CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy
Plain Language Short Title:	Study of Magrolimab Versus Placebo in Combination With Venetoclax and Azacitidine in Participants With Acute Myeloid Leukemia (ENHANCE-3)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147229
EudraCT Number:	2021-003434-36
Clinical Trials.gov Identifier:	NCT05079230
Indication:	Acute Myeloid Leukemia
Protocol ID:	GS-US-590-6154
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 30 June 2021 Amendment 1: 08 September 2021 Amendment 2: 01 November 2021 Amendment 3: 29 November 2021 Amendment 3.1-FRA 13 December 2021 Amendment 4: 30 March 2022 Amendment 4.1-FRA 30 March 2022 Amendment 5: 27 July 2022 Amendment 6: 10 October 2023 Amendment 7: 15 December 2023 High-level summaries of amendments are provided in Appendix 16.
Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 15.

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

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EudraCT Number: 2021-003434-36

Clinical Trials.gov Identifier: NCT05079230

Study Centers Planned: Approximately 170 centers, globally

Objectives and Endpoints:

Objective	Endpoint
Primary:	
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in patients with previously untreated acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy as measured by overall survival (OS)	• OS, measured from the date of randomization to the date of death from any cause. Those whose deaths are not observed during the study will be censored at their last known alive date
Secondary:	
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of complete remission (CR) + complete remission with partial hematologic recovery (CRh) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of CR within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by event-free survival (EFS) • To evaluate the duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment	• Rate of CR + CRh within 6 cycles of treatment • Rate of CR within 6 cycles of treatment • EFS • Duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment • DCR in patients who achieved CR within 6 cycles of treatment • Rate of CR/CRh$_{MRD-}$ within 6 cycles of treatment • Rate of CR$_{MRD-}$ within 6 cycles of treatment • Transfusion independence conversion rate

• To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRh without minimal residual disease (MRD-) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR without minimal residual disease (CR_{MRD-}) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by conversion rate of transfusion dependence to transfusion independence • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by time to first deterioration (TTD) on the global health status/quality of life (GHS/QoL) and the physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • To assess the safety and tolerability of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab	• TTD on the GHS/QoL and the physical functioning scales of the EORTC QLQ-C30 • Incidence of treatment-emergent adverse events (AEs) and clinical laboratory abnormalities during the study • Magrolimab serum concentrations over time • Incidence/prevalence rate and magnitude of anti-magrolimab antibodies in serum

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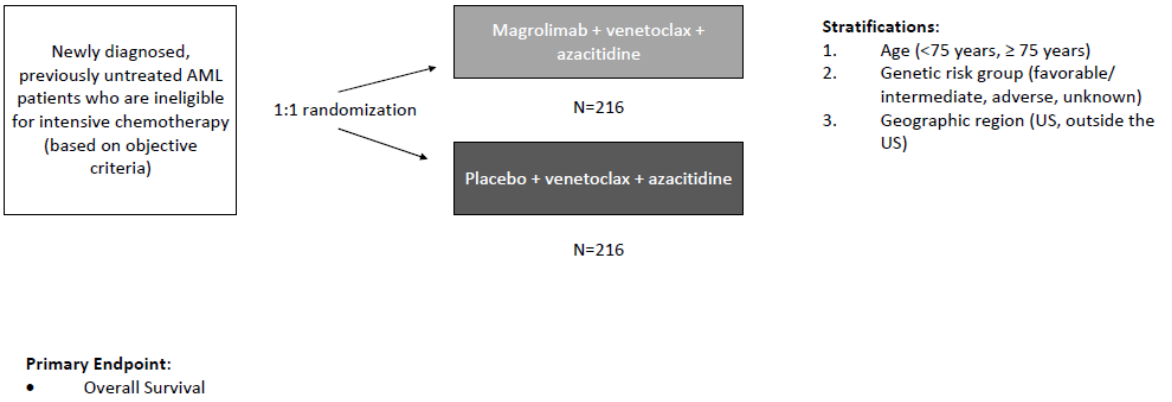
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRi without minimal residual disease (MRD-) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by EFS (including CR and CRh) • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by hematological improvement • To evaluate the duration of response (DOR) and the duration of CR + CRi achieved within 6 cycles of treatment • To evaluate minimal residual disease (MRD) negativity in patients with CR + CRh • To evaluate minimal residual disease (MRD) negativity in patients with CR + CRi • To evaluate minimal MRD negativity by flow cytometry and next generation sequencing (NGS) • To compare the rate of stem cell transplant (SCT) between magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To evaluate 30- and 60-day mortality in patients treated with magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To assess biomarkers of immune cell recruitment and immune cell signaling • To assess the mechanism of intrinsic and acquired resistance to magrolimab + venetoclax + azacitidine	• DOR in patients who achieved response within 6 cycles of treatment • Duration of CR + CRi achieved within 6 cycles of treatment • Rate of MRD negativity in patients with CR + CRi • Rate of MRD negativity in patients with CR + CRh • Rate of MRD negativity in patients with CR + CRi • Rate of MRD negativity by flow cytometry and NGS, and concordance between methods • Rate of SCT • 30- and 60-day mortality rate • Changes and percentage changes from baseline of biomarkers including biomarkers of immune cell recruitment or of immune cell signaling • Biomarkers related to resistance, including mutational profile of leukemic clones, and immune profile of tumor microenvironment

Study Design: This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of magrolimab versus placebo in combination with venetoclax and azacitidine in newly diagnosed, previously untreated patients with AML who are ineligible for intensive chemotherapy. Approximately 432 patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo + venetoclax + azacitidine (control arm). Randomization will be stratified by 3 factors:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown)
- geographic region (United States [US], outside the US)



The primary endpoint is OS. Two interim OS analyses will be conducted, the first one after 121 deaths (40% of the expected 303 deaths), and the second one after 227 deaths (75% of the expected 303 deaths) are observed among all patients; the primary OS analysis will be conducted after 303 deaths have occurred.

