Performance Status Assessment

The Karnofsky performance scale index[3] (KPS) is an assessment tool for functional status that can be used to compare effectiveness of different therapies and to assess the prognosis in individual subjects. In most serious illnesses, the lower the KPS score, the worse the likelihood of survival.

For all subjects ≥ 17 years, the KPS will be performed as outlined in Section 2. Assessments may be done ≤ 3 days before the scheduled visit.

It is recommended, when possible, that a subject's performance status will be assessed by the same person throughout the study. A specific educational level to perform the KPS is not required. KPS status will be assessed as follows:

Value (%)	Condition	Level of Functional Capacity
100	Able to carry on normal activity and to work; no special care needed	No complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease	
80	Normal activity with effort; some signs or symptoms of disease	
70	Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs	
50	Requires considerable assistance and frequent medical care	
40	Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	Disabled; requires special care and assistance
30	Severely disabled; hospital admission indicated although death not imminent	
20	Very sick; hospital admission necessary; active supportive treatment necessary	
10	Moribund; fatal processes progressing rapidly	
0	Dead	

3.13 Lansky Play-Performance Scale

The Lansky play-performance scale[4] (LPPS) is a widely used instrument to assess physical and emotional functioning of children age ≤ 16 years. It may be delivered by any care giver.

Rating	Description
100	Fully active, normal
90	Minor restrictions with strenuous physical activity
80	Active, but gets tired more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Lying around much of the day, but gets dressed; no activity play; participates in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	Stuck in bed; needs help even for quiet play
20	Often sleeping; play is entirely limited to very passive activities
10	Does not play nor get out of bed
0	Unresponsive

If a subject is 12-16 at the time of screening and turns 17 during the study, the subject will continue with the LPPS.

3.14 Patient-Reported Outcomes

Patient-reported outcome assessments for adults include PROs Measurement Information System (PROMIS) Fatigue Short Form (SF) 7a for adults, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30-item (EORTC QLQ-C30), the European Quality-of-Life-5 dimensional-5-level (EQ5D-5L) questionnaire, and for adolescents include the Pediatric Quality of Life Inventory (PedsQL) and PedsQL Cancer Module of the PedsQL. These assessments will be administered as outlined in Section 2. PRO assessments will be self-administered by subjects using the electronic tablets (electronic PRO [ePRO] devices) supplied by the sponsor and site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Completing PRO questionnaires on paper is not permitted. In Part 1 only, if ePRO devices are not available during a subject's baseline (Cycle 1 Day 1[predose]) visit; administration of the ePRO questionnaires are not required at Cycle 1 Day 1 nor any subsequent timepoints for that subject. However, ePRO questionnaires should be administered for all subjects enrolled in Part 1 if ePRO devices are on-site at the time of a subject's Cycle 1 Day 1 visit.

In pediatric subjects, the care provider may support the subject while answering the questionnaire.

PRO assessments should generally be completed prior to any other procedures or clinical assessments and prior to dosing; however, they should be administered following confirmation that the subject is able to receive study treatment at the visit.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

Due to the geo-political conflict in Israel and surrounding impacted regions, subject visits may be conducted via phone or video conference. PROs will be eligible for completion by interview at routine visits. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by video conference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. Telephone scripts may be utilized, if required by the questionnaire owner. The date and time of PRO data collection should be recorded along with who collected the information.

PROMIS Fatigue SF 7a

PROMIS is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being.[5] PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety and social function. Fatigue will be assessed using the PROMIS Fatigue SF that has been developed for use in oncology populations.[6,7] PROMIS Fatigue SF 7a is a 7-item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always. For Question 7, scores will be reversed. The recommended minimum important difference range is 3 to 5 points; the lower bound (3) is being used as the minimum important difference in this study.[8]

EORTC QLQ-C30

Health-related quality-of-life (QoL) and symptoms will be assessed with the EORTC-QLQ-C30, version 3.0.[9-11] The EORTC-QLQ-C30 is a 30-item patient-reported questionnaire composed of both multi-item and single scales including 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status/QoL scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a 4-point scale ranging from 1 to 4 (1 = Not at All, 2 = A Little, 3 = Quite a Bit, and 4 = Very Much). The EORTC-QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language-cultural groups. A change of 5 to 10 points is considered a small change and the upper bound (10) will be used to define the minimum important difference. A change of ≥ 10 to < 20 points is considered a moderate change.

