

Safety and Efficacy of Venetoclax and Azacitidine for Newly Diagnosed Non-Elderly Adult Patients (aged 18-59) with Acute Myeloid Leukemia

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Study Locations	Up to (3) U.S. Academic Institutions
Protocol / COMIRB#	18-0709
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Indication to be studied	Previously untreated non-elderly adult patients with acute myeloid leukemia (AML)
Study Agents	1. Venetoclax (ABT-199, Abbvie) 2. Azacitidine (Vidaza™, Celgene)

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Daniel A. Pollyea, is conducting the study and the University of Colorado is acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

In accordance with 21 CFR 25.30/25.31, this protocol qualifies for a categorical exclusion from the requirement for an environmental assessment for the manufacture and formulation for use in human clinical trials. All waste from the investigational drug(s) will be properly controlled. The amount of waste expected to enter the environment may reasonably be expected to be nontoxic. To the Sponsor-Investigator's knowledge, no extraordinary circumstances exist.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Daniel A. Pollyea, MD

Print/Type Name

Signed by:



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Signature

November 3, 2025 | 3:46:53 PM MST

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STUDY PERSONNEL

A complete and current listing of investigators, research personnel, research facilities and other study centers, as applicable, participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *Delegation of Authority Log* or a *Protocol Contact List*.

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
IIT	Investigator-Initiated Trial
LSC	Leukemia stem cell
AML	Acute myeloid leukemia
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
TLS	Tumor lysis syndrome
CR	Complete emission
CRi	Complete remission with incomplete blood count recovery
MLFS	Morphologic leukemia free state
AE	Adverse event
SAE	Serious adverse event
UGT	UDP-glucuronosyltransferases
OATP	Organic anion transporting polypeptide
BCRP	Breast cancer resistance protein
CYP	Cytochrome P
RBC	Red blood cell
AUC	Area under the curve
CLL	Chronic lymphocytic leukemia
NHL	Non-Hodgkin lymphoma
eCRF	Electronic case report form
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
LDH	Lactate dehydrogenase
PT	Prothrombin time
INR	International normalized ratio
PTT	Partial thromboplastin time

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE: Safety and Efficacy of Venetoclax and Azacitidine for Newly Diagnosed Non-Elderly Adult Patients with Acute Myeloid Leukemia
INDICATION: Previously untreated non-elderly adult patients with acute myeloid leukemia (AML) and biologically adverse risk disease features
STUDY PHASE: II
<p>BACKGROUND AND RATIONALE: Although intensive induction chemotherapy is the standard of care for non-elderly newly diagnosed AML patients, there is growing consensus that while it has been the long-standing approach to this disease, it is highly toxic and results in beneficial long-term outcomes in only a minority of patients. More active therapies are needed. Historically, when active agents have been identified in AML, they are paired with induction chemotherapy; this potentially perpetuates a flawed backbone therapy, results in overlapping toxicity with an already toxic treatment, and, because response rates with induction chemotherapy may be high, makes it difficult to assess in the non-randomized setting whether added benefit is occurring. The regimen of azacitidine with venetoclax has resulted in very high response rates in intermediate to poor risk elderly, previously untreated AML patients who are deemed unfit for intensive chemotherapy. In addition, the responses are deep and durable, and compared to the toxicity profile of induction chemotherapy, azacitidine and venetoclax is very well tolerated. Therefore, we propose a pilot study of the azacitidine and venetoclax regimen for non-elderly, newly diagnosed AML patients with intermediate or adverse risk biological disease features per the ELN 2017, in the hopes that it will be equivalent with respect to responses compared to intensive induction chemotherapy, and safer and better tolerated.</p>
<p>STUDY OBJECTIVES:</p> <p>Primary: To determine whether venetoclax with azacitidine has an acceptable response rate in newly diagnosed non-elderly adult (aged 18-59) AML patients</p> <p>Secondary:</p> <ul style="list-style-type: none"> • To determine the safety and toxicity profile of venetoclax and azacitidine in newly diagnosed non-elderly adult AML patients. • To determine the remission duration of venetoclax with azacitidine in newly diagnosed non-elderly adult AML patients. • To determine the incidence of minimal residual disease negativity in newly diagnosed non-elderly adult AML patients who receive venetoclax and azacitidine.

- To determine the one-year event free survival (EFS) and overall survival (OS) of newly diagnosed non-elderly adult AML patients who receive venetoclax and azacitidine.

STUDY DESIGN:

This is an open label, Phase 2 study for adult patients aged 18-59, previously untreated with AML using azacitidine with venetoclax.

After consent and screening, patients will be admitted to the hospital for induction, which begins with dose escalation of venetoclax. After dose escalation has completed patients may discharge and continue management in the outpatient setting if appropriate.

On day 1 of cycle 1, azacitidine 75 mg/m² SC or IV will be given, and will continue for 7 days (a 5 days on 2 days off 2 days on [5-2-2] schedule is also acceptable). Starting on day 1 of cycle 1, venetoclax will be escalated to a target dose of 600 mg. This will involve administration of 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and 600 mg on day 4. Subsequently, patients will take venetoclax 600 mg daily for the remainder of the 28-day cycle.

On cycle 1 day 14, a bone marrow biopsy will be performed. On day 28 of cycle 1 a bone marrow biopsy will be performed to determine response status. Patients who do not achieve a CR, CRi or MLFS after first induction may receive a second induction, in which no intra-patient venetoclax dose escalation or day 14 bone marrow biopsy is required. Patients who do not achieve a CR, CRi or MLFS after the second induction will come off study. Patients who do achieve a CR, CRi or MLFS after the first or second induction may continue with consolidation, maintenance, or come off study to pursue an allogeneic stem cell transplantation.

Consolidation will consist of up to 3 additional cycles of azacitidine 75 mg/m² SC or IV on days 1-7 (or 5-2-2), with venetoclax 600 mg PO daily on days 1-28. Bone marrow biopsies will be performed after each cycle of consolidation.

After induction or consolidation, patients may come off study to pursue an allogeneic stem cell transplantation, or receive maintenance therapy. Patients who achieve a CR/CRi/MLFS with minimal residual disease (MRD) negativity after induction may proceed directly to maintenance. Patients who achieve a CR/CRi/MLFS with MRD negativity after cycles 1, 2 or 3 of consolidation may proceed to maintenance. Patients who achieve a CR/CRi/MLFS with MRD positivity after cycle 3 of consolidation may also proceed to maintenance. Discontinuation of the study to pursue an allogeneic stem cell transplantation will also be considered in all of these scenarios.

Maintenance for patients who achieve MRD negativity after induction/consolidation will consist of azacitidine 75 mg/m² SC or IV on days 1-5 with venetoclax 400 mg PO daily on days 1-28 of each 28-day cycle. Maintenance for patients who have MRD after induction and 3 cycles of consolidation will consist of azacitidine 75

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mg/m² SC or IV on days 1-7 (or 5-2-2) with venetoclax 600 mg PO daily on days 1-28, for a maximum of 12 cycles and an option to cross over to the MRD negative maintenance plan if MRD negativity is achieved.

Bone marrow biopsies will occur for patients on maintenance therapy after every third cycle, until 1 year after achieving a remission. Subsequent bone marrow biopsies will be performed at the discretion of the investigator.

STUDY ENDPOINTS

Primary: Response rate excluding partial response using the European LeukemiaNet definition (CR_{MRD}+CR+CRi+MLFS) showing non-inferiority of venetoclax with azacitidine when compared with historical controls who received induction chemotherapy

Secondary:

- Incidence of and time to achieve MRD negative responses (CR+CRi+MLFS)
- Remission duration
- One-year overall survival, stratified by response type and achievement of MRD negative state
- One-year event-free survival, stratified by response type and achievement of MRD negative state
- Incidence and severity of adverse events

STUDY DURATION: up to 10 years

TOTAL SAMPLE SIZE: 36

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2 SCHEDULE OF STUDY ASSESSMENTS¹

Procedures	Screen ²	Induction Cycle 1				Induction Cycle 2		Consolidation (max of 3 cycles)		Maintenance Cycles		End of Treatment	Safety Follow Up ³
		Day 1	Days 2 to 7	Day 14	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28		
Allowable Window	28 days			±2 days	±3 days	±7 days	±3 days	±7 days	±3 days	±7 days	±3 days	±14 days	±10 days
Informed Consent	X												
History	X												X
Physical Exam	X	X		X	X	X		X		X		X	X
Vital Signs ⁴	X	X	X	X	X	X		X		X		X	X
ECOG PS	X	X			X	X		X		X		X	
Cytogenetics	X				X		X ⁵		X ⁵		X ⁵	X	
MRD	X				X		X ⁵		X ⁵		X ⁵	X	
AE & Con Meds	X	X	X	X	X	X		X		X		X	X ⁶
12-lead EKG ⁷	X												
TLS Labs ⁸		X	X										
Hematology/Chemistry/Coagulation	X ⁹	X	X		X	X		X		X		X	
Pregnancy Testing ¹⁰	X	X				X		X		X			
Azacitidine		X	X			X ¹¹		X ¹²		X ¹²			
Venetoclax ¹³		X	X	X	X	X		X		X			
BM aspirate and biopsy	X			X	X		X ⁵		X ⁵		X ⁵	X	
Calendar & Diary- Dispense/Collect		X			X	X		X		X		X	

¹ For detailed description of all elements please see section 5.10

² Screening assessments must occur within 28 days of cycle 1 day 1

³ Initial safety visit required for all subjects except those whose last visit was greater than 30 days post study drug. After initial safety visit, subjects will be followed at least annually for 5 years with visits/email/phone calls for survival status and disease progression until death, study discontinuation or until the subject withdraws consent

⁴ Includes temp, blood pressure, pulse, respiratory rate and, if needed, oxygen saturation. Weight collected 1x/cycle. Height at screening only. All methods of measurement will be per institutional practice

⁵ Bone marrow aspirate/biopsy will occur after each cycle of consolidation and after every third cycle of maintenance until 1 year after remission

⁶ Only adverse events need to be followed through safety follow up, see section 6.7. ConMed collection to end at EOT

⁷ A single 12-lead resting EKG will be obtained at screening, and as needed

⁸ Within 4 hours prior to the venetoclax dose and again 6 and 12 hours after the dose (+/- 2 hours). These labs include: Calcium, Phosphorus, Potassium, Uric Acid, Creatinine

⁹ Coagulation testing only occurs at screening

¹⁰ Pregnancy (serum or urine) required prior to Day 1 dosing of each cycle. If screening pregnancy test is done within 3 days of day 1 of each cycle it does not need to be repeated

¹¹ Administer azacitidine on days 1-7

¹² Administer azacitidine on days 1-5 (MRD negative). Or days 1-7 (MRD positive), a 5-2-2 schedule is also acceptable.

¹³ Venetoclax to be administered on days 1-28 of every cycle

3 INTRODUCTION

3.1 Background and Rationale

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with over 21,000 cases expected this year in the United States. Outcomes are very poor, with the majority of patients dying from disease or disease related complications¹.