Number of Patients Planned: Approximately 432 patients in total

Target Population: Patients with untreated AML who are ≥ 18 years of age and ineligible for intensive chemotherapy

Duration of Treatment: Cycle length is 28 days and all patients will continue on study treatment unless they meet study treatment discontinuation criteria.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

1) Previously untreated patients with histological confirmation of AML by 2016 World Health Organization criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age, or comorbidity. Patients must be considered ineligible for intensive chemotherapy, defined by the following:
   a) ≥ 75 years of age

      Or

   b) ≥ 18 to 74 years of age with at least 1 of the following comorbidities:
      i) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3
      ii) Diffusing capacity of the lung of carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%
      iii) Left ventricular ejection fraction ≤ 50%

iv) Baseline creatinine clearance ≥ 30 mL/min to < 45 mL/min calculated by the Cockcroft Gault formula or measured by 24-hour urine collection

v) Hepatic disorder with total bilirubin > 1.5 × upper limit of normal (ULN)

vi) Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy that must be approved by the sponsor's medical monitor before study enrollment

2) ECOG performance status:

a) Of 0 to 2 for subjects ≥ 75 years of age

Or

b) Of 0 to 3 for subjects ≥ 18 to 74 years of age

3) Patients with white blood cell (WBC) count ≤ 20 × 10^3/µL prior to randomization. If the patient's WBC is > 20 ×10^3/µL prior to randomization, the patient can be enrolled, assuming all other eligibility criteria are met. However, the WBC should be ≤ 20 × 10^3/µL prior to the first dose of study treatment and prior to each magrolimab/placebo dose during Cycle 1.

NOTE: Patients can be treated with hydroxyurea and/or leukapheresis prior to randomization and throughout the study to reduce the WBC to ≤ 20 × $10^{3/}$µL to enable eligibility for study drug dosing.

4) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment based on complete blood count result.

NOTE: Transfusions are allowed to meet hemoglobin eligibility.

5) Patient has provided informed consent.

6) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.

7) Male or female, ≥ 18 years of age

8) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection.

9) Adequate liver function as demonstrated by:

a) aspartate aminotransferase ≤ 3.0 × ULN

b) alanine aminotransferase ≤ 3.0 × ULN

c) total bilirubin ≤ 1.5 × ULN, or primary unconjugated bilirubin ≤ 3.0 × ULN if patient has a documented history of Gilbert's syndrome or genetic equivalent

d) Patients ≥ 18 to 74 years of age may have total bilirubin ≤ 3.0 × ULN

10) Pretreatment RBC phenotype or genotype completed (Section 7.8.1).

11) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

12) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow assessments (aspirate and trephines). For France-specific requirements regarding bone marrow assessments, please see Appendix 15.

Exclusion Criteria:

1) Positive serum pregnancy test
2) Breastfeeding female
3) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.
4) Patients receiving any live vaccine within 4 weeks prior to initiation of study treatments.
5) Prior treatment with any of the following:
   a) CD47 or signal regulatory protein alpha-targeting agents
   b) Antileukemic therapy for the treatment of AML (eg, hypomethylating agents (HMAs), low-dose cytarabine, and/or venetoclax), excluding hydroxyurea

      NOTE: Patients with prior myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) who have not received prior HMAs or venetoclax or chemotherapeutic agents for MDS/MPN may be enrolled in the study. Prior treatment with MDS/MPN therapies including, but not limited to lenalidomide, erythroid-stimulating agents, or similar red blood cell (RBC-), WBC-, or platelet-direct therapies or growth factors is allowed for these patients.
6) Current participation in another interventional clinical study
7) Known inherited or acquired bleeding disorders
8) Patients who have received treatment with strong and/or moderate CYP3A inducers (eg, preparations containing St. John's wort) within 7 days prior to the initiation of study treatments
9) Patients who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment and are unwilling to discontinue consumption of these throughout the receipt of study drug
10) Patients who have malabsorption syndrome or other conditions that preclude enteral route of administration
11) Clinical suspicion of or documented active central nervous system (CNS) involvement with AML
12) Patients who have acute promyelocytic leukemia

13) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active, uncontrolled infection, and congestive heart failure New York Heart Association Class III to IV.

14) Known history, diagnosis, or suspicion of Hemophagocytic Lymphohistiocytosis (HLH) syndrome.

15) Second malignancy (except MDS), treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapies and have had no evidence of active malignancy for at least 1 year

    NOTE: Patients on maintenance therapy alone who have no evidence of active malignancy for at least ≥ 1 year are eligible.

    NOTE: Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy for prostate cancer, hormonal therapy or maintenance for breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are also not criteria for exclusion.

16) Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or HIV infection in medical history within 3 months of study entry.

17) Active HBV, and/or active HCV, and/or HIV following testing at screening:

    a) Patients who test positive for hepatitis B surface antigen and patients who test positive for hepatitis B core antibody will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

    b) Patients who test positive for HCV antibody will require HCV RNA quantitative PCR for confirmation of active disease.

    c) Patients who test positive for HIV antibody will require viral load testing; those who have an undetectable viral load in the prior 3 months may be eligible for the study.

Study Procedures/Frequency:

Following completion of screening and admission assessments, eligible patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo + venetoclax + azacitidine (control arm).