EQ-5D-5L

The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations.[12,13] The EQ-5D-5L has 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a 5-point scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scores for the 5 dimensions are used to compute a single utility index score ranging from zero to 1 representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall

health. The minimum important difference for the EQ-5D-5L utility index score in cancer patients is 0.08, and the minimum important difference for EQ-5D-5L VAS is 7.[14,15]

PedsQL and PedsQL Cancer Module (For Part 2 Only)

Pediatric patients' health-related and cancer specific QoL will be assessed using the Pediatric Quality of Life Inventory (PedsQL) and PedsQL Cancer Module of the PedsQL. The PedsQL is a 23-item patient self-reported multidimensional questionnaire composed of 4 functioning domains (physical, emotional, social and school). The PedsQL Cancer Module is a 27-item patient self-reported questionnaire composed of 8 domains (pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication). For both the PedsQL and PedsQL Cancer Module, subject rate their problem with functioning and cancer specific QoL, respectively, in the past one month on a 5-point Likert scale ranging from 0 to 4 (0= Never, 1 = Almost Never, 2 = Sometimes, 3 = Often, and 4 = Almost always). Scores will be reversed and are transformed on a scale from 0 to 100. Higher scores indicate better QoL from the PedsQL and lower problems in the PedsQL Cancer Module.

The PRO assessments and corresponding administration time are presented in Table 2.

Table 2. Patient-Reported Outcome Assessments and Administration Time

Subjects	Test	Administration Time
Adult Subjects	PROMIS Fatigue SF 7a	Approximately 5 minutes
Adult Subjects	EORTC QLQ-C30	Approximately 12 minutes
Adult Subjects	EQ-5D-5L	Approximately 5 minutes
Total Administration Time: Approximately 22 minutes		
Adolescent Subjects Only	PedsQL and PedsQL Cancer Module	Approximately 5 minutes each
Total Administration Time: Approximately 10 minutes		

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality-of-Life-5 dimensional-5-level; PedsQL = Pediatric Quality of Life Inventory; PROMIS = Patient Reported Outcomes Measurement Information System; SF = short form

3.15 Pharmacokinetic Sampling

Collect blood samples for PK assays of venetoclax, azacitidine, and their possible metabolites by venipuncture at each study visit indicated in Table 3. An indwelling catheter may be used to collect blood samples if circumstances do not permit collection by venipuncture. In pediatric subjects and in cases of needle phobia, venipuncture may be ethically inappropriate. In these instances, a sufficient blood volume needs to be drawn before the PK sample is taken. That blood volume must be greater than the internal volume of the line. If there is more than one lumen, then the PK sample is to be drawn from the line has never been used to infuse azacitidine. Refer to the study specific laboratory manual for more detailed instructions.

Plasma concentrations of venetoclax will be determined by the Drug Analysis Department at AbbVie using a validated method. Plasma concentrations of azacitidine will be determined under the

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

Table 3. Schedule of Blood Collection for Venetoclax and Azacitidine Pharmacokinetic Assay

Study Drug	Cycle 1 Day 1	Cycle 1 Day 5	Cycle 2, 4, 6 Day 5
Venetoclax[a]	6 hours postdose[b]	0 hour (predose) and 6 hours postdose[b]	0 hour (predose)
Azacitidine	End-of-IV infusion or 30 minutes after the end of SC injection	End-of-IV infusion or 30 minutes after the end of SC injection	End-of-IV infusion or 30 minutes after the end of SC injection

IV = intravenous; SC = subcutaneous

a. All venetoclax samples are relative to venetoclax administration.

b. A subject on a narrow therapeutic index P-gp substrate may be exempt from the 6-hour PK sampling if clinic scheduling does not permit.

The date and time (start and end times to the nearest minute), of each azacitidine administration will be recorded on the eCRF. The date and time (to the nearest minute) of each venetoclax dose taken will be recorded on the eCRF for every scheduled venetoclax PK day and for the 2 doses prior to every scheduled venetoclax PK day. On scheduled venetoclax PK days, venetoclax will be administered at the clinic after the first PK sample is drawn.

Additional information on the collection, handling/processing, disposition, and measurement methods can be found in the most current version of Study M19-063 laboratory manual.