Leukemia stem cells (LSCs) are the relatively small population of cells with proliferative and self-renewal capacity, can be immunophenotypically and functionally identified, are quantifiably associated with worse clinical outcomes, and persist in remission resulting in relapse²⁻⁵. A more sophisticated understanding of the unique biology of this population, and the subtle differences between them and normal hematopoietic stem cells from which they originate, has presented the opportunity to target them in the clinical setting. We have predicted that a true LSC-directed therapy would be more successful in the untreated setting compared with relapse, would be effective irrespective of traditional biological adverse disease features, and would result in deep and durable remissions, with the potential to cure AML^{6,7}. To date, we are not aware of an intentionally designed LSC directed therapy that has resulted in clinical activity or satisfied the above criteria.

Azacitidine (Vidaza™, Celgene) is a pyrimidine nucleoside analog of cytidine. It incorporates into DNA and RNA and binds to DNA methyltransferase enzymes, preventing the methylation of cytosine residues at CpG dinucleotides and resultant transcription of genes with heavily methylated promoter regions.⁸ In patients with myelodysplastic syndrome (MDS) and AML, treatment with azacitidine decreases the methylation of tumor suppressor gene promoters, which correlates with clinical outcomes.⁹ Furthermore, in AML patients who attain a clinical remission, methylation levels correlate with relapse risk and are inversely related to relapse-free survival.¹⁰ In older patients with AML who were thought to be poor risk candidates for induction chemotherapy, the use of single-agent azacitidine had an overall response rate of 60%, a CR rate of 20%, and in patients who responded, a median survival of over 15 months.¹¹

The B-cell lymphoma 2 (BCL-2) protein is an anti-apoptotic member of the BCL-2 family of proteins¹². BCL-2 is overexpressed in LSCs, and pre-clinical testing reveals its targeting results in the preferential elimination of LSCs¹³⁻¹⁵. Venetoclax (ABT-199, Abbvie) is an orally bioavailable BH3 mimetic protein that selectively inhibits BCL2¹⁶; pre-clinical testing showed activity in AML, as did a single-agent clinical trial in patients with relapsed or refractory disease^{17,18}. This prompted a dose escalation study of venetoclax with a hypomethylator backbone of azacitidine or decitabine for newly diagnosed older AML patients (NCT02203773), which showed it to be a highly active and well tolerated therapy with an overall response rate of 78%, median duration of response of 11 months and overall survival of 15.2 months¹⁹.

However, there is nothing about this therapeutic strategy that would suggest its impact would be restricted to AML in elderly patients; specifically, no data suggests that BCL-2 has higher expression levels in the bulk tumor or LSC compartment of older vs. younger patients. Furthermore, venetoclax with azacitidine has shown activity in biologically-

defined intermediate and poor risk subgroups that constitute the majority of patients 18-60 years old.

The traditional approach of intensive induction chemotherapy using an anthracycline for three days with a seven-day infusion of cytarabine (7+3) has been the standard of care in the United States for younger patients with AML for decades²⁰. Patients with core-binding factor (CBF) AML have a reasonable chance that this constitutes curative therapy (~40%)²¹. However, the vast majority of AML patients (>80%) do not have CBF; their outcomes with induction chemotherapy are significantly worse, and most die from relapsed disease²². The second most common cause of death in this population is treatment-related mortality (TRM)²³. Although it is lower in younger patients than older patients who receive induction, death or severe toxicity is a major limitation of induction chemotherapy.

There is a strong case to be made for why intensive induction chemotherapy should be limited. For patients <60 years, the complete remission (CR) rate is around 60% but the treatment-related mortality (TRM) rate may be as high as 13%; 5-year overall survival (OS) is only around 30%²⁴. Not surprisingly given that it has not substantially changed in over 40 years²⁵, induction chemotherapy is not improving with time; no meaningful improvements in outcomes have occurred for decades that are not attributable to advancements in supportive care or transplantation²⁶.

However, the problems with induction chemotherapy are more pernicious than simply its lack of efficacy. Induction chemotherapy does not eliminate pre-leukemic hematopoietic stem cells, and clonal evolution of this population after exposure to chemotherapy during remission is the likely cause of relapse^{5,27}. Induction chemotherapy provokes clonal hematopoiesis from non-leukemic progenitor cells, the consequences of which are unknown and possibly deleterious²⁸. Gene expression profiling studies performed on AML patients pre and post treatment with cytarabine revealed the activation of resistance pathways that occurred as the direct result of chemotherapy²⁹. Most concerning is the recent discovery of the increased number and heterogeneity of leukemia stem cells after induction fails and patients relapse³⁰. In light of these reports, we now understand that induction chemotherapy may make AML worse, and there is a growing ethical question not regarding whether we can withhold it from younger patients but rather whether we can continue to administer it. Finding a safer, more effective therapy to replace induction chemotherapy for non-elderly adult AML patients is a priority.

Therefore, we propose to extend the extremely successful elderly AML study of venetoclax with azacitidine to younger adult newly diagnosed patients. We propose this in the setting of a non-inferiority study using remission rate as an endpoint and a well-accepted historical control, in which induction was employed in a younger population, as a comparator. Frequent statistical analyses to ensure the study is not falling behind the expected historical endpoint are included, and stringent rules that will ensure the study is abandoned early if there is a suggestion that it is not equivalently efficacious compared to induction. There is precedence for this approach in acute promyelocytic leukemia, in which a non-inferiority study design for a non-chemotherapy approach was found to be superior to chemotherapy^{31,32}.

Hypothesis: Venetoclax with azacitidine will be as efficacious as and better tolerated than intensive induction chemotherapy for untreated non-elderly adult AML patients when compared to historical controls.

3.2 Venetoclax

3.2.1 Preclinical Pharmacokinetic Profile

In mouse, rat, monkey, and dogs, the venetoclax pharmacokinetic profile was characterized by low plasma clearance ($CL_p = 0.02$ to 0.27 L/hr•kg) and low volumes of distribution ($V_{ss} = 0.3$ to 1.1 L/kg). Half-lives ranged from 2.2 hours in monkeys to 12.0 hours in dogs. Formulation-dependent oral bioavailability was noted in all species. Studies in both rat and dog have defined the behavior of the amorphous solid dispersion for both toxicology and first-in-human evaluation. Plasma concentrations obtained from fed dogs were 30% to 50% higher than those obtained from fasted animals.

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

3.2.2 Preclinical Toxicology

Toxicology studies completed with venetoclax are general toxicology studies with periods of once-daily oral dosing ranging from 2 weeks to 6 months in mice, from 2 weeks to 13 weeks in rats, and from 1 week to 9 months in dogs. In vitro and in vivo genetic toxicology and dose range-finding studies in mice and rats to support dose selection for possible carcinogenicity assessments, embryo-fetal development in mice and rabbits, fertility and early embryonic development in male and female mice, dose range-finding in juvenile mice, and phototoxicity in mice studies have been performed. Other studies were in vitro genetic toxicity testing of the M27 major human metabolite and in vitro and in vivo impurity qualification. Reversibility of venetoclax-related changes was assessed in the 4-week study in mice and in the 2- and 4-week studies in dogs. The primary toxicities associated with repeat-dose administration of venetoclax are effects on the hematologic system (decreased lymphocytes and red blood cell mass in mice, rats and dogs), the male reproductive system (testicular germ cell depletion in dogs), and embryo-fetal toxicity in mice. Other noteworthy findings are epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs. Maximum venetoclax plasma exposures (mean AUC_{0-24 h}, combined

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male and female values) achieved in the 4-week studies were 92 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (at 600 mg/kg/day) in mice and 572 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (at 150 mg/kg/day) in dogs. In the 6-month mouse and 9-month dog chronic toxicity studies, AUCs reached 34.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ (at 300 mg/kg/day) in mice and 85.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ (at 20 mg/kg/day) in dogs. In rats, exposures were higher in females than in males; at dosages of 150 and 400 mg/kg/day in the 13-week maximum tolerated dose study, exposures ranged up to 83.1 to 127.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ in females and up to 26.4 to 44.3 $\mu\text{g}\cdot\text{h}/\text{mL}$ in males. Venetoclax produced generally dose-related decreases in lymphocytes in the peripheral blood (up to -75% in mice, -64% in rats, and -81% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacology of venetoclax (a selective Bcl-2 inhibitor)³³. Following a 4-week recovery period, lymphocyte counts remained minimally decreased by 21% to 26% in mice, indicating that reversibility was occurring but was not complete. In dogs, the recovery of decreases in peripheral blood total lymphocytes and lymphocyte subsets (CD4+ T-cells and CD8+ T-cells and [CD21+] mature B cells) was prolonged, requiring up to 18 weeks after a single dose or after completion of 2 weeks of dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> 90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs, but as with peripheral blood lymphocytes, required up to 18 weeks in dogs. Decreases in lymphocyte counts can be readily monitored in clinical trial subjects.

In the 4-week mouse and dog studies, dose-related reversible decreases in red blood cell (RBC) mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached 21% in mice at 600 mg/kg/day and 23% in dogs at 150 mg/kg/day, and were considered to be adverse based on a criterion of 20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached 30% to 49% at ≥ 150 mg/kg/day in female rats. Hematologic parameters are readily monitored in clinical trial subjects.

No effects of venetoclax have been identified on the female reproductive tract of mice, rats, and dogs. However, in dogs venetoclax produced adverse, non-dose-related microscopic findings of testicular germ cell loss at all dosages tested (2 to 150 mg/kg/day). In the 4-week study, testicular spermatogonia were decreased at the end of the dosing period, and their loss was consistent with the observed depletion of all germ cell types at the end of the 4-week recovery period. There were no testicular effects in mice or rats; in these animal species, exposures overlapped those in dogs. Venetoclax-induced testicular changes may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.³⁴⁻³⁶ There are currently no data assessing the effect of venetoclax on human spermatogenesis, and the actual risk to humans for testicular findings similar to those observed in dogs remains unknown. In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies. In the mouse embryo fetal development study, increased post-implantation loss and decreased fetal body weights occurred at the highest dosage administered (150 mg/kg/day); the NOAEL was defined at the mid

dosage of 50 mg/kg/day. No fetal toxicity was observed in rabbits, but exposures were approximately one-tenth those in mice. Venetoclax was not teratogenic in mice or rabbits, and there were no other effects on development or fertility.

Additional effects of venetoclax were white hair coat discoloration in dogs at ≥ 6 mg/kg/day and single-cell necrosis in multiple epithelial tissues at ≥ 2 mg/kg/day in dogs. Hair coat discoloration (increased amount of hair that was white) was observed in the dog after approximately 3 months of dosing in the 9-month chronic toxicity study. This change was consistent with loss of pigment in the hair and correlated histopathologically with decreased pigment in hair follicle bulbs. A change to gray coat color was also seen in NZBWF1 mice treated daily with 33 or 100 mg/kg venetoclax, but not at lower dosages. Evidence from Bcl-2 knockout mouse (Bcl-2 $-/-$) studies indicates that hair hypopigmentation occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.³⁷ In the dog, pigmentation of the skin and in the eye (particularly in the pigmented iris and fundus) appeared unaffected; this was confirmed by the absence of associated histopathologic findings in skin (other than in hair follicles) and in the eye. The risk of hair graying in clinical trial subjects treated with venetoclax is unknown.