The study treatments within each arm are as follows:

Treatment Arm	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	**Cycle 2**	**Cycle 3+**
Experimental arm (magrolimab + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9
	Magrolimab Administration			
	Magrolimab 1 mg/kg IV (over 3 hours)	Days 1, 4		
	Magrolimab 15 mg/kg IV (over 3 hours)	Day 8		
	Magrolimab 30 mg/kg IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Magrolimab 30 mg/kg IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly 30 mg/kg dose		
Control arm (placebo + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1–5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1–7 or Days 1-5 and 8-9
	Placebo Administration			
	Placebo IV (over 3 hours)	Days 1, 4		
	Placebo IV (over 3 hours)	Day 8		
	Placebo IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Placebo IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly		

IV = intravenous; QW = every week; Q2W = every 2 weeks; SC = subcutaneous
a Azacitidine administered per region-specific labeling or within Days 1-9 of a 28-day cycle per protocol recommendation.

Cycle lengths are 28 days, and all patients will continue on study treatment until disease progression, relapse, loss of clinical benefit, unacceptable toxicities or other study treatment discontinuation criteria are met. Clinical benefit, as determined by the investigator, can include transfusion independence, adequate blood counts, symptomatic improvement, or other criteria as determined by the investigator.

Acute myeloid leukemia disease response assessment will be performed at the end of Cycle 1, Cycle 2, Cycle 4, Cycle 6, and every 3 cycles thereafter.

Patients will continue follow-up study visits unless they withdraw completely from the study.

All patients who discontinue study treatment for reasons other than death or start of new anti-AML therapy (except maintenance and SCT) will participate in long-term follow-up for disease response unless the patient withdraws consent for such follow-up and withdraws completely from study.

In the event one or more components of the study treatment (magrolimab/placebo, azacitidine and/or venetoclax) are discontinued, the following combinations are permitted:

- Magrolimab/placebo + azacitidine
- Azacitidine (single agent)
- Venetoclax + azacitidine

The following combinations are not permitted:

- Magrolimab/placebo (single agent)
- Venetoclax (single agent)
- Magrolimab/placebo + venetoclax

If azacitidine is permanently discontinued, the patient must discontinue the remaining study treatment. Patients who discontinue study treatment but continue in a response or are achieving clinical benefit will continue to be followed on study for response assessments to ascertain relapse and for long-term survival.

All patients will be followed for survival until death, withdrawal of consent, loss to follow-up, completion of survival follow-up, or study termination by the sponsor, whichever occurs first. Duration of survival follow-up will be limited to 5 years from the end of treatment visit for each patient. If a patient discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the patient's consent. However, an investigator may consult public records to establish survival status. For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

Test Product, Dose, and Mode of Administration:

Magrolimab 1 mg/kg intravenous (IV)

Magrolimab 15 mg/kg IV

Magrolimab 30 mg/kg IV

In combination with:

Venetoclax 10 mg oral

Venetoclax 50 mg oral

Venetoclax 100 mg oral

In combination with:

Azacitidine 75 mg/m^2 IV or SC

Reference Therapy, Dose, and Mode of Administration:

Placebo for Magrolimab IV

In combination with:

Venetoclax 10 mg oral

Venetoclax 50 mg oral

Venetoclax 100 mg oral

In combination with:

Azacitidine 75 mg/m^2 IV or SC

Criteria for Evaluation:

Safety:

Safety will be evaluated by data including the incidence of AEs, clinical laboratory test findings, physical examination, and vital signs measurements. Adverse events will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

Efficacy will be evaluated by OS, CR + CRh rate, CR rate, EFS, duration of CR + CRh, DCR, CR/CRh_{MRD-} rate, CR_{MRD-} rate, transfusion independence conversion rate, and GHS/QoL and physical functioning scale scores from EORTC QLQ-C30. Assessment of leukemia response in AML patients will be conducted using the European LeukemiaNet 2017 recommendations for AML and the 2003 and 2006 International Working Group criteria with modifications.

Pharmacokinetics:

Magrolimab serum drug concentrations will be assessed in the magrolimab + venetoclax + azacitidine group based on the sample collection schedule until treatment discontinuation. Samples will also be collected for the detection of antidrug antibodies (ADA) against magrolimab. Presence of neutralizing antibodies to magrolimab will also be assessed in the ADA positive samples.

Statistical Methods:

Analysis Data Set

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients according to the treatment arm to which the patient is randomized, unless otherwise specified. This is the primary analysis set for efficacy analysis.

Safety Analysis Set

The Safety Analysis Set will include all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received.

Efficacy Analysis

Time-to-event endpoints, including OS, EFS, DCR, and duration of CR + CRh, will be summarized using Kaplan-Meier estimates, which include median and the proportion of event-free patients at benchmark timepoints such as 6 months and 12 months. Kaplan-Meier plots will be provided.

Hypothesis testing will be performed on the ITT Analysis Set for OS and EFS using the log-rank test stratified by randomization stratification factors. The hazard ratio (HR) with the corresponding 2-sided 95% CIs estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will also be presented for OS and EFS.

Categorical endpoints including CR + CRh rate, CR rate, CR/CRh$_{MRD-}$ rate, CR$_{MRD-}$ rate, and transfusion independence conversion rate will be compared between the 2 arms using the Cochran-Mantel-Haenszel test stratified by randomization stratification factors. The point estimate of these rates and the corresponding 2-sided exact 95% CIs based on the exact Clopper-Pearson method will be provided for each treatment arm.

Time to first deterioration, with at least 1 threshold value deterioration from baseline or death, on the EORTC QLQ-C30 GHS/QoL scale and TTD on the EORTC QLQ-C30 physical functioning scale will be summarized using the Kaplan-Meier method. The log-rank test stratified by randomization stratification factors will be conducted for comparison between treatment arms, and the HR estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will be provided.

To strongly control the overall type I error across the testing of primary and key secondary endpoints, a hierarchical testing strategy will be performed with a predefined order as listed in the protocol and the statistical analysis plan.

Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications in the Safety Analysis Set by treatment arm. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized.

Interim Analysis

There are two planned interim analyses.

The first interim futility analysis of OS will be performed when 121 deaths (40% of the expected deaths) have occurred, with a non-bounding futility boundary of HR = 1.1.

The second interim analysis with O'Brien-Fleming boundary for efficacy will be performed when 227 deaths (75% of the expected 303 deaths) have occurred. If the null hypothesis of OS is not rejected in the interim analysis, the nonbinding futility test with a futility boundary of HR = 0.9 will be performed.

Primary Analysis

The primary analysis will be conducted when 303 death events occur.

Sample Size

The study will randomize approximately 432 patients in total into the control arm (placebo + venetoclax + azacitidine) and the experimental arm (magrolimab + venetoclax + azacitidine) at a 1:1 ratio, determined by formal hypothesis testing performed on the primary efficacy endpoint: OS, with family-wise Type I error controlled at 1-sided significance level of 0.025.

It is assumed that administration of magrolimab + venetoclax + azacitidine to study patients will result in a median OS of approximately 21 months, improved from a median OS of 14.7 months in patients treated with placebo + venetoclax + azacitidine. This corresponds to an OS HR of 0.7. Assuming that the duration of OS is exponentially distributed in each of the 2 arms, with an HR equal to 1 under the null hypothesis of no difference between the 2 treatment arms, 303 events are needed to detect an HR of 0.7 with 86.4% power at a 1-sided significance level of 0.025 using a log-rank test. The design includes the first interim analysis with a futility test only when 40% of the information (121 deaths) is available, and the second interim analysis with a superiority test together with a futility test when 75% of the information (227 deaths) is available, and one primary analysis. For the second OS interim analysis and the OS primary analysis, the Lan-DeMets alpha spending function with O'Brien-Fleming stopping boundary will be used. The futility boundaries for two interim analyses are obtained using a Gamma beta-spending function with parameter -5.

With an accrual period of 19 months (with approximately 51% of the patients enrolled during the initial 12 months, and the remaining 49% of the patients enrolled during the last 7 months), 24 months of follow up, and an annual 1.43% dropout rate (5% dropout chance by 43 months with time to dropout assuming exponentially distributed time-to-dropout), a total sample size of 432 patients (216 patients per treatment group) is needed to observe the required 303 events.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

5F9	magrolimab
ABO	any of the 4 blood groups A, B, AB, and O composing the ABO system
ADA	antidrug antibody
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AxMP	auxiliary medicinal product
AZA	azacitidine
BUN	blood urea nitrogen
CBC	complete blood count
cCR	cytogenetic complete remission
CD47	cluster of differentiation 47
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CR_{MRD-}	complete remission without minimal residual disease
$CR_{MRD+/unk}$	complete remission with positive or unknown minimal residual disease
CR/CRh_{MRD-}	complete remission or complete remission with partial hematologic recovery without minimal residual disease
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP3A	cytochrome P450 enzyme 3A
CXR	chest x-ray
DAT	direct antiglobulin test
DCR	duration of complete remission
DHHS	Department for Health and Human Services
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eCRF	electronic case report form
EFS	event-free survival
ELN	European LeukemiaNet
EOT	end-of-treatment
EQ VAS	EQ visual analogue scale
EQ-5D	EuroQoL (5 dimensions, 5 levels)
EU	European Union
FDA	Food and Drug Administration
Fc	crystallizable fragment
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GHS/QoL	global health status/quality of life
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GS	glutamine synthetase
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	Hemophagocytic Lymphohistiocytosis Syndrome
HMA	hypomethylating agent
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IgG4	immunoglobulin G4
IIS	investigator-initiated study
IND	investigational new drug
INR	international normalized ratio
IPSS-R	International Prognostic Scoring System
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	Intent-to-Treat
IUD	intrauterine device
IV	intravenous
IWG	International Working Group
LDH	lactate dehydrogenase

mAb	monoclonal antibody
Macro	macrophage
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MNS	any of the blood groups M, N, and S composing the MNS system
MOA	mechanism of action
MRD	minimal residual disease
MTD	maximum tolerated dose
MPN	myeloproliferative neoplasm
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamics
PDX	patient-derived xenograft
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	pharmacokinetics
PP	per protocol
PR	partial remission
PRO	patient-reported outcome
PS	patient safety
PT	prothrombin time
R/R	relapsed/refractory
RBC	red blood cell
Rh	Rhesus factor
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SCT	stem cell transplant
SD	stable disease
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

SIRPα	signal regulatory protein alpha
SOC	standard of care
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TLS	tumor lysis syndrome
TTD	time to first deterioration
ULN	upper limit of normal
US	United States
VEN	venetoclax
w/v	weight-to-volume ratio
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive clonal hematopoietic malignancy of myeloid cells in the blood and bone marrow leading to cytopenias and ultimately mortality via sequelae of bone marrow failure. The incidence of AML rises from 3 cases per 100,000 people in young adults to greater than 20 cases per 100,000 people in older adults. Initial treatment for AML is dependent on age and comorbidities. For patients < 60 years of age, 5-year overall survival (OS) is approximately 40% to 50% but is only 5% for patients > 60 years of age. For younger patients who are fit for intensive chemotherapy, induction chemotherapy with cytarabine and an anthracycline chemotherapy is the standard of care (SOC). In patients who are older and/or have comorbidities that preclude the use of induction chemotherapy, lower-intensity therapy is given with hypomethylating agents (HMAs) and low-dose cytarabine, with or without venetoclax, a Bcl-2 inhibitor. In all settings of AML, disease relapse is common despite an initial therapeutic response and is the most common reason for death.