3.16 Bone Marrow Biopsy and Aspirate

Bone marrow biopsies and/or aspirates must be performed at the time points described in Section 2 and whenever blood counts are suggestive of relapse or when otherwise clinically indicated. Bone marrow biopsy and/or aspirate may be performed up to 7 days prior to a scheduled visit and within 30 days of Cycle 1 Day 1. Refer to the laboratory manual for details on sample processing.

Disease assessments using bone marrow aspirate samples are to be split and sent to local laboratory for disease status assessment as well as central laboratories for biomarker analysis.

Results from bone marrow biopsy and/or aspirate analysis (generated locally) should be captured on the appropriate eCRF, including those performed off-schedule to confirm or rule out disease relapse.

Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

If the geo-political conflict in Israel and surrounding impacted regions prevents the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. Local laboratory results should be reviewed by the investigator as soon as possible.

Due to the geo-political conflict in Israel and surrounding impacted regions, bone marrow aspirates can be delayed up to 1 month. The subject should be scheduled for bone marrow biopsies and/or aspirates as soon as feasible within 1 month from the scheduled visit.

3.17 Disease Status Assessment

Subject's disease assessment is based on physical examination, bone marrow results (when applicable), and hematology values.

Disease relapse is defined as either morphologic relapse or non-morphologic relapse, and is based upon the criteria for evaluation as follows:

- Morphologic Relapse: Bone marrow blasts of ≥ 5% or reappearance of blasts in the peripheral blood not attributable to any other cause (e.g., bone marrow regeneration) in at least 2 peripheral blood samples at least one week apart or development of extramedullary disease after achieving a complete remission (CR) or complete remission with incomplete count recovery (CRi).

  Note: In cases with bone marrow blast percentages of 5% - 10%, a repeat marrow should be performed 1 week later to distinguish from bone marrow regeneration.

- Non-morphologic Relapse: Increase in disease burden determined by standard methods with reappearance or acquisition of new findings with or without change in anti-leukemic treatment per investigator decision due to any of the following:
  - Cytogenetic abnormalities, or
  - Change in molecular marker, or
  - Measurable residual disease (MRD) by multiparameter flow with sensitivity to at least 10^{-3}

Laboratory values to be considered to quantify leukemia load may include, but are not limited to, the following: bone marrow blast count, peripheral blood count, FISH, cytogenetics, MRD based upon flow cytometry or reverse transcriptase quantitative polymerase chain reaction, NGS, free plasma DNA (liquid biopsy), specific gene expression such as WT1, and enzyme activities.

Only the bone marrow aspirate/biopsy and peripheral blood collection are required per protocol for the disease status assessment, however, if any additional tests were performed as part the local standard of care clinical disease assessment (e.g.,: any of the tests listed above), that data should also be considered in the clinical disease assessment for the study, the data captured on the appropriate eCRF, and the reports submitted to the Independent Review Committee (IRC). Submitting reports to the IRC is only applicable to Part 2 of the study.

Test results (e.g., pathology reports) (generated locally) used to assess disease status will be provided to an IRC for review. Outcome of the IRC review will not be shared with the investigator. Disease status (e.g., relapse) shall be determined by study investigator and decisions regarding continuation of study drug treatment (or BSC) is per investigator disease status assessment.

3.18 Biomarker Research Sampling

Biospecimens (peripheral blood and bone marrow aspirate) will be collected to support the biomarker research objectives of the study. Refer to Table 4 for the schedule of biomarker research sample collections. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug, or those believed to be related to the disease(s) being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to AML and/or in the development of new therapies and diagnostic tests.

Cells isolated from the peripheral blood/bone marrow may be analyzed to assess specific genetic mutations and/or to track the tumor cells to determine the presence of measurable residual disease (MRD). The expression levels (ribonucleic acid [RNA] or protein) of molecules (e.g., molecules involved in the apoptosis machinery or disease related) may be assessed and evaluated for correlations with efficacy. Additionally, changes in immune cell functions and phenotypes may also be evaluated. The analyses are exploratory in nature, may be conducted in non-Good Laboratory Practice (GLP) laboratories, and the results may not be included with the clinical study report.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store these samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on venetoclax/azacitidine, or drugs in these classes, or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Optional Whole Blood

Optional whole blood samples for pharmacogenetics (DNA and RNA) will be collected on Cycle 1 Day 1, Cycle 3 Day 1, and End of Treatment/End Visit from each subject who consents to optional biomarker analysis.