Single cell necrosis occurred in the gallbladder, exocrine pancreas, epididymides, prostate, and stomach of dogs. These changes were minimal except for non-dose dependent minimal to mild single cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9-month study. After 4 weeks of dosing and a 4-week recovery period, reversibility was observed in the gallbladder and exocrine pancreas, but minimal single cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single-cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed microscopically. Single cell necrosis was not found in the mouse or rat; maximum achieved exposures were comparable to or greater than the lowest exposures at which this finding occurred in dogs.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity (tested in vivo in hairless mice). Venetoclax administration in dogs in the 4-week study was associated with dose related, transient post-dose emesis, increased salivation, and fecal alterations (unformed or watery feces) at dosages of ≥ 5 mg/kg/day. These clinical signs were present throughout the dosing phase, but were not dose-limiting and were not observed in the recovery phase. In the 9-month dog study, non-adverse decreases in mean body weight and body weight gain, associated with decreases in food consumption, were present at ≥ 2 mg/kg/day. Dogs at the high dosage of 150 mg/kg/day in the 4-week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in three dogs the swelling reaction was observed after the first dose. The clinical signs were limited to the 150 mg/kg/dosage, were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis.

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M27 is a major human metabolite observed at steady state in chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL) patient plasma samples. It is present at significantly lower exposure levels (0.04- and 0.06-fold, respectively) in the mouse and dog, and therefore is a disproportionate metabolite. M27 was negative in Ames and chromosome aberration in vitro assays, has at least 58 fold less in vitro potency than venetoclax, and demonstrates low off-target toxicity potential based on in vitro secondary pharmacology assays. Taken together, these nonclinical results suggest that M27 does not represent a significant safety risk, and does not change the benefit/risk ratio for clinical trial subjects with advanced hematologic malignancies treated with venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the central nervous system /neurobehavioral or respiratory studies in mice at oral doses up to and including the highest oral dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 µg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (C_{max} = 16 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (6% to 13%) and cardiac output (11% to 19%) at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average C_{max} = 6.09 µg/mL at the 1200 mg/day dose).

On the basis of nonclinical toxicology and safety pharmacology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia, signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Although no effects of venetoclax on female reproductive tissues have been observed in general repeat-dose toxicology studies, embryo-fetal toxicity studies in animals have identified a fetal toxicity risk. Thrombocytopenia has not been a significant finding in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-XL sparing) inhibitor. Consequently, thrombocytopenia is not expected to be dose limiting.

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

3.2.3 Clinical Data

As of 28 November 2015, based on the data available in the AbbVie and Genentech/Roche clinical databases, a total of 1509 subjects have been exposed to at least 1 dose of venetoclax in the oncology development program. Of these, data are available for 1498 subjects; 102 had AML, 935 subjects had CLL/SLL, 346 subjects had NHL, and 115 subjects had multiple myeloma. An additional 66 subjects were healthy volunteers who participated in the DDI studies. Based on the available data, a total of 564 oncology subjects received the drug as monotherapy and 933 subjects received the drug in combination with other therapies.

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

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

In this completed single agent venetoclax trial (Study M14-212) in subjects with relapsed/refractory (R/R) AML 32 subjects have been dosed. Exposure, safety, and efficacy data are available for this study³⁸. The most common adverse events observed in $\geq 10\%$ of the subjects in study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia).

As of 11 March 2015, efficacy data for Study M14-212 are available for 32 subjects, the majority (30, 94%) of the subjects had R/R AML and a few were (2, 6%) deemed unfit for intensive therapy. The ORR was 19% (6 of 32 subjects), with complete remission (CR) in 2 (6%) and complete remission with incomplete marrow recovery (CRi) in 4 (13%) subjects. Anti-leukemic activity was observed in and additional 6 (19%) subjects, with 2 (6%) subjects each showing $\geq 50\%$ reduction with 2 cell line recovery with transfusion independence, 1 cell line recovery, and no hematologic recovery, respectively. Treatment failure due to progressive disease or less than a partial remission (PR) was observed in 20 (63%) subjects.

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

As of March 9, 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m² intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m² intravenously or subcutaneously on Days 1 – 7 once every

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28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.

The most common adverse events for all subjects in Study M14-358 were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutrophil count decreased (31.1%), platelet count decreased, cough, and fatigue (28.9% each), edema peripheral and hypokalemia (26.7% each). Events grade 3 and above were reported for the majority (91.1%) of subjects; the most common event was febrile neutropenia (40.0%). Serious adverse events were reported for 27 (60.0%) subjects, including febrile neutropenia (11 subjects), malignant neoplasm progression (3 subjects) atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis, bone pain (2 subjects each). All other events occurred in 1 subject each. The combination of venetoclax with decitabine and azacitidine demonstrates a tolerable safety profile.

As of March 9, 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

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

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

3.3 Azacitidine

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, DNA synthesis and metabolism, and causes cytotoxicity. Since the early 1970s, azacitidine has been investigated in the US for the treatment of acute leukemia, with clinical trials focused primarily on patients with refractory disease. These investigations indicated azacitidine has activity in the treatment of AML.

The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation is attributed to its activity as a hypomethylating agent. Therefore, an inhibitor of DNA methylation such as azacitidine would be a rational approach to revert epigenetic changes in the malignant clone and re-establish the antiproliferative signals extinguished by hypermethylation.

3.3.1 Preclinical Pharmacokinetic Profile

Early PK studies used ^{14}C -radiolabeled azacitidine to evaluate drug disposition. Based on total radioactivity in plasma, azacitidine was absorbed when given subcutaneously (SC), with maximum concentrations found 0.5 to 2 hours after dosing. Azacitidine and/or its metabolites were then cleared by the kidneys. The plasma $t^{1/2}$ (3.4 to 6.2 hours) and amount of radioactivity recovered in urine (50-98% of administered dose) were similar after IV and SC dosing.

Drug-drug interaction studies of azacitidine have not been conducted in clinical trials. Two in vitro metabolism studies and three in vitro drug interaction studies have been completed. Some evidence of hepatic metabolism was observed when azacitidine was incubated in human liver fractions. The metabolism of azacitidine was compared using [^{14}C]5-azacitidine and hepatic S9 fractions from human and mouse origin; the formation of deaminated metabolites (formylamidino-ribofuranosylbiuret and ribofuranosylbiure) was independent of nicotinamide adenine dinucleotide phosphate (NADPH), implying that metabolism was catalyzed by cytosolic enzymes. Azacitidine was not an inducer of the isozymes 1A2, 2C19, or 3A4/5. Azacitidine showed no notable inhibition of P450 isoenzymes (Cytochrome P450 [CYP450] 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) in the concentration range of 0.1 to 100 μM . Therefore, clinically relevant inhibitory or inductive effects on the metabolism of CYP450 substrates are unlikely. Azacitidine is neither a substrate nor an inhibitor of P-glycoprotein (P-gp) and therefore unlikely to produce any clinically relevant interactions as a P-gp substrate or an inhibitor. The effect of inducers or inhibitors on the metabolism of azacitidine has not been studied.

3.3.2 Clinical Data

The safety profile of azacitidine has been well characterized and is based on an extensive amount of patient exposure across a wide range of doses and indications. Adverse events (AEs) reported most frequently were hematologic events of thrombocytopenia, neutropenia, anemia, and leukopenia, and were typically assessed as grade 3 or 4 events. Despite the increased percentages of these hematologic events, azacitidine did not appear to increase the risk of events of infection or bleeding when compared with patients treated with best supportive care only. Non-hematological AEs that were reported most often were events related to either the administration of the drug (injection site reactions, nausea, vomiting) or consequences of the antiemetic treatment (constipation). These events were generally graded 1 or 2 in intensity. The reporting frequencies for the common hematologic and non-hematological events were generally highest during cycles 1 and 2, after which time the frequencies decreased over subsequent treatment cycles. Within the cycle, the hematologic events tended to occur across the first 3 to 4 weeks of the cycle, whereas the events associated with the administration of azacitidine tended to occur in the first week. These findings suggested a lack of cumulative toxicity and that adverse effects of azacitidine attenuate over time.

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A recent randomized phase 3 study of older newly diagnosed patients with AML who received azacitidine versus conventional care regimens showed a CR+CRi rate of 27.8% and a median OS of 10.4 months.³⁹

3.4 Differences Statement

This study will investigate the use of the highly active azacitidine with venetoclax clinical trial in non-elderly, untreated adult AML patients. There are ongoing clinical trials of the combination of hypomethylators and low dose cytarabine with venetoclax for elderly unfit AML patients, as well as a combination with cobimetinib or idasunutin for patients with relapsed or refractory AML. In addition, studies with venetoclax are ongoing for other indications, including multiple myeloma, MDS and CLL/NHL.

4 STUDY OBJECTIVES

4.1 Primary Objective

To determine whether venetoclax with azacitidine has an acceptable response rate in newly diagnosed non-elderly adult (aged 18-59) AML patients.

4.2 Secondary Objectives

- To determine the safety and toxicity profile of venetoclax and azacitidine in newly diagnosed non-elderly adult AML patients.
- To determine the remission duration of venetoclax with azacitidine in newly diagnosed non-elderly adult AML patients.
- To determine the incidence of minimal residual disease negativity in newly diagnosed non-elderly adult AML patients who receive venetoclax and azacitidine.
- To determine the one-year event free survival (EFS) and overall survival (OS) of newly diagnosed non-elderly adult AML patients who receive venetoclax and azacitidine.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

The traditional approach of intensive induction chemotherapy using an anthracycline for three days with a seven-day infusion of cytarabine (7+3) has been the standard of care in the United States for younger patients with AML for decades²⁰. However, with this strategy, most patients die from relapsed disease²². The second most common cause of death in this population is treatment-related mortality (TRM)²³. There is a strong case to be made for why intensive induction chemotherapy should be limited based on suboptimal efficacy, but the limitations of this treatment are more pernicious. There is now

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data to suggest that with the exception of the minority of cases in which induction chemotherapy is curative, this strategy can make the disease worse^{5,27-30}. Therefore, finding a safer, more effective therapy to replace induction chemotherapy for non-elderly adult AML patients is a priority.

This study is an open label, phase II multi-institutional pilot study for previously untreated non-elderly adult AML patients (aged 18-59) with intermediate or adverse risk biological disease features (per the ELN 2017) to receive azacitidine and venetoclax instead of 7+3, due to concerns about futility and harm from this historical regimen and optimism about the activity of azacitidine with venetoclax that has been seen in older patients.

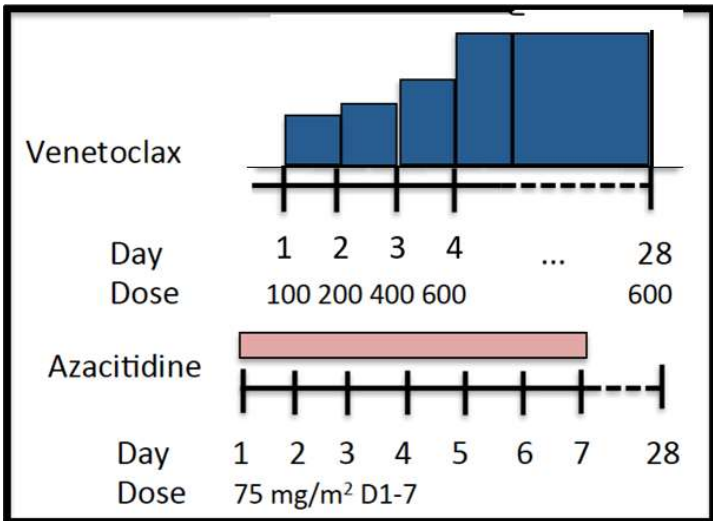
5.1.1 Study Schema

After consent and screening, patients will be admitted to the hospital for Cycle 1 of induction, which involves venetoclax dose escalation. After dose escalation has completed patients may discharge and continue management in the outpatient setting if appropriate.