1.1.2. Patients Newly Diagnosed with AML Who Are Ineligible for Intensive Induction Chemotherapy

Patients who are older (approximately 75 years of age and older) or who have comorbidities precluding the use of intensive induction chemotherapy are treated with HMAs (ie, azacitidine or decitabine), low-dose cytarabine, and these agents in combination with venetoclax. In 2018, venetoclax in combination with HMAs or low-dose cytarabine was granted accelerated approval in the United States (US) for this population. This approval was based on results from multiple single-arm studies in which venetoclax demonstrated a complete remission (CR) rate of 37% in combination with azacitidine, 54% in combination with decitabine, and 21% in combination with low-dose cytarabine {VENCLEXTA 2020}. The median duration of CR was approximately 4.8 to 6.0 months. Final results from a subsequent randomized Phase 3 trial that evaluated venetoclax + azacitidine versus azacitidine monotherapy in the same patient population demonstrated a significant benefit in median OS compared with the control arm (14.7 vs 9.6 months, hazard ratio [HR] 0.66) {DiNardo 2020}. In addition, the CR/complete remission with incomplete hematologic recovery (CRi) rate was higher in the venetoclax + azacitidine arm than the azacitidine control arm (66.4% vs. 28.3%). These data have supported the use of venetoclax in combination with HMAs as the SOC for newly diagnosed patients with AML who are ineligible for intensive chemotherapy.

1.2. Magrolimab

1.2.1. General Information

Cluster of differentiation 47 (CD47) is a key molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic

"eat me" signals {Jaiswal 2009, Majeti 2009}. The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal {Chao 2012}. Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint {Chao 2012}. Increased CD47 expression was identified first on leukemic stem cells in human AML {Majeti 2009}, and since then it has been found that CD47 expression is increased on the surface of cancer cells in a diverse set of human tumor types.

In mouse xenograft models, CD47-blocking monoclonal antibodies (mAbs) inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors {Chao 2011a, Chao 2010a, Chao 2011b, Edris 2012, Kim 2012, Majeti 2009, Willingham 2012}. Binding of CD47 expressed by cancer cells to its ligand, signal regulatory protein alpha (SIRPα), expressed on phagocytes leads to inhibition of tumor cell phagocytosis. Thus, blockade of the CD47 SIRPα–signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of prophagocytic signals expressed mainly on tumor cells and not on normal cell counterparts {Chao 2010b}. In addition, the anti-CD47 antibody can induce an anti-cancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis {Liu 2015b, Tseng 2013}.

Magrolimab is a humanized anti-CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells {Liu 2015a}. The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of crystallizable fragment (Fc)–dependent effector functions, although the presence of the immunoglobulin G4 (IgG4) Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells {Liu 2015a}. Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

The magrolimab program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia, non-Hodgkin lymphoma [NHL], myeloma, myelodysplastic syndrome [MDS], and others).

Magrolimab is being investigated as an anti-cancer therapeutic in several global ongoing clinical studies, as monotherapy or in combination with other therapeutics, for the treatment of NHL, AML, MDS, and several solid tumor types.

While magrolimab has single-agent preclinical and clinical activity, efficacy is best enhanced in combination with other anti-cancer agents. Preclinical and clinical studies have shown that magrolimab combinations with cytotoxic agents can enhance prophagocytic signals on tumor cells, which can lead to synergistic phagocytosis of cancer cells by macrophages. As such, magrolimab is being evaluated clinically in several combinations with cytotoxic agents including chemotherapy.

For further information on magrolimab, refer to the current investigator's brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

The combination of magrolimab + azacitidine was evaluated in leukemic nonclinical models. Nonclinical synergy was observed based on the upregulation of prophagocytic signals (including calreticulin) on leukemic cells of a *TP53* mutated cell line by azacitidine combined with blockade of the antiphagocytic signal CD47 with magrolimab {Feng 2018}. Magrolimab + azacitidine led to synergistic phagocytosis of leukemic cells in vitro and near 100% long-term durable remissions in an aggressive nonclinical leukemia mouse model, compared with modest effects with either monotherapy. These data support the mechanistic and nonclinical rationale for combining magrolimab with azacitidine in AML. Further nonclinical data including efficacy, toxicology, and pharmacology are provided in the current IB.

1.2.3. Clinical Studies of Magrolimab

1.2.3.1. Summary of Clinical Pharmacology

Clinical pharmacokinetic (PK) data have been collected in all ongoing studies of magrolimab conducted to date. Pharmacokinetic data have been analyzed in a Phase 1 study (SCI-CD47-001) in patients with solid tumors. In this study, patients were treated with weekly magrolimab doses ranging from 0.1 to 45 mg/kg, with increasing plasma concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance was observed over this dose range. However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen, and trough levels associated with magrolimab efficacy in nonclinical studies were achieved. Nine of 88 (10%) evaluable patients tested positive for antidrug antibody (ADA) against magrolimab at any time point including baseline; ADA positivity had no impact on PK or clinical safety in these patients.

In a Phase 1 AML study (SCI-CD47-002), similarly to the solid tumor Phase 1 study, nonlinear PK consistent with target-mediated clearance was observed. Three of 20 (15%) evaluable patients tested positive for ADA against magrolimab at any time point including baseline; ADA positivity had no impact on PK. Antidrug antibody positivity in either study was not associated with increased adverse events (AEs).

Preliminary PK data of magrolimab from other ongoing studies (5F9003, 5F9004, 5F9005, and 5F9006) indicate similar PK properties across all tumor populations and in the presence of co-administered drugs. Across all studies, 34 of 507 (6.7%) patients tested positive for ADA against magrolimab at any time point including baseline. Antidrug antibody positivity was not associated with changes in PK or AE profile.