Table 4. Sampling Times for Biomarkers

Sample Matrix	Purpose	Screening	Cycle 1, Day 1	Cycle 3, Day 1	Cycle 5, Day 1	Cycle 7, Day 1	Cycle 9, Day 1	Cycle 13, Day 1	Cycle 19, Day 1	Cycles ≥ 25, Day 1[a]	End of Treatment/ End Visit for Relapse Confirmation	Scheduled Follow-Up Visits
Peripheral Blood Collections												
Peripheral blood[c]	Plasma markers	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood[c]	Serum markers	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood[c]	Viable PBMC	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood[c]	Flow Cytometry		X	X		X		X		X	X	X
Bone Marrow Aspirate Collections												
Bone marrow aspirate	Translational research 1	X				X		X			X	X[b]
Bone marrow aspirate	Translational research 2	X				X		X			X	X[b]
Bone marrow aspirate	MRD	X				X		X			X	X[b]
Bone marrow aspirate	Mutational profiling	X				X		X			X	X[b]

Sample Matrix	Purpose	Screening	Cycle 1, Day 1	Cycle 3, Day 1	Cycle 5, Day 1	Cycle 7, Day 1	Cycle 9, Day 1	Cycle 13, Day 1	Cycle 19, Day 1	Cycles ≥ 25, Day 1[a]	End of Treatment/ End Visit for Relapse Confirmation	Scheduled Follow-Up Visits
Optional Peripheral Blood Collections												
Peripheral blood	DNA/RNA		X	X							X	

DNA = deoxyribonucleic acid; MRD = measurable residual disease; PBMC = peripheral blood mononuclear cell; RNA = ribonucleic acid

a. After Cycle 24, bone marrow aspirate and peripheral blood biomarkers are only collected when relapse is suspected. Aspirate samples to be split for disease assessment and biomarker assessment.

b. At Scheduled Follow-Up Visits, peripheral blood collection is mandatory in Part 2. Bone marrow biopsy/aspirate samples are collected only when relapse is suspected (aspiration sample to be split for disease assessment and biomarker assessment).

c. Only 1 specimen is needed at either screening or C1D1.

3.19 Dispense Study Drug

For those subjects in Part 1 and those in Arm A of Part 2, the first dose of study drug will be administered after all other baseline (Cycle 1 Day 1) procedures are completed. At the visits specified in Section 2, the site personnel will review and retain the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

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

3.20 Dosing Diary

For all subjects, dosing diaries will be provided as specified in Section 2. Subjects will be instructed to bring their dosing diaries to the site to be reviewed as specified in Section 2.

Subjects in Arm A will be instructed to record the date and time each dose of venetoclax is taken (indicating if any doses of study drug are missed) and whether or not doses were taken within 30 minutes after the completion of a meal. All subjects will be instructed to record adverse events symptoms and concomitant medications in the dosing diary.

Subject diaries will be dispensed at Cycle 1 Day 1 and at Day 1 of every cycle thereafter. Subjects will be instructed to bring their diaries back to the site to be reviewed and collected at Day 1 of each cycle.

Diaries are to be appropriately filed with the subject's source documents for this study.

3.21 Scheduled Follow-Up Visits and Survival Period

Scheduled Follow-Up Visits

Subjects who discontinue study treatment for reasons other than relapse (morphologic or non-morphologic) will return for follow-up disease status assessment visits every 12 weeks (± 1 week) until documented relapse. Scheduled follow-up visit activities are to be primarily used for disease assessment. If disease relapse is suspected, based on other laboratory tests (e.g., hematology labs, CBC counts, etc.), a bone marrow biopsy and/or aspirate should be collected to confirm relapse. If a bone marrow aspirate was performed at the scheduled follow up visit, part of the bone marrow aspirate sample collected for local laboratory assessment should be split for biomarker analysis, if enough sample is collected. Additionally, peripheral blood samples should be collected for biomarker analysis. Further details are provided in Section 3.16, Section 3.17, and Section 3.18.

Survival Follow-Up

All subjects will be followed for overall survival. Subjects who have documented disease relapse will enter the survival follow-up phase. Survival information will be collected, including subsequent anti-cancer therapies (dates and responses), survival status and the date and cause of death (via telephone calls, clinical visits, public database searches) every 12 weeks (± 4 weeks) (or as requested by

the sponsor to support data analyses) for up to 5 years after the last subject has been enrolled (provided informed consent has not been withdrawn for collection of such information).