On day 1 of cycle 1, azacitidine 75 mg/m² SC or IV will be given and will continue for 7 days (a 5 days on, 2 days off, 2 days on [5-2-2] schedule is also acceptable). Antiemetic premedication will be administered per institutional protocol. Depending on the cycle or the clinical situation, azacitidine may be administered in the inpatient or outpatient setting. The route of administration will be at the discretion of the investigators. Administration will be performed in accordance with institutional protocols.

Starting on day 1 of cycle 1, venetoclax will be initiated. It will be dose escalated to a target dose of 600 mg in the following manner: 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and 600 mg on day 4 (Figure 1). Subsequently, patients will take venetoclax 600 mg daily and may be discharged from the hospital 24 hours after they receive the 600 mg dose if medically appropriate. See Figure 1.

Figure 1: Dose escalation of venetoclax (mg) during induction

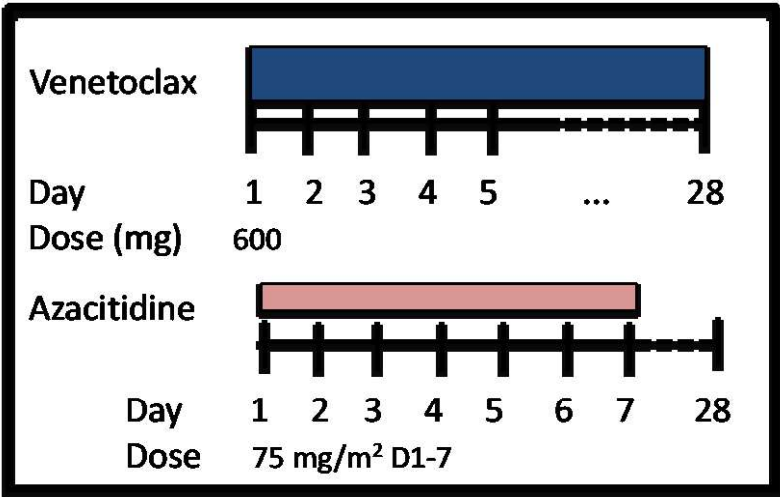


On cycle 1 day 14, a bone marrow biopsy will be performed (with a 2-day window). On day 28 of cycle 1 (with a 3-day window), a bone marrow biopsy will be performed to determine response status (see Section 5.1.2). This will include an assessment of MRD by multi-dimensional flow cytometry^{40,41} allowing for quantification of disease to at least 0.1%. Undetectable disease by multi-dimensional flow cytometry will be defined as MRD negative. If results of the day 28 bone marrow biopsy are equivocal, follow up bone marrow biopsies may be obtained, at weekly intervals or less if deemed medically necessary.

Patients who do not achieve a CR, CRi or MLFS after Cycle 1 of induction will be eligible for a second cycle of induction with the exception that intra-patient dose escalation and C2D14 biopsy will not be required. Patients who do not achieve a CR, CRi or MLFS after the second cycle of induction will come off treatment. Patients who do achieve a CR, CRi or MLFS after the first or second induction may continue with consolidation and/or maintenance.

Consolidation will consist of up to 3 additional cycles of azacitidine 75 mg/m² SC or IV on days 1-7 (or 5-2-2), with venetoclax 600 mg PO daily on days 1-28. Bone marrow biopsies will be performed after each cycle of consolidation. See Figure 2.

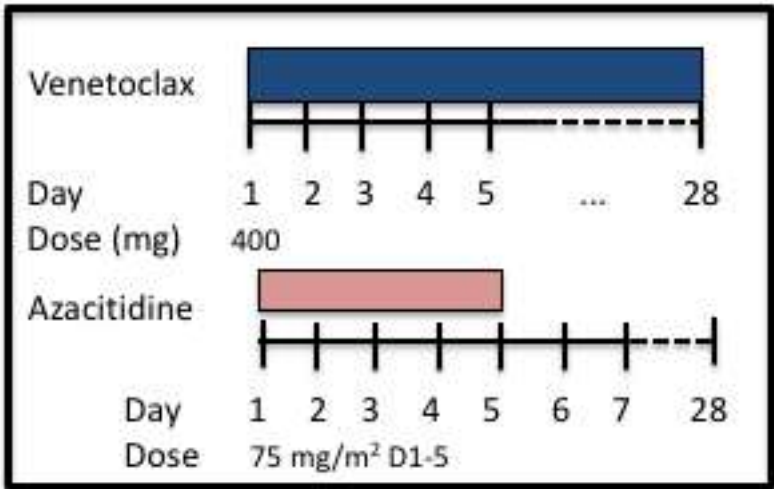
Figure 2: Consolidation dose and schedule (Venetoclax in mg)



After induction or consolidation, patients may receive maintenance therapy. Patients who achieve a CR/CRi/MLFS with MRD negativity after induction may proceed directly to MRD negative maintenance. Patients who achieve a CR/CRi/MLFS with MRD negativity after cycles 1, 2 or 3 of consolidation may proceed to MRD negative maintenance. Patients who achieve a CR/CRi/MLFS with MRD positivity after cycle 3 of consolidation may proceed to MRD positive maintenance.

MRD negative maintenance will consist of 400 mg PO daily venetoclax with azacitidine 75 mg/m² SC or IV on days 1-5 of a 28-day cycle. This will continue for two years or longer, if felt to be clinically appropriate and tolerated. See Figure 3.

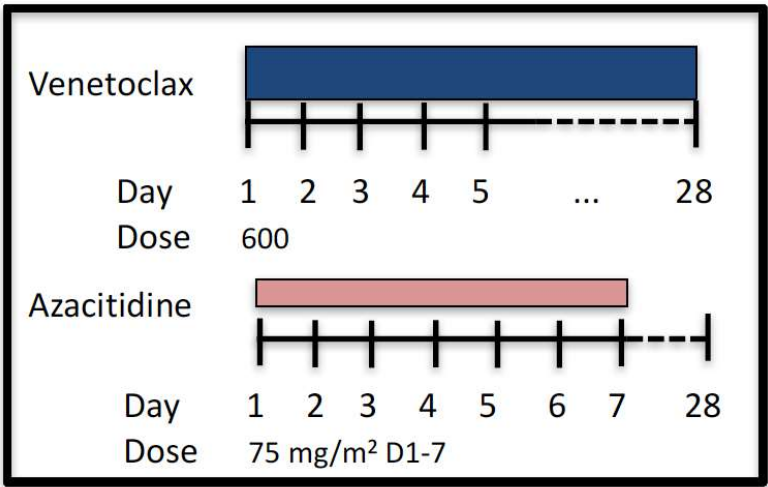
Figure 3: MRD negative maintenance. Venetoclax dosed in mg.



Maintenance for patients who have MRD positivity after induction and 3 cycles of consolidation will consist of azacitidine 75 mg/m² SC or IV on days 1-7 (or 5-2-

2), with venetoclax 600 mg PO daily on days 1-28, for a maximum of 12 cycles and an option to cross over to the MRD negative maintenance plan if MRD negativity is achieved. See Figure 4. Dose de-escalation of azacitidine and/or venetoclax will be permitted after induction if required due to toxicity. See Section 5.14.3.

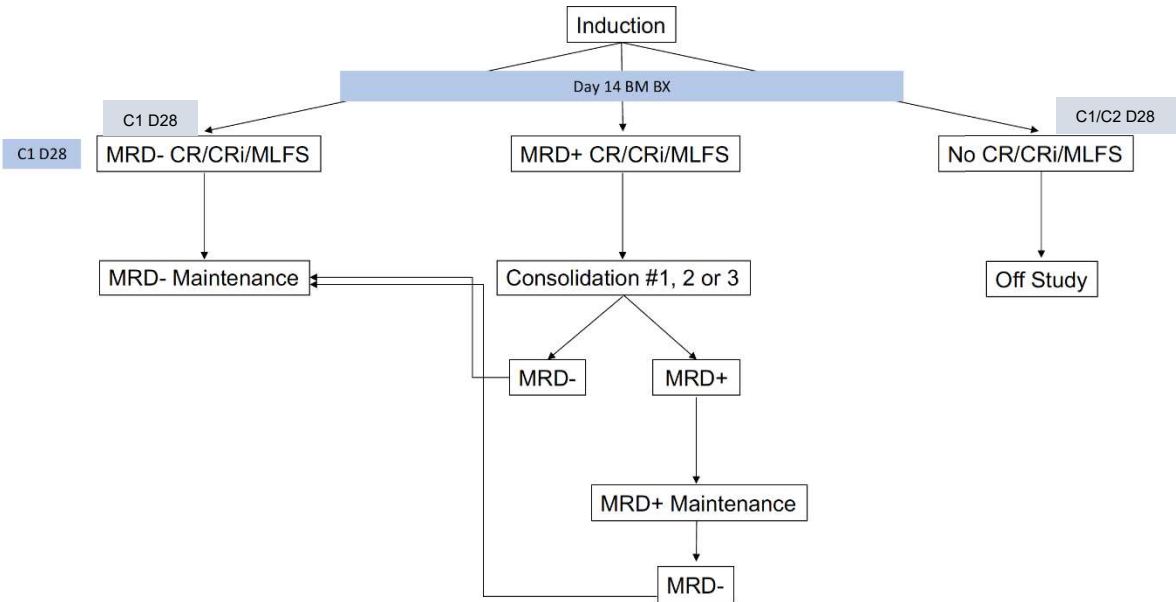
Figure 4: MRD positive maintenance. Venetoclax dosed in mg.



Bone marrow biopsies will occur for patients on maintenance therapy after every third cycle until 1 year from remission. Subsequent bone marrow biopsies will be performed at the discretion of the investigator.

The overall study schema is summarized in Figure 5 below.

Figure 5: Overall study schema



5.1.2 Response Assessments

Response assessments will be made by physical examination and evaluation of peripheral blood findings and bone marrow biopsies at the required time points (see Section 5.1.1), using the 2017 ELN AML response criteria⁴² and the definition of disease progression made according to the IWG⁴³ (see Section 5.11).

5.1.3 Continuation and Interruptions

Patients who achieve a response and are tolerating therapy can continue to receive sequential treatment cycles of maintenance therapy for two years or longer, if felt to be clinically appropriate and tolerated. Patients who experience disease progression or significant treatment-related toxicity, as assessed by the investigator or the patient, will discontinue therapy. Patients may discontinue treatment to proceed to a stem cell transplantation.

After cycle 1, patients who achieve a response without full recovery of blood counts (CRI or MLFS) will have treatment interrupted for up to 14 days, with or without myeloid growth factor support. After blood count recovery, patients will proceed with cycle 2; if blood count recovery does not occur, or occurs but is not complete, cycle 2 will resume by no more than 14 days after the end of cycle 1.

After induction, the start of consolidation and maintenance can proceed in the absence of possibly/related > grade 2 non-hematologic toxicity. In the presence of possibly/related > grade 2 non-hematologic toxicity, venetoclax will be interrupted until resolution to grade 1 and then resumed at the current dose (first occurrence) or dose reduced (second occurrence) (see Section 5.14.4 for dose de-escalation).

Grade 3 neutropenia with infection or fevers, or grade 4 neutropenia that lasts beyond 42 days, will result in a venetoclax interruption. If these events recur after resumption of venetoclax, dose reduction is required (Section 5.14.4).