A preliminary population PK analysis of combined magrolimab PK data indicated that results for magrolimab population PK were typical of other nonlinear antibodies. No clinically significant covariates of PK variability were identified.

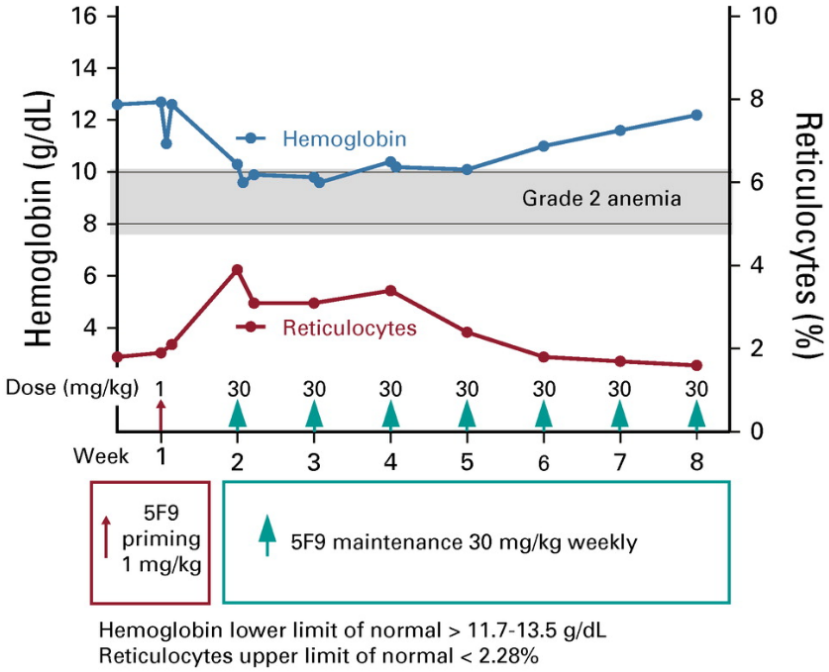
1.2.3.2. Summary of Clinical Safety

Magrolimab is administered as an intravenous (IV) infusion and it is being studied in several clinical studies in MDS, AML, and solid tumors.

Magrolimab has been evaluated as a monotherapy or in combination in multiple solid tumor types. In the Phase 1 study SCI-CD47-001 of magrolimab monotherapy, 88 patients with advanced solid tumors were treated with magrolimab doses up to 45 mg/kg. No maximum tolerated dose (MTD) was reached. Across 548 patients treated with magrolimab, including patients with both solid tumors and hematologic malignancies, fatigue, anemia, and headache were the 3 most frequently reported AEs (43.0%, 40.8%, and 36.4% of patients, respectively). Patients experienced mostly Grade 1 and 2 fatigue (2.8% of patients reported severe fatigue).

Anemia is the most common treatment-related AE, reported in 35.4% of patients. Approximately 13% of all patients experienced anemia Grade 1 or 2, and 22% experienced severe anemia. Notably, many events of severe anemia occurred in patients with AML and MDS who had severe anemia at baseline. Anemia was typically manifested as a decline in hemoglobin observed within the first 2 weeks of treatment. The initial decrease in hemoglobin after the first dose averages 0.4 to 1.5 g/dL, with hemoglobin improving in many patients on therapy back to baseline, with a decrease in red blood cell (RBC) transfusion requirements for those patients who were transfusion-dependent at baseline. In patients with solid tumors, the decrease in hemoglobin was followed by a compensatory reticulocytosis, with many patients experiencing a gradual return to baseline despite continued dosing. The changes in hemoglobin and reticulocytes described with magrolimab treatment are fairly consistent across tumor types and are shown in Figure 1. Hyperbilirubinemia (predominately unconjugated) indicates extravascular hemolysis consistent with phagocytic removal of RBCs arising from the blockade of CD47 signaling. Administration of a low priming dose of magrolimab mitigated on-target anemia, an effect that is mostly observed after the first dose.

Figure 1. Effect of Magrolimab on Anemia, and Mitigation with a Priming/Maintenance Dosing Regimen



5F9 = magrolimab
The red blood cell profile of a solid tumor patient treated with magrolimab monotherapy is shown {Sikic 2019}.

Infusion-related reactions (IRRs) are also a commonly reported AE with magrolimab. Of 548 patients across 5 studies, 29% had at least 1 IRR. Most common signs and symptoms of IRR related to magrolimab included chills, pyrexia, back pain, headache, nausea, vomiting, dyspnea, anemia, and blood bilirubin increase. These IRRs were generally observed during the initial 2 doses of magrolimab. Current recommendations for premedication and IRR management are described in Sections 5.5.3 and 5.5.4.

Lastly, hemagglutination (RBC agglutination) as observed on the peripheral smear is a common treatment effect and was reported as a treatment-related AE in 11.8% of all patients. Transient hemagglutination is observed after the initial priming or first maintenance dose of drug; however, it is less common thereafter, and has not been consistently correlated with any clinical sequelae.

As of December 2020, 52 untreated induction chemotherapy-ineligible AML patients have been enrolled in Study 5F9005 and received the combination of magrolimab + azacytidine {Sallman 2020b}. The safety profile of magrolimab in combination with azacitidine was acceptable and consistent with azacitidine monotherapy, with no significant increases in cytopenias or immune-related AEs. No MTD was reached with magrolimab dosing of 30 mg/kg weekly. The most common treatment-related AEs with magrolimab were anemia (31%), fatigue (19%), blood bilirubin increased (19%), neutropenia (19%), thrombocytopenia (17%), and nausea (15%). Treatment discontinuation due to any drug-related AEs occurred in 2 of 52 patients (3.8%).