3.22 Subject Relapse or Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page.

The visit in which the subject has had documented relapse, or at which the subject meets other criteria for treatment discontinuation, will be considered the End of Treatment Visit (Part 1 and Part 2 Arm A)/End Visit (Part 2 Arm B). Subjects that have not had a relapse event at Cycle 24 will have a formal End of Treatment Visit/End Visit at the end of Cycle 24. All subjects will have an End of Treatment Visit/End Visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. Subjects in Part 2 Arm A who have been granted extended venetoclax treatment prior to communication with investigators regarding the change in continued treatment will be allowed to receive continued study treatment (for up to 12 additional cycles beyond the 24 cycles of treatment, up to 36 cycles total). Subjects in Part 1 who have been receiving continued study treatment may end treatment when they meet discontinuation criteria, as outlined in Protocol Section 5.5.

Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.23 Unscheduled Visits and Detection of Disease Relapse

An unscheduled visit is performed when the subject comes in for a medical visit for evaluation and assessment. During unscheduled visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3.9.

When the subject has an unscheduled visit for any reason and disease relapse is suspected, an unscheduled disease status assessment should be performed and data entered into the eCRF (Section 3.16). If a bone marrow biopsy or aspirate for disease assessment (Section 3.17) is performed, the aspirate should be split for biomarker assessments (Section 3.18).

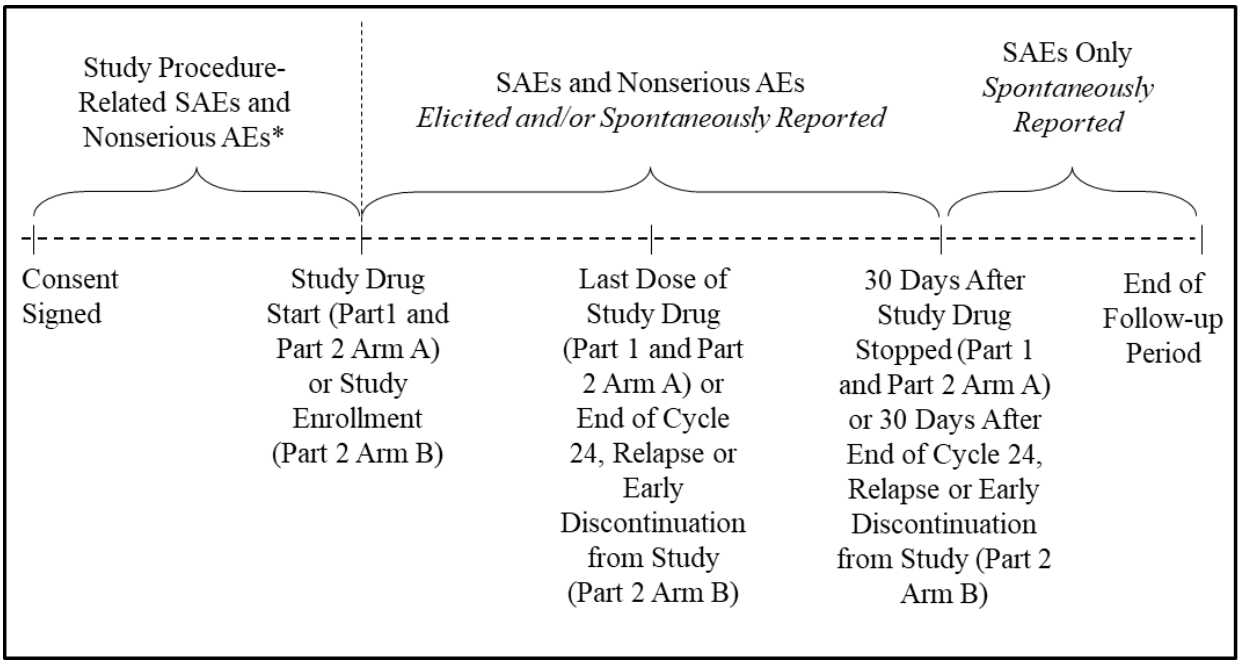
Visits for dispensing new study drug in case of temperature excursion, loss, or damage are not considered an unscheduled visit. In addition, visits to only retest a laboratory tests will not be considered an unscheduled visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs which could be related to study procedures, (e.g., infection at bone marrow biopsy site performed during screening) will be collected from the time the subject signed the study specific informed consent until study drug is started for subjects in Part 1 and Arm A of Part 2, or