After induction, delays of consolidation and maintenance are not required for any grade of hematologic toxicity, with the exception of grade 3 neutropenia with infection or fevers, or grade 4 neutropenia that lasts beyond 42 days, as listed above. However, cycles may be delayed for any grade of hematologic toxicity, and myeloid growth factors may be used according to standard practices, in the absence of evidence of ongoing disease (Section 5.1.3).

Subjects who require brief interruption or delay of venetoclax for reasons other than progression of disease (venetoclax-related AEs, Section 5.14) will continue on azacitidine therapy alone until they resume venetoclax. When the following cycle is resumed, venetoclax and azacitidine will resume on the same day, and inpatient dose escalation will not be required at any time after cycle 1, even after a dose interruption. Azacitidine will be delayed or interrupted for azacitidine-related AEs, according to Section 5.14, and may be resumed once the condition

has improved or been stabilized with adequate treatment. Delays of azacitidine do not require delays of venetoclax.

5.2 Study Endpoints

5.2.1 Primary Endpoint

- Response rate excluding PR using the European LeukemiaNet definition ($CR_{MRD} + CR + CRi + MLFS$) that shows non-inferiority of venetoclax with azacitidine when compared with historical controls who received induction chemotherapy (see appendix C).

5.2.2 Secondary Endpoints

- Incidence of and time to achieve MRD negative responses ($CR + CRi + MLFS$)
- Remission duration
- One-year event-free and overall survival, stratified by response type and achievement of MRD negative state
- Incidence and severity of adverse events

5.3 Selection of Study Population and Enrollment Procedures

All subjects will be screened for eligibility. The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for entry into the study. After the patient has signed and dated the informed consent form, all screening procedures have been completed and clinical eligibility has been confirmed, the patient can be officially enrolled in the study. All patients must meet the qualifications as outlined below.

5.3.1 Inclusion Criteria

A subject will be eligible for study participation if the subject meets the following criteria within 28 days prior to the first day of therapy (bone marrow biopsy can be performed 28 days prior to the first day of therapy). Historical records are permitted per Investigator discretion.

1. Subject must have confirmation of non-APL and AML by WHO criteria⁴⁴
2. Subject must have received no prior treatment for AML
3. Age ≥ 18 years, ≤ 59 years
4. Without clinical signs of active central nervous system disease
5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status of ≤ 2
6. Subject must have adequate renal function as demonstrated by a calculated creatinine clearance ≥ 30 mL/min; determined via urine

collection for 24-hour creatinine clearance or by the Cockcroft Gault formula

7. Subject must have adequate liver function as demonstrated by:
 - aspartate aminotransferase (AST) $\leq 3.0 \times \text{ULN}^*$
 - alanine aminotransferase (ALT) $\leq 3.0 \times \text{ULN}^*$
 - bilirubin $\leq 3.0 \times \text{ULN}$, unless due to Gilbert's syndrome*

* Unless considered due to leukemic organ involvement
8. Non-sterile male subjects must use contraceptive methods with partner(s) prior to beginning study drug administration and continuing up to 90 days after the last dose of study drug. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.
9. Female subjects who are pre-menopausal and have not had a tubal ligation, hysterectomy or oophorectomy must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting therapy; 2) throughout the entire duration of treatment; 3) during dose interruptions; and 4) for at least 90 days after discontinuation of therapy (last dose of study drug).
10. Subject is informed that consumption of the following fruits is prohibited 3 days prior to the initiation of study treatment and throughout participation: grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit.
11. Subject must voluntarily sign and date an informed consent, approved by an Institutional Review Board (IRB), prior to the initiation of any research directed screening procedures.
12. Subject must have intermediate or adverse risk disease as defined by the European LeukemiaNet⁴⁵ (Appendix B)

5.3.2 Exclusion Criteria

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

1. Subject has AML with monocytic features; this determination can be made by morphologic assessment, flow cytometry or immunohistochemical staining
2. Subject has received disease modifying treatment for myelodysplastic syndrome (MDS) or AML. ATRA given for clinical suspicion of APL will not be exclusionary and no washout will be required in this scenario.
3. Subject is known to be positive for HIV. HIV testing is not required.

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4. Subject is known to be positive for hepatitis B or C infection with the exception of those with an undetectable viral load. Hepatitis B or C testing is not required and subjects with serologic evidence of prior vaccination to HBV (i.e., HBs Ag-, anti-HBs+ and anti-HBc-) may participate
5. Subject has received within 7 days prior to the first dose of study drug: steroid therapy for anti-neoplastic intent; strong and moderate CYP3A inhibitors; strong and moderate CYP3A inducers.
6. Subject has any history of clinically significant condition(s) that in the opinion of the investigator would adversely affect his/her participating in this study including, but not limited to:
 - New York Heart Association heart failure > class 2
 - Renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or bleeding disorder independent of leukemia
7. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration
8. Subject exhibits evidence of uncontrolled systemic infection requiring therapy (viral, bacterial or fungal)
9. Subject has a history of other malignancies prior to study entry, with the exception of:
 - Adequately treated in situ carcinoma of the breast or cervix uteri
 - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
 - Prostate cancer with no plans for therapy of any kind
 - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
10. Subject has a white blood cell count $>25 \times 10^9/L$ or absolute blast count of $>50 \times 10^9/L$. Hydroxyurea and leukapheresis are permitted, if clinically indicated.
11. Pregnant and breastfeeding females.

5.4 Duration of Study

After treatment discontinuation (last dose of study drug), all patients will be followed at least annually, in the form of a telephone call, email or clinic visit, for information on whether the patient has relapsed or not, and whether they are alive or deceased.

Study can be terminated prior to the completion of five years, per Investigator discretion. Patients still in follow-up will be contacted by study team if study is terminated prematurely.

As of v10SEP2025, all subjects remaining on follow up will be discontinued from trial and data collection will be complete.

5.5 Drug Administration

5.5.1 Venetoclax Administration

Tumor lysis syndrome (TLS) may occur upon initiation of dosing with venetoclax with azacitidine. To mitigate the risk of TLS in AML patients the regimen is designed to escalate the dose of venetoclax rapidly and safely with standard doses and schedules of azacitidine to optimize the opportunity for achieving a response and enable close subject monitoring. For additional safety and efficacy data please refer to the current Investigator Brochure.

During cycle 1, venetoclax will be administered orally once daily on days 1 through 28. See Table 1. Each dose of venetoclax will be self-administered with approximately 240 mL of water within 30 minutes after the completion of a meal.

If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be taken and the second dose noted in the drug log. Otherwise, no replacement dose is to be taken.

Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

For induction, subjects will be admitted to the hospital where they will be confined from cycle 1 day 1 until at least 24 hours after receiving the 600 mg target dose. Dose modifications of venetoclax during escalation will be implemented for individuals at risk for TLS or any new adverse events > Grade 2 (see Section 5.14.4). To mitigate the potential risk of TLS⁴⁶ subjects will receive TLS prophylaxis which will include hospitalization for observation, administration of a uric acid reducing agent and adequate oral and intravenous hydration.

If a subject develops any laboratory changes suggestive of TLS during escalation, venetoclax dose escalation will stop; laboratory TLS that persists for over 48 hours will require a dose de-escalation. Any case of clinical TLS will require a dose de-escalation (Section 5.14.4). Any laboratory or clinical TLS will involve maximization of supportive care. Refer to Section 6.10, Management of Tumor Lysis Syndrome, for details on TLS prophylaxis.

Venetoclax dose decreases may be considered, see Section 5.14.4, and for adverse event management guidelines please refer to Section 6.

Patients who take more than the prescribed dose of venetoclax should be instructed to seek emergency medical care if needed and contact study staff

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immediately. If a dose of venetoclax is missed or forgotten, it should be taken as soon as possible, ensuring it is taken within 8 hours of the missed dose with food; otherwise the dose should not be taken. Missed doses should not be made up.

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles or blister cards. Each bottle or blister card will be labeled per institutional requirements. It must be stored at 15° to 25°C (59° to 77°F). Venetoclax is for investigational use only and is to be used only within the context of this study. It must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned. Abbvie will provide venetoclax and it will be kept by the investigational pharmacy.

If in extreme circumstances, after a patient has begun therapy and they become unable to swallow (eg: intubation for respiratory compromise), crushed venetoclax may be administered via feeding tube⁴⁷.

5.5.2 Azacitidine Administration

Azacitidine 75 mg/m² should be prepared and administered per the package insert and institutional guidelines. IV or subcutaneous administration is permitted.

5.6 Assuring Patient Compliance

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

Patients will receive all dosages of azacitidine in the inpatient or outpatient setting.

After discharge from the hospital or completion of induction, whichever occurs first, venetoclax will be self-administered at home. Patients will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses. Patient compliance will be assessed on day 28 of a completed cycle or day 1 of a subsequent treatment cycle. Patients will be required to bring their diary, any remaining capsules, and the bottle, even if empty, to clinic during this visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary. Compliance will be monitored and documented by the study coordinator. Poor compliance will result in counseling of the subject by study site personnel. Any unused venetoclax will be returned to the pharmacy.

5.7 Drug Accountability

The investigator and his representatives will verify that study drug supplies are received intact and in the proper amounts. This will be documented. The investigator or his representatives will administer study drug only to subjects

enrolled in the study. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed to the subject. Upon completion or termination of the study, all original containers (containing partially used or unused study drug) will be handled per institutional practices. Empty containers will be destroyed at the site.

5.8 Concomitant Therapy

5.8.1 Permitted Concomitant Therapy

Transfusion of blood and blood products, antibiotics, anti-emetics and other standard supportive care medications are permitted as needed. After initiation of the study, hydroxyurea or leukapheresis are permitted as needed according to institutional guidelines. Filgrastim may be used according to institutional guidelines. Antibiotics will be used for patients with known infections or neutropenic fevers.

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

Strong and moderate CYP3A inducers and inhibitors are prohibited during intra-patient dose escalation (See Appendix A). Once at the maximal target dose, these agents may be used with caution. If the investigator concludes that a moderate or strong CYP3A inhibitor is medically necessary, dose modification of venetoclax will be required and will follow **Table 1**:

Venetoclax Dose	Venetoclax Dose Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose Co-Administered with a Strong CYP3A Inhibitor
100 mg (cycle 1 only)	50 mg	25 mg
200 mg (cycle 1 only)	100 mg	50 mg
400 mg	200 mg	100 mg
600 mg	300 mg	100 mg

5.8.2 Prohibited Concomitant Therapy

Chemotherapy, systemic or intrathecal, immunotherapy, radiotherapy and prednisone >20 mg/day are prohibited.

Strong and moderate CYP3A inducers and inhibitors are prohibited during inpatient dose escalation, and may be used with caution at the maximal target dose (See Appendix A).

A sample list of excluded medications and cautionary medications that fall into the categories within section can be found in Appendix A. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label and/or FDA website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

5.9 Contraception Recommendations

Female subjects who are pre-menopausal and have not had a hysterectomy or oophorectomy must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting therapy; 2) throughout the entire duration of treatment; 3) during dose interruptions; and 4) for at least 90 days after discontinuation of therapy.