The most common treatment-emergent adverse events (TEAE) reported in > 10% of frontline AML patients treated with magrolimab and azacitidine are presented in Table 1 (data on file). The most common TEAEs reported in > 10% of AML patients with the *TP53* mutation are presented in Table 2 (data on file) and are similar to those reported in all AML patients.

Additional patients continue to be enrolled on the Phase 1b study. In addition, a randomized Phase 3 study (GS-US-546-5857) of magrolimab in combination with azacitidine versus venetoclax plus azacitidine in previously untreated patients with AML with the *TP53* mutation who are ineligible for intensive induction chemotherapy is planned to initiate in 2021.

Table 1. Study 5F9005: Treatment Emergent Adverse Events Reported in > 10% of Subjects with First-Line Unfit AML (biomarker unselected) Treated with Magrolimab and Azacitidine by Preferred Term

Preferred Term	All Grades n (%) N = 64
Nausea	29 (45.3)
Febrile neutropenia	28 (43.8)
Constipation	27 (42.2)
Diarrhoea	24 (37.5)
Fatigue	23 (35.9)
Decreased appetite	22 (34.4)
Anaemia	20 (31.3)
Dizziness	18 (28.1)
Abdominal pain	17 (26.6)
Platelet count decreased	17 (26.6)
Pyrexia	17 (26.6)
Fall	16 (25.0)
Oedema peripheral	16 (25)
Blood bilirubin increased	15 (23.4)
Hypokalaemia	15 (23.4)
Chills	14 (21.9)
Cough	14 (21.9)
Dyspnoea	14 (21.9)
Hypophosphataemia	14 (21.9)
Confusional state	13 (20.3)
Epistaxis	13 (20.3)

Preferred Term	All Grades n (%) N = 64
Vomiting	13 (20.3)
Alanine aminotransferase increased	12 (18.8)
Hypotension	12 (18.8)
Pneumonia	12 (18.8)
White blood cell count decreased	12 (18.8)
Arthralgia	10 (15.6)
Insomnia	10 (15.6)
Aspartate aminotransferase increased	9 (14.1)
Headache	9 (14.1)
Neutropenia	9 (14.1)
Neutrophil count decreased	9 (14.1)
Thrombocytopenia	9 (14.1)
Anxiety	8 (12.5)
Asthenia	8 (12.5)
Hyponatraemia	8 (12.5)
Muscular weakness	8 (12.5)
Weight decreased	8 (12.5)
Contusion	7 (10.9)
Dyspepsia	7 (10.9)
Hypomagnesaemia	7 (10.9)
Hypoxia	7 (10.9)
Pleural effusion	7 (10.9)
Rash maculo-papular	7 (10.9)

AE = adverse event; AML = acute myeloid leukemia
Treatment emergent AEs are defined as AEs with onset date between the first treatment date and 30 days after the last treatment date.
AEs are coded according to MedDRA v23.1.
Data extracted 04 November 2020

Table 2. Study 5F9005: Treatment Emergent Adverse Events Reported in > 10% of Subjects with First-Line TP53-Mutated Unfit AML Treated with Magrolimab and Azacitidine by Preferred Term

Preferred Term	All Grades n (%) N = 47
Febrile neutropenia	24 (51.1)
Constipation	20 (42.6)
Diarrhoea	18 (38.3)
Nausea	18 (38.3)
Decreased appetite	17 (36.2)
Fatigue	17 (36.2)
Abdominal pain	14 (29.8)
Anaemia	14 (29.8)
Dizziness	14 (29.8)
Oedema peripheral	13 (27.7)
Blood bilirubin increased	12 (25.5)
Cough	12 (25.5)
Hypophosphataemia	12 (25.5)
Fall	11 (23.4)
Hypokalaemia	11 (23.4)
Infusion-related reaction	11 (23.4)
Platelet count decreased	11 (23.4)
Vomiting	11 (23.4)
Chills	10 (21.3)
Hypotension	10 (21.3)
Pneumonia	10 (21.3)
Epistaxis	9 (19.1)
Pyrexia	9 (19.1)
White blood cell count decreased	9 (19.1)
Alanine aminotransferase increased	8 (17.0)
Headache	8 (17.0)
Aspartate aminotransferase increased	7 (14.9)
Confusional state	7 (14.9)
Pleural effusion	7 (14.9)

Preferred Term	All Grades n (%) N = 47
Anxiety	6 (12.8)
Arthralgia	6 (12.8)
Contusion	6 (12.8)
Dyspnoea	6 (12.8)
Hypomagnesaemia	6 (12.8)
Hyponatraemia	6 (12.8)
Muscular weakness	6 (12.8)
Weight decreased	6 (12.8)
Acute kidney injury	5 (10.6)
Hypoxia	5 (10.6)
Injection site reaction	5 (10.6)
Neutrophil count decreased	5 (10.6)
Pruritis	5 (10.6)
Sinus Tachycardia	5 (10.6)
Thrombocytopenia	5 (10.6)
Urinary incontinence	5 (10.6)

AE = adverse event; AML = acute myeloid leukemia
Treatment emergent AEs are defined as AEs with onset date between the first treatment date and 30 days after the last treatment date.
AEs are coded according to MedDRA v23.1.
Data extracted 04 November 2020