from the time the subject signs the study-specific informed consent until study enrollment for subjects in Arm B of Part 2. All nonserious AEs and serious adverse events (SAEs) will be collected whether solicited or spontaneously reported by the subject from the time study drug is started or study enrollment until 30 days after 1) the last dose of study drug administration for Part 1 and Part 2 Arm A, *or* 2) the end of Cycle 24, relapse, or early discontinuation from study for Part 2 Arm B. After the 30 days following the last dose of study drug and throughout the scheduled follow-up period, only spontaneously reported SAEs will be collected (nonserious AEs will not be collected) for subjects in Part 1, Part 2 Arm A, and Part 2 Arm B.



AE = adverse event; SAE = serious adverse event

4.2 Recording Data and Analyses of Safety Findings

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

For terms with medically overlapping meaning such as "neutropenia" and "neutrophil count decreased" or "thrombocytopenia" and "decreased platelet number" or "leukopenia" and "decreased white blood cell count" a separate table will be created that combines the overlapping terms and presents the

percentage of subjects having one of them otherwise following the same rule as the primary table described above.

Details on the statistical analyses for safety will be provided in the Statistical Analysis Plan.

4.3 Reporting Adverse Events and Intercurrent Illnesses

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

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 806-2062 Backup: +1-847-935-2844

For safety concerns, contact the Oncology Safety Team at:

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

For discussions regarding drug doses and any subject safety concerns, please contact the physician listed below:

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

Contact Information:

Mobile: [redacted]
Email:

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

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with global and local requirements, including EU Clinical Trial Regulation.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

SARS-CoV-2 infections should be captured as AEs. If the event meets the criteria for a SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and nonserious events):

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

If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including EU Clinical Trial Regulation, and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period will be used to determine expectedness until the RSI that was submitted at the time of the DSUR becomes approved by all applicable regulatory authorities. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.2 China-Specific Requirements

The bone marrow aspirate for MRD analysis is the only biomarker sample required from subjects in China. The other peripheral blood, bone marrow aspirate, and optional peripheral blood collections for biomarkers are not applicable to China.

The venetoclax PK sample will be the only PK sample required from subjects in China. Azacitidine PK will not be collected in China.

The following central laboratory and disposal laboratory will be used.

Central Laboratory	Disposal Laboratory
LabCorp Pharmaceutical Research and Development (Shanghai) CO. LTD. No. 9, 338 Jia Lilue Road, Pudong New Area, Shanghai, China	Shanghai Solid Waste Disposal Co., Ltd. No.2491 Jiazhu Highway, Jiading District, Shanghai, China

5.3 Study Drugs for Which Safety Information is Reported in Japan

In Japan, safety information will be reported on the following "drugs used in the clinical study" in accordance with local guidelines.

Table 5. Study Drugs for Which Safety Information is Reported in Japan

Venetoclax
Azacitidine

5.4 Acceptable Protocol Modifications Due to Geo-Political Conflict in Israel

The geo-political conflict in Israel and surrounding impacted regions has posed significant challenges in performing protocol-specified procedures. To ensure the safety of study participants and minimize risks to the integrity of the study, alternative methods for study assessments, activities, and data collection are being implemented for impacted sites and study participants in these regions. Protocol modifications as noted throughout this Operations Manual may be followed for study sites and participants impacted by the geo-political conflict in these regions.

6 STUDY DRUG

6.1 Treatments Administered

For subjects in Part 1 and Arm A of Part 2, the study drug venetoclax, manufactured by AbbVie, will be dispensed in the form of 10-, 50-, and 100-mg film-coated tablets beginning on Cycle 1 Day 1 at the visits listed in Section 2. Each dose of venetoclax will be taken with approximately 240 mL of water, or equivalent lower volume for pediatric subjects. Subjects and legal guardian will be trained for self-administration of venetoclax orally once daily **within 30 minutes after the completion of a meal, preferably breakfast**. On days the subject is given azacitidine, venetoclax should be administered prior to the start of azacitidine injection/infusion.