No contraception is required if male subjects are surgically sterile (vasectomy with medical assessment confirming surgical success) or if the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree from enrollment through 90 days after the last dose of investigational product to practice contraception with a partner who agrees to at least one of the following contraceptive measures:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to enrollment
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to enrollment
- Bilateral tubal occlusion/ligation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Additionally, male subject agrees not to donate sperm from randomization through 90 days after the last dose of investigational product.

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5.10 Study Procedures

Study procedures listed in section 2 are detailed in this section, with the exception of adverse event information (see Section 6). All study data will be recorded on eCRFs.

Procedures performed at screening will serve as baseline, unless repeated on cycle 1 day 1 prior to dosing, in which case this will serve as baseline. Any abnormal laboratory or vital sign between screening and prior to administration of therapy will be recorded in the subject's medical history and will also serve as the subject's baseline.

Subjects who signed the informed consent will obtain a screening/subject number. Subjects who signed informed consent, have had at least one study procedure conducted, and who are determined to be a screen failure will not proceed to the study. The reason for the screen failure will be documented in the source document and captured in the eCRF. Screening procedures must be performed within 28 days prior to study drug administration. Subjects who complete all screening procedures and meet the inclusion criteria (see section 5.3.1) and none of the exclusion criteria (see Section 5.3.2) will proceed to enrollment.

Informed consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in the study. The IRB approved informed consent must be signed and dated by the subject or representative prior to undergoing any research directed procedures or before any prohibited medications are withheld from the subject in order to participate in the study. Laboratory or procedural results obtained as standard of care procedures, and prior to consent to research procedures, are considered historical records and may be used at the discretion of the investigator.

History

Involves a complete medical history, with documentation of clinically significant medical conditions, and AML history including the date of diagnosis of AML and any precursor conditions. Also includes review of current medications and allergies.

Physical Exam

Symptom directed, per institutional protocol.

Vital Signs

Includes temperature, blood pressure, pulse, respiratory rate and if needed, oxygen saturation. Weight should be collected once per cycle. Height measured at screening only; other time points per standard of care. All methods of measurement and practices will be per institutional protocol.

ECOG PS⁴⁸

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

Cytogenetics

By FISH or metaphase cytogenetics, per institutional standards

MRD

Performed by up to 2 procedures, when relevant. 1) Cytogenetic testing, both metaphase cytogenetics and FISH; 2) Multidimensional flow cytometric approach based on differences from normal. Flow cytometry will always be performed; if a patient has a cytogenetic abnormality, cytogenetic testing will be performed. MRD will be considered positive if any of the two above modalities is positive.

AE and Con Meds

On cycle 1 day 1, any serious adverse events observed from the signing of informed consent but prior to administration of study drug will be reported, if considered by the investigator to be causally related to study-required procedures. At each visit, including the end of treatment visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medications, prescription and over the counter, including vitamins and/or herbal supplements, will be recorded beginning with the screening visit and continuing until end of treatment. Administration of IV fluids does not need to be recorded.

12 Lead EKG

A single 12-lead resting EKG will be obtained at screening or as clinically needed. It will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain stationary for the duration of the recording. An investigator will then evaluate it as clinically significant or not clinically significant, which will be entered into the CRFs.

TLS Prophylaxis

See Section 6.10

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Clinical Laboratory Tests

All laboratory tests will be performed at the time points listed in the schedule of study assessments and will be performed at additional time points based on institutional guidelines.

Hematology

- Hematocrit
- Hemoglobin
- WBC count
- Differential (if WBC high enough, per institutional standard)
- Platelet count

TLS Chemistry

- Calcium
- Phosphorus
- Potassium
- Uric Acid
- Creatinine

Chemistry

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Albumin
- Alkaline phosphatase
- Sodium
- Potassium
- Chloride
- Carbon dioxide
- Glucose
- Blood urea nitrogen (BUN)
- Creatinine
- Calcium
- Magnesium
- Phosphorus
- Total Protein
- Uric acid
- Lactate dehydrogenase (LDH)

Coagulation

- Prothrombin time (PT)
- International normalized ratio (INR)
- Partial thromboplastin time (PTT)
- Fibrinogen

Pregnancy Test

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Serum or urine pregnancy test is required for FCBP prior to dosing on Day 1 of each cycle. If patient has had a pregnancy test within 3 days of each cycle, a repeat is not required. Thereafter, serum or urine pregnancy tests are required for FCBP prior to each cycle of therapy.

Azacitidine

See Section 5.5.2

Venetoclax

See Section 5.5.1

Bone marrow aspirate and biopsy

To be performed at all time points outlined in the schedule of study assessments, in addition to at any time upon concern for relapse. Historical bone marrow aspirates and biopsy at screening may be acceptable per Investigator discretion.

Attempts to obtain an aspirate and biopsy are required at all listed time points. If a patient is not aspirable after an attempt is made, additional core biopsy specimens should be attempted per institutional protocol. On all time points samples should be sent for morphological assessment, flow cytometry, cytogenetic analysis and molecular testing, as is clinically appropriate. All results will be captured on a CRF.

Dispensing and Collecting Calendar and Diary

Subject calendars/diaries will be provided at the time of discharge from the hospital. Subjects will bring their calendars/diaries back to be reviewed at each visit.

Subjects will record the date and time of each dose of study drug taken, including whether any doses of the study drug are missed, and whether or not doses were taken within 30 minutes after the completion of a meal.

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

Safety Follow Up

A safety follow up visit should be performed approximately 30 days following discontinuation of study drug, and should include a history, physical examination and review of systems, and then should be repeated as clinically appropriate until any adverse events have resolved. A separate safety visit does not need to be performed for subjects with a final visit ≥ 30 days after discontinuation of study drug and did not require additional AE follow up. Patient refusal or inability to attend safety follow up visits will be noted in the source documentation. All patients will be followed at least annually for 5 years via clinic visit, email or phone call for survival and progression status until death, study discontinuation or until the patient withdraws consent.

5.11 Response Assessments

Assessment of clinical responses will be made according to 2017 ELN AML Recommendations.⁴² Definition of disease progression will be made according to IWG criteria.⁴³ The major criteria for judging responses will include physical examination and examination of blood and bone marrow. In the event that peripheral blood findings improve 14 days after a bone marrow biopsy, whether or not in the setting of a delay in treatment, the response assessment will be adjusted accordingly. Only subjects who complete cycle 1 will be evaluable for response. Patients with un-evaluable bone marrows should be reported as indeterminate and a repeat bone marrow should be completed within 1 week. Response duration is measured from the time all response criteria are first met until relapse is documented.

Complete Remission (CR)

CR requires all of the following:

- Bone marrow blasts <5%
- Absence of circulating blasts and blasts with Auer rods.
- Absence of extramedullary disease
- Absolute neutrophil count $>1.0 \times 10^9/L$
- Platelet count $>100 \times 10^9/L$

Complete Remission with Incomplete Blood Count Recovery (CRi)

CRi meets all CR criteria except for residual neutropenia or thrombocytopenia:

- Absolute neutrophil count $<1.0 \times 10^9/L$ OR
- Platelet count $<100 \times 10^9/L$

Morphologic Leukemia Free State (MLFS)

- No hematologic recovery required
- Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should be at least 10%

CR/CRi/MLFS with MRD Negativity

- Any of the above responses with negativity by multi-dimensional flow cytometry with a sensitivity to 0.1% and/or cytogenetic testing

Partial Remission (PR)

PR meets all hematologic criteria of CR:

- Absolute neutrophil count $>1.0 \times 10^9/L$

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- Platelet count $>100 \times 10^9/L$

AND

- Decrease of bone marrow blast percentage to 5% to 25%
- Decrease of pretreatment bone marrow blast percentage by at least 50%

Treatment Failure

Treatment failure will be classified as one of the following:

- Resistant disease (RD): No CR or CRi or MLFS or PR in subjects who survive at least 7 days after completion of cycle 1, with evidence of persistent disease by blood and/or bone marrow biopsy
- Death in aplasia: Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic, or with an aplastic or hypoplastic bone marrow obtained within 7 days of death that shows no evidence of persistent leukemia
- Death from indeterminate cause: Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

Relapsed Disease

Relapse for patients with prior CR/CRi/MLFS/PR, independent of MRD status will be defined as:

- Evidence of morphologic relapse with the appearance or reappearance of leukemic blasts in the peripheral blood or $\geq 5\%$ blasts in the bone marrow not attributable to any other cause. If questionable, a bone marrow biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration
- The appearance or reappearance of cytologically proven extramedullary disease
- If the best response was a PR, progression will be considered to be a doubling of the blast percentage

5.12 Reporting of Results

At the conclusion of each bone marrow biopsy performed, starting with the end of cycle 1 time point, all patients will be assessed as one of the following responses:

- CR
 - With/Without MRD
- CRi
 - With/Without MRD

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- MLFS
 - With/Without MRD
- PR
- RD
- Death in Aplasia

5.13 Stopping Rules

5.13.1 Individual Patient Stopping Rules

All subjects will be included for analysis of safety data. Subjects have the right to withdraw from the study at any time. The investigator will discontinue a subject from treatment if this is felt to be necessary for any reason including:

- Non-compliance with the study protocol
- It is believed to be in the best interests of the subject
- Disease progression
- Toxicity related to study drug that requires more than a 4-week dose interruption of therapy and in the absence of clinical benefit
- Need for other anti-neoplastic agents or radiotherapy for the development of a new primary cancer diagnosis
- Adverse event that precludes further investigational drug administration
- Development of unrelated illness which compromises further participation in the study
- Decision to proceed to a stem cell transplantation

In the event of withdrawal or discontinuation, the reason for discontinuation will be recorded and a final end of treatment visit, including a physical examination, vital signs, ECOG PS, bone marrow aspirate and biopsy with cytogenetics and MRD, AE assessment with ConMeds, hematology/chemistry laboratories and collection of the calendar/diary, will be performed as soon as possible after discontinuation. If the subject had a bone marrow aspirate and biopsy with cytogenetics and MRD within 14 days of the end of treatment visit, then a repeated procedure is not required.

5.13.2 Study Stopping Rules

Rules for stopping the study for futility are detailed in the statistical analysis plan (Section 8.6). In addition, if the investigator determines that continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. All enrolled subjects will be notified of the premature discontinuation and the investigator will administer treatments with other regimens as is appropriate.

Stopping rules for excessive toxicity are as follows: Assuming 10% as an acceptable rate of grade 4/5 toxicity events and assuming 15% as an

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unacceptable rate of grade 4/5 toxicity events for this trial, we determine the following stopping rule (equivalent to determining Pocock boundaries with the same significance level used at both looks and an overall alpha level of 0.05): stop the trial if more than 2 grade 4/5 toxicity events are observed in the first 6 patients, if more than 3 grade 4/5 toxicity events are observed in the first 12 patients, if more than 4 grade 4/5 toxicity events are observed in the first 18 patients, if more than 5 grade 4/5 toxicity events are observed in the first 24 patients, or if more than 6 grade 4/5 toxicity events are observed in the first 30 patients.

The study will continue until the last patient is followed 90 days beyond receiving the last dose of study drug. Annual contact (phone calls, emails or visits) will be made as appropriate for 5 years after discontinuation of treatment, or until death or withdrawal of consent.

5.14 Dosing Delays and Modifications

5.14.1 Missed Doses

If a dose of venetoclax is missed, it should be taken as soon as possible on the same day, as long as the dose is taken within 8 hours of the scheduled time. If it is missed for the entire day, it should not be made up. Patients will be encouraged to stay on schedule even if a dose is missed. Dosing will be tracked in the patients' diaries.