If vomiting occurs after taking venetoclax, another dose should not be taken on 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. Otherwise, the missed dose should not be taken, and the subject should take the next dose at the next scheduled dosing time.

The study drug azacitidine will be administered by SC or IV, daily on Days [redacted] of each [redacted]-day cycle for [redacted] cycles (visits listed in Section 2).

Azacitidine must be prepared and administered by the route indicated in the package insert, prescribing information, local SmPC, or equivalent.

AbbVie will not supply drugs other than venetoclax and azacitidine.

Study drug information is presented in Table 6.

Table 6. Study Drug Information

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength
Venetoclax (ABT-199)	AbbVie	Oral	Film-coated tablet	10, 50, or 100 mg
Azacitidine	Celgene or generic manufacturer	Subcutaneous or intravenous	powder for suspension or solution or equivalent	100 mg (25 mg/mL or 10 mg/mL after reconstitution) or equivalent

For additional details on dispensing study drug see Section 3.19.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of each treatment period or at the final visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

For Part 2 Arm B, BSC will be determined for each subject by the investigator. AbbVie will not provide or reimburse for treatments administered as part of the BSC arm.

6.2 Packaging and Labeling

Venetoclax will be supplied in high-density polyethylene (HDPE) plastic bottles.

Azacitidine will be supplied in single-use vials and packaged in cartons to accommodate the study design.

Venetoclax will be packaged in bottles with quantities sufficient to accommodate study design. Azacitidine will be in single-use vials packaged in cartons to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit

number. This kit number is assigned to a subject via Interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drugs will only be used for the conduct of this study.

Each bottle/vial/carton will be labeled as required per country requirements. The labels must remain affixed to the bottles/vials/cartons. All blank spaces should be completed by site staff prior to dispensing to subject.

Subject dosing will be recorded on a dosing diary (as described in Section 3.20). The subject will be instructed to return all study drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

6.3 Storage and Disposition of Study Drug

Venetoclax and azacitidine must be stored at controlled room temperature (15° to 25°C/59° to 77°F).

The investigational products are for investigational use only and are to be used only within the context of this study. The investigational products supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, returned to AbbVie and/or destroyed on-site as appropriate. All return or destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures.

Sites are responsible for maintaining the investigational study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.4 Method of Assigning Subjects to Treatment Groups

This is a Phase 3, randomized, open-label, multicenter study, with initial dose finding component (Part 1). In Part 2 of the study, subjects will be randomized to 1 of 2 arms. All subjects randomized to the venetoclax/azacitidine arm (Part 2 Arm A) will receive venetoclax orally for each 28-day cycle. In addition, during the first 6 cycles subjects in Part 1 and Arm A of Part 2 will receive azacitidine SC or IV. All subjects randomized to the BSC arm (Part 2 Arm B) will receive BSC per the investigator and institutional guidelines without AML directed therapy.

At the Registration Visit, all subjects will be assigned a unique subject number via the Screening transaction in IRT. For subjects who do not meet the study entry criteria, or if a subject withdraws consent prior to enrollment, the site personnel must contact the IRT system and identify the subject as a screen failure. For subjects who rescreen, the subject number assigned by the IRT at the initial Registration Visit should be used.

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

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

6.5 Selection and Timing of Dose for Each Subject

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

All subjects should take all doses of study drugs as detailed in Section 6.1.

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Document Approval

M19063 - A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T) - Operations Manual for Protocol Version 9-0 - 08Apr2025

Version: 1.0 **Date:** 08-Apr-2025 **Company ID:** 20250408-0900f9f6896145a0-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	08-Apr-2025 19:35 UTC	Approver
	08-Apr-2025 19:19 UTC	Approver - Statistics
	08-Apr-2025 19:06 UTC	Approver - Statistics
	08-Apr-2025 19:06 UTC	Approver

Document Approval

Study M19063 - A Randomized, Open Label Phase 3 Study Evaluating Safety and Efficacy of Venetoclax in combination with Azacitidine after allogeneic Stem Cell Transplantation in Subjects with Acute Myeloid Leukemia (AML) (VIALE-T) - Protocol Version 9-0 - EU CT 2023-507222-17 - 08Apr2025

Version: 1.0 **Date:** 08-Apr-2025 **Company ID:** 20250408-0900f9f6896146fc-1.0-en

Signed by:	Date:	Meaning of Signature:
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