5.14.2 Additional Doses

Patients who take more than the prescribed dose of venetoclax should be instructed to seek emergency medical care if needed and contact study staff immediately.

5.14.3 Dose Delays

After induction, the start of consolidation and maintenance can proceed in the absence of possibly/related > grade 2 non-hematologic toxicity. In the presence of possibly/related > grade 2 non-hematologic toxicity, venetoclax will be interrupted until resolution to grade 1 and then resumed at the current dose (first occurrence) or dose reduced (second occurrence) (see Section 5.14.4 for dose de-escalation).

Grade 3 neutropenia with infection or fevers, or grade 4 neutropenia that lasts beyond 42 days, will result in a venetoclax interruption. If these events recur after resumption of venetoclax, dose reduction is required (Section 5.14.4).

After induction, delays of consolidation and maintenance are not required for any grade of hematologic toxicity, with the exception of grade 3 neutropenia with infection or fevers, or grade 4 neutropenia that lasts beyond 42 days, as listed above. However, cycles may be delayed for any grade of hematologic toxicity,

and myeloid growth factors may be used according to standard practices, in the absence of evidence of ongoing disease (Section 5.1.3).

Subjects who require brief interruption or delay of venetoclax for reasons other than progression of disease (venetoclax-related AEs) will continue on azacitidine therapy alone until they resume venetoclax. When the following cycle is resumed, venetoclax and azacitidine will resume on the same day, and inpatient dose escalation will not be required at any time after cycle 1, even after a dose interruption. Azacitidine will be delayed or interrupted for azacitidine-related AEs, and may be resumed once the condition has improved or been stabilized with adequate treatment. Delays of azacitidine do not require delays of venetoclax.

If a subject develops any laboratory changes suggestive of TLS during escalation, venetoclax dose escalation will stop; laboratory TLS that persists for over 48 hours will require a dose de-escalation. Any case of clinical TLS will require a dose de-escalation. Any laboratory or clinical TLS will require maximization of supportive care.

5.14.4 Dose De-Escalation

In the presence of the following, the investigator will reduce the dose of venetoclax using the below table:

- Clinical TLS
- Possibly/related > grade 2 non-hematologic toxicity that resumes after a hold and a return to grade 1
- Grade 3 neutropenia with infection or fevers, or grade 4 neutropenia that lasts beyond 42 days that recurs after a hold and resumption
- Grade 3 neutropenia/thrombocytopenia that persists >14 days off therapy

Clinical Scenario	Venetoclax Dose
First episode of >grade 3 neutropenia/thrombocytopenia >14 days	600 mg daily
Second episode of >grade 3 neutropenia/thrombocytopenia >14 days	400 mg daily
Third episode of >grade 3 neutropenia/thrombocytopenia >14 days	400 mg 21/28 days

Azacitidine will be dose adjusted according to the package insert.

During maintenance phase, after MRD negativity has been achieved, dose de-escalation of venetoclax can be considered using the following table:

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Clinical Scenario	Venetoclax Dose
First episode of >grade 3 neutropenia/thrombocytopenia >14 days	300 mg daily
Second episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg daily
Third episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg 21/28 days
Fourth episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg 14/28 days

If an additional dose reduction is felt to be necessary, the patient will discontinue the study.

6 SAFETY PLAN

6.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject on the study. This can include any unfavorable or unintended sign, symptom or disease temporally associated with the use of the therapy, regardless of causality with the therapy. This may include use of the therapy as stipulated in the protocol or as labeled or from accidental or intentional overdose. Worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are AE only if they result in study discontinuation, necessitate medical intervention, meet protocol specific criteria, and/or are considered by the investigator to be clinically significant or AEs. Elective surgeries or procedures scheduled to occur during a study are not AEs 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 deteriorated unexpectedly during the study (e.g. the surgery must be performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of study drug is administered until 30 days have elapsed following last dose of study drug.

6.2 Serious Adverse Events

If an AE meets any of the following criteria it is to be considered a serious adverse event (SAE) and must be reported to HCTU.Quality@ucdenver.edu and Abbvie within 24 hours, see Section 6.8.2.

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The Sponsor-Investigator will then review and submit to the University of Colorado regulatory authorities and the FDA, if applicable, in accordance with 21 CFR 312.32.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death in the opinion of the investigator. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization or prolongation of hospitalization:	AE that required hospitalization for any length of time or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan are not SAEs by this criterion. Admissions to an outpatient facility, emergency room, palliative unit or hospice care facility are not considered to be hospitalizations and are not SAEs.
Disabling/incapacitating	AE that results in substantial and permanent disruption of the patient's ability to carry out normal life functions. Does not include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. ankle sprain)
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
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, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly or persistent or significant disability/incapacity). Any elective or spontaneous abortion or stillbirth is considered a SAE.

For SAEs that result in death, the date and cause of death will be recorded in the case report form.

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Deaths due to disease progression will not be recorded as SAEs. Patient deaths that are later determined to be unrelated to disease progression may be reported outside the 24-hour window.

Hospitalization to allow observation and management for the purpose of TLS prophylaxis will not be considered SAEs unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention).

Hospitalization of a subject in post-treatment follow up or survival 30 days or more after discontinuation of the therapy will not be recorded as a SAE.

SAEs occurring after informed consent but prior to initiation of therapy will be collected only if felt by the investigator to be causally related to the study required procedures.

For hospitalizations or surgical or diagnostic procedures, the illness leading to the hospitalization or surgical or diagnostic procedure will be recorded as the SAE, not the procedure itself. The procedure will be captured in the narrative as part of the action taken in response to the illness.

6.3 Adverse Events Commonly Associated with AML

Certain AEs are anticipated to occur in this study population at some frequency independent of drug exposure. For example, cytopenias (anemia, neutropenia, thrombocytopenia) are part of the natural history of AML. Therefore, persistent cytopenias at the same CTCAE grade as at baseline are not be reported as AEs, unless they meet criteria for an SAE, result in permanent discontinuation of a study drug, or the investigator has an identifiable cause other than the underlying disease.

6.4 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0). If a reported AE increases in severity, the initial AE should be given final outcome date and a new AE must be reported to reflect the change in severity.

For AEs not captured by the 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)

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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 requiring urgent intervention (severe)
Grade 5	The AE resulted in death of the subject (severe)

6.5 Relationship to Study Drug

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

Reasonable Possibility of Relationship with Azacitidine	An AE where this is evidence to suggest a causal relationship between azacitidine and the AE
No Reasonable Possibility of Relationship with Azacitidine	An AE where this is no evidence to suggest a causal relationship between azacitidine and the AE
Reasonable Possibility of Relationship with Venetoclax	An AE where this is evidence to suggest a causal relationship between venetoclax and the AE
No Reasonable Possibility of Relationship with Venetoclax	An AE where this is no evidence to suggest a causal relationship between venetoclax and the AE

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered “associated.” Events assessed as having no reasonable possibility of being related to study drug will be considered “not associated.” When no reasonable possibility of an association between a study drug and a SAE exists, the investigator must provide another cause.

6.6 Deaths

Death is an outcome of an event. Deaths that occur during the AE reporting period that are attributed by the investigator to AML progression will be recorded as such. For all deaths, the event or condition that caused or contributed to the fatal outcome will be recorded as the single medical concept on the AE CRF. If the cause of death is unknown and cannot be ascertained, “unexplained death” should be recorded. If the cause later becomes available, “unexplained death” should be replaced with the established cause of death.

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6.7 Recording Adverse Events

Patient safety will be assessed by reviewing AEs during planned and unplanned visits and physical and laboratory examinations from the time the patient receives the first dose of study drug until 30 days after the patient's last study treatment. The investigator will assess and record AEs in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to the study drug, and any action taken. For SAEs considered unrelated to study drug, the investigator will provide another cause for the event. AEs may be recorded as the result of a response to a query, an observation by site personnel, or due to a report from a subject. All AEs will be followed for 30 days following discontinuation of study drugs or until a subsequent therapy or conditioning for a stem cell transplant, whichever occurs first.

6.8 Investigator Reporting Responsibilities

The conduct of the study will comply with all Food and Drug Administration (FDA) safety reporting requirements. If the FDA determines an IND is necessary, it is a requirement of 21 CFR 312.33 that an annual report be provided to the FDA within 60 days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The annual report should be filed in the study's regulatory binder, and a copy provided to Abbvie as a supporter of this study.

6.8.1 Adverse Event Reporting

All AE reports will include the patient's number, severity of reaction (mild, moderate, severe), relationship to the study (fatal relationship, definitely related, possibly related, unrelated), date of administration of test medications and the investigators will notify the IRB and DSMC of a SAE according to institutional policy.

6.8.2 Reporting to Abbvie

Serious adverse events (SAE) are defined in Section 6.2.

In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Site Investigator shall:

- a) Report to Abbvie all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition, report all non-serious adverse events

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of tumor lysis syndrome for studies involving venetoclax. Copy:
HCTU.Quality@ucdenver.edu.

- b) The Sponsor-Investigator will copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and,
- c) The Site Investigator will notify AbbVie upon any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be PPDINDPharmacovigilance@abbvie.com and copy, HCTU.Quality@ucdenver.edu.

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints shall be RD_PQC_QS@abbvie.com

6.8.3 Reporting From Abbvie

Abbvie will notify the investigators via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

Sponsor-Investigator will inform all sites of IND Safety Reports from Abbvie. The investigators will notify the IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The investigators must keep copies of all AE information, including correspondence with Abbvie and the IRB, on file.

6.9 Pregnancy

Pregnancies and suspected pregnancies (including positive pregnancy tests regardless of age or disease state) of a female subject occurring while the patient is on venetoclax, or within 28 days of the subject's last dose of venetoclax, are

considered immediately reportable events. Venetoclax is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Abbvie Drug Safety immediately by facsimile or email. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation.

The investigator will follow the female subject until completion of the pregnancy and must notify Abbvie Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Abbvie Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported to Abbvie Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form (see Section 6.2)

6.10 Prophylaxis and Management of Tumor Lysis Syndrome

TLS is a potential risk for all patients with AML, particularly those with risk factors such as renal dysfunction and increased WBCs. To mitigate this risk, in addition to intra-patient dose escalation over the course of several days, patients will receive TLS prophylactic measures prior to initial therapy; in some cases, these measures may need to be re-implemented in the setting of a treatment interruption or dose delay prior to resuming therapy.

Below are the minimum requirements for TLS prophylaxis and monitoring, which will be performed in addition to institutional standards:

- All subjects will be hospitalized on or before cycle 1 day 1 prior to the administration of the initial dose of study treatment, and remain in the hospital for at least 24 hours after reaching the final escalated dose of venetoclax.
- Administration of uric acid reducing agent, adequate oral and intravenous hydration while monitoring the fluid status of the subject prior to and during the venetoclax dose escalation will be performed per institutional standards.
- TLS chemistry tests (calcium, phosphorus, potassium, uric acid and creatinine) will be drawn (± 2 hours): A) On the first day of venetoclax dosing, within 4 hours prior to the dose and again 6 and 12 hours after the first dose, and B) On each day of dose escalation, within 4 hours prior to the dose and again 6 and 12 hours after the dose.

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Additional laboratory assessment may be performed at the investigator's discretion post-dose during the escalation and up to 48 hours after reaching the final dose.

- After dose escalation, TLS will be monitored with serial chemistry measurements (see Section 5.10) and more intensive measures may be considered for patients felt to be at higher risk.
- Abnormal chemistry tests should be corrected promptly
- If a subject develops any laboratory changes suggestive of TLS during escalation, venetoclax will be held; laboratory TLS that persists for over 48 hours will require a dose de-escalation. Any case of clinical TLS will require a dose de-escalation (Section 5.14.4).
- Prophylactic reductions of potassium, phosphorus and/or uric acid above normal ranges are recommended prior to beginning study treatment and should continue based on the ongoing risk of TLS.
- In the setting of rasburicase, follow institutional sample handling procedures to ensure the proper measurement of TLS laboratory values

6.11 Decreased Spermatogenesis

Based on preclinical data, venetoclax has the potential to decrease spermatogenesis. Male subjects considering preservation of fertility should consider sperm banking before treatment with venetoclax.

6.12 Management of Infection

Anti-infective prophylaxis will be implemented per institutional guidelines with consideration for possible drug interactions. Please see Appendix A for excluded and cautionary medications.

6.13 Management of Other Toxicities

If other events occur that are related to the study drugs, the investigator may interrupt or dose reduce the therapies as appropriate. Grade 3 or greater non-hematologic toxicity that is related to the study drugs will require interruption and possible discontinuation. Therapy may be re-introduced, potentially at a reduced dose, if the toxicity returns to baseline if grade 2 at study entry or \leq grade 1. In the event of a second occurrence of the same toxicity, study drug(s) must be dose reduced.

7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, good clinical practice or standard operating procedure requirements. The noncompliance may be

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either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

Intentional deviations are not allowed unless necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirement and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the study team will keep record of deviations and is responsible for reporting to the IRB as required.

8 STATISTICAL METHODS

Patients who receive at least one dose of venetoclax or azacitidine will be evaluable for safety and efficacy. Patients who do not complete at least one cycle of therapy may be replaced.

8.1 Demographics

Descriptive statistics will be provided for demographic variables.

8.2 Efficacy Analysis

Efficacy will include analyses of overall response rate defined as CR+CRi+MLFS+PR, MRD positive responses (CR+CRi+MLFS), and MRD negative CR+CRi+MLFS (MRD-negative composite responses), median time to achieve a MRD negative response, duration of overall response, event free survival and overall survival.

8.3 Safety Analysis

Safety will be assessed by analysis of AEs, SAEs, all deaths, changes in laboratory values and vital sign parameters. Analysis of AEs will include only treatment-emergent events (events that had onset on or after the first dose of study drug). Analysis of AEs and SAEs will not include those that have an onset >30 days after the last dose of study drug. Toxicity grades using NCI CTCAE V4.0 and relationships to study drugs will be assessed. In addition, incidence of febrile neutropenia, ≥ grade 2 bleeding complications.

8.4 Deaths

The number of subject deaths will be analyzed by those that occurred within 30 days of the last dose of study drug, those that occurred more than 30 days after

the last dose of study drug, those that occurred within the first 30 days of the study, those that occurred within the first 60 days of the study, those that were related to study drug and those that were unrelated to study drug based on investigator assessment.

8.5 Sample Size Determination

The overall response rate using 7+3 in younger patients with newly diagnosed unfavorable risk AML is typically reported at ~50%^{49,50}. These patients with intermediate risk disease typically have higher response rates (~65%)^{24,49,51,52}. Mixed populations of intermediate and adverse risk patients have variable response rates, but these are often still ~50%⁵³.

Therefore, for a cohort of younger newly diagnosed patients with predominately adverse risk disease but also some with intermediate risk disease receiving venetoclax plus azacitidine, we will define failure as an observed overall response rate (described in detail as the primary end point) of less than 55%, based on historical control studies of patients who received induction chemotherapy (null hypothesis = $H_0: p_0 \leq 0.55$). Under the assumption that venetoclax plus azacitidine administration has similar results as those seen in older untreated patients¹⁹ with complete response rates of at least 78% (i.e. $H_1: p_1 \geq 0.78$), then in utilizing a one-sided O'Brien Fleming 6-stage design (O'Brien & Fleming, 1979), we will require 36 patients to allow for 80% power to detect this difference with a significance level of 0.05. Point estimates and associated 95% confidence intervals of the proportion of complete response patients in the population will be calculated at the conclusion of the study.

8.6 Statistical Analysis Plan

The study will be suspended pending further review if, at any time, there is sufficient evidence to suggest that the true probability of efficacy is inferior to standard induction chemotherapy.

Therefore, this study will be suspended if there is sufficient evidence to suggest that the true probability of overall response rate (as defined in primary end point and appendix C) falls below 55%. Statistically significant evidence for maintaining a non-inferior response rate compared to historical control will be defined as an observed response rate whose lower two-sided 80% confidence limit is lower than 55% at the conclusion of the last O'Brien Fleming Stage. Table 2 displays the total number of subjects for this study and the number of subjects to be accrued in each of four stages in an O'Brien Fleming multi-stage procedure (n_k is the cumulative number of participants enrolled up to Stage k) implemented by PASS. If r_k or fewer responses are observed during stage k , the trial will be stopped early for futility. If r_4 or fewer responses are observed by the end of stage 4, then no further investigation of venetoclax is warranted.

Table 2: O'Brien Fleming Sample Size and Observed Response Rate Requirements

O'Brien Fleming Stage	n_k	r_k	Minimum # Responses Required to Continue Study	Observed Response Rate	80% Confidence Interval for Response Rate = r_k/n_k	80% Confidence Interval for Response rate = $(r_k+1)/n_k$
1	6	1	2	33.3%	(1.7%, 51.0%)	(9.3%, 66.7%)
2	12	6	7	58.3%	(28.8%, 71.2%)	(36.2%, 78.1%)
3	27	18	19	70.4%	(52.5%, 78.8%)	(56.4%, 81.9%)
4	36	25	26	72.2%	(57.6%, 79.6%)	(60.5%, 82.0%)

The study will continue until the last patient is followed 90 days beyond receiving the last dose of study drug. Annual contact (phone calls, emails or visits) will be made as appropriate for 5 years after discontinuation of the study, or until death or patient withdraws the consent.

Secondary measures of event free survival, overall survival, and duration of response will be explored using Kaplan Meier survival analysis methods. Furthermore, other secondary endpoints will be calculated along with their 95% confidence intervals. Laboratory test measures and physical exam findings will be described using summary measures. Exploratory analyses can describe differences in these findings based on demographic variables.

9 ETHICS

9.1 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Academic Site's Institutional Review Board of Record (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by IRB before the changes are implemented to the study. All changes to the consent form will IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.2 Ethical Standards

Good clinical practice (GCP) requires that the protocol, amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study and any other necessary documents be reviewed by the IRB. The IRB will review the ethical, scientific and medical appropriateness

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of the study before it is conducted. IRB approval of the protocol, informed consent and subject information will be obtained prior to the authorization of drug shipment to the study site.

Amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive essential documents.

During the conduct of the study the investigator will promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

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

9.3 Informed Consent Process

Prior to the initiation of any screening or study-specific procedures, the IRB approved consent form(s) describing in detail the study agent, study procedures, and risks will be given to the subject, and the investigator or their representative will explain the nature of the study to the subject and answer all questions regarding the study. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent (per IRB guidance). Written documentation of informed consent will be required prior to starting intervention/administering study procedures and a copy of the signed informed consent will be given to the subject with the original placed in the subject's file. An entry will be made in the source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10 SOURCE DOCUMENTS AND CASE REPORT FORMS

Accurate, complete, legible and timely records and data will be kept in the source documents of all drug administration, including prescribing and dosing. Source documents are defined as original documents, data and records that pertain to the conduct of the study and distribution of the protocol therapy. These may include but are not limited to, copies of CRFs, hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, SAE reports, pharmacy dispensing and other records, recorded data from automated instruments, and/or imaging studies. Data collected must be recorded on the appropriate source document.

Study documents will be retained for as long as necessary to comply with all applicable regulations and institutional requirements. By signing the protocol, the investigators agree to adhere to the document/records retention procedures.

The investigator and institution will permit study-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data documents.

Case report forms (CRFs) must be completed for each subject screened/enrolled in the study.

11 STUDY OVERSIGHT – Quality Assurance and Quality Control

11.1 Data Safety and Study Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- Has the authority to suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

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The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's DSM progress report.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

11.2 Clinical Monitoring

Clinical site monitoring visits will be performed by the CU Clinical Monitor on a regular basis, pursuant to the Clinical Monitoring Plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants 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/ amendment(s), with GCP, and with applicable regulatory requirement(s). During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

11.3 Study Auditing

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following good clinical practices. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

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Appendix A: Sample List of Excluded and Cautionary Medications

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration
Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent: Excluded 30 days prior to first dose and throughout venetoclax administration
Excluded during ramp-up phase and Cautionary at the Cohort Designated Dose:
Strong and Moderate CYP3A inhibitors Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose.
Strong and Moderate CYP3A inducers Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and contact AbbVie medical monitor for guidance.
Cautionary
Warfarin
P-gp substrates
BCRP substrates
OATP1B1/1B3 substrates
P-gp inhibitors
BCRP inhibitors

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

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

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Appendix B: ELN Risk Stratification of AML⁵⁴

2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	<ul style="list-style-type: none">t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11†,‡Mutated NPM1†,§ without FLT3-ITDbZIP in-frame mutated CEBPA‖
Intermediate	<ul style="list-style-type: none">Mutated NPM1†,§ with FLT3-ITDWild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions)t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	<ul style="list-style-type: none">t(6;9)(p23.3;q34.1)/DEK::NUP214t(v;11q23.3)/KMT2A-rearranged#t(9;22)(q34.1;q11.2)/BCR::ABL1t(8;16)(p11.2;p13.3)/KAT6A::CREBBPinv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)t(3q26.2:v)/MECOM(EVI1)-rearranged–5 or del(5q); –7; –17/abn(17p)Complex karyotype,** monosomal karyotype††Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡Mutated TP53ª

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Appendix C: Response Assessments⁵⁴

Table 6. Response criteria in AML

Category	Definition	Comment
Response		
CR without minimal residual disease (CR _{MRD} -)	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9/\text{L}$ (1000/ μL); platelet count $\geq 100 \times 10^9/\text{L}$ (100 000/ μL)	MRD ⁺ or unknown
CR with incomplete hematologic recovery (CR _i)	All CR criteria except for residual neutropenia (<1.0 $\times 10^9/\text{L}$ [1000/ μL]) or thrombocytopenia (<100 $\times 10^9/\text{L}$ [100 000/ μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CR _i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR _{MRD} -, CR, CR _i , PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
Progressive disease (PD) ^{*,†}	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: <ul style="list-style-type: none"> >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level ($>0.5 \times 10^9/\text{L}$ [500/μL]), and/or platelet count to $>50 \times 10^9/\text{L}$ [50 000/μL] nontransfused); or >50% increase in peripheral blasts (WBC \times % blasts) to $>25 \times 10^9/\text{L}$ (>25 000/μL) (in the absence of differentiation syndrome)[‡]; or New extramedullary disease 	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR _{MRD} -, CR, CR _i)	Bone marrow blasts $\geq 5\%$; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR _{MRD} -)	If studied pretreatment, recurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

^{*}The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

[†]Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.