1.2.3.3. Summary of Clinical Safety and Efficacy of Magrolimab + Venetoclax + Azacitidine in AML

In Study 5F9005, clinical activity was assessed for magrolimab + azacitidine in patients with treatment-naive/unfit AML and treatment-naive intermediate to higher risk (by Revised International Prognostic Scoring System [IPSS-R]) MDS {Sallman 2020b}. As of December 2020, a total of 52 AML patients (including 65% with *TP53* mutation) were treated with magrolimab + azacitidine and 34 of them were evaluable for efficacy. The objective response rate (ORR) was 65% (22 patients), with 44% achieving a CR, 12% achieving CRi, 3% achieving partial response, and 6% achieving morphologic leukemia-free state (MLFS). Time to response was rapid, with a median of 2.04 months. Of the responding patients who had abnormal cytogenetics at baseline, 47% achieved complete cytogenetic response. Additionally, 37% of responding AML patients achieved minimal residual disease (MRD) negativity, as assessed by multiparametric flow cytometry. In AML patients harboring TP53 mutations, the ORR was 71% (15 of 21 patients) with a CR rate of 48% (10 of 21 patients), 19% (4 of 21 patients) of patients achieving CRi, and 5% (1 of 21 patients) achieving MLFS {Sallman 2020b}. The

efficacy of magrolimab + azacitidine appears improved compared to azacitidine monotherapy based on data from historical trials, in which CR rates are between 10% and 20%. High rates of MRD negativity and prolonged OS are encouraging.

An investigator-initiated study (IIS) sponsored by the MD Anderson Cancer Center (protocol ID 2020-0027) commenced in the second half of 2020 to evaluate the safety, tolerability, recommended Phase 2 dose, and preliminary efficacy of magrolimab in combination with azacitidine and venetoclax in patients with relapsed/refractory (R/R) AML and patients with newly diagnosed AML who are ineligible for intensive chemotherapy or with poor-risk karyotype or molecular markers. In the 6 patients with R/R AML enrolled in the safety run-in cohort, no dose-limiting toxicity (DLT) was reported. None of the 19 patients with AML (9 frontline and 10 R/R) enrolled before 01 March 2021 died within 60 days of receiving their first dose of study drugs. Of the 9 newly diagnosed patients with AML considered ineligible for intensive therapy due to age/comorbidities/poor-risk karyotype or molecular markers, the ORR was 88.9 % (CR of 66.7% and CRi of 22.2%). Out of these 9 first-line AML patients, 5 harbored *TP53* mutations and ORR in this population was 80 % (CR and CRi of 40% respectively).

Adverse events reported in more than 2 patients in the IIS are presented in Table 3 (data on file). Adverse events reported in more than 2 patients in the IIS with the *TP53* mutation are presented in Table 4 (data on file) and are similar to those reported in all AML patients.

Overall, these preliminary data suggest that the combination of magrolimab with azacitidine and venetoclax has an acceptable safety profile and encouraging clinical efficacy in limited follow up in frontline AML ineligible for intensive chemotherapy (Unpublished data, PPD Anderson Cancer Center, MDACC).

Table 3. 2020-0027: MDACC Investigator Initiated Study: Adverse Events Reported in ≥ 2 Subjects with AML Treated with Magrolimab + Venetoclax + Azacitidine by Preferred Term

Preferred Term	All Grades n (%) N = 19
Blood bilirubin increased	11 (57.9)
Dizziness	11 (57.9)
Hypophosphatemia	11 (57.9)
Fever	10 (52.6)
Hypokalemia	10 (52.6)
Anorexia	9 (47.4)
Fatigue	9 (47.4)
Hyponatremia	9 (47.4)
Insomnia	9 (47.4)
Nausea	9 (47.4)

Preferred Term	All Grades n (%) N = 19
Sinus tachycardia	9 (47.4)
Constipation	8 (42.1)
Cough	8 (42.1)
Dyspnea	8 (42.1)
Edema limbs	8 (42.1)
Bruising	7 (36.8)
Diarrhea	7 (36.8)
Febrile neutropenia	7 (36.8)
Hypotension	7 (36.8)
Alanine aminotransferase increased	6 (31.6)
Alkaline phosphatase increased	6 (31.6)
Epistaxis	6 (31.6)
Generalized muscle weakness	6 (31.6)
Headache	6 (31.6)
Hypoalbuminemia	6 (31.6)
Infections	6 (31.6)
Lung infection	6 (31.6)
Abdominal pain	5 (26.3)
Back pain	5 (26.3)
Chills	5 (26.3)
Hypocalcemia	5 (26.3)
Hypomagnesemia	5 (26.3)
Mucositis oral	5 (26.3)
Paresthesia	5 (26.3)
Pruritus	5 (26.3)
Vomiting	5 (26.3)
Arthralgia	4 (21.1)
Gait disturbance	4 (21.1)
Hyperglycemia	4 (21.1)
Pain	4 (21.1)
Sepsis	4 (21.1)
Anxiety	3 (15.8)

Preferred Term	All Grades n (%) N = 19
Creatinine increased	3 (15.8)
Dental caries[a]	3 (15.8)
Ear pain	3 (15.8)
Erythema multiforme	3 (15.8)
Fall	3 (15.8)
Hematuria	3 (15.8)
Infusion-related reaction	3 (15.8)
Pain in extremity	3 (15.8)
Peripheral motor neuropathy	3 (15.8)
Rectal pain	3 (15.8)
Skin infection	3 (15.8)
Sore throat	3 (15.8)
Anemia	2 (10.5)
Bacteremia	2 (10.5)
Blurred vision	2 (10.5)
Flank pain	2 (10.5)
Myalgia	2 (10.5)
Papulopustular rash	2 (10.5)
Platelet count decreased	2 (10.5)
Pleural effusion	2 (10.5)
Rash pustular	2 (10.5)
Respiratory failure	2 (10.5)
Somnolence	2 (10.5)
Spinal cord compression	2 (10.5)
Thrush	2 (10.5)
Deep vein thrombosis	2 (10.5)

AML = acute myeloid leukemia; MDACC = MD Anderson Cancer Center
a Not coded by MedDRA
Multiple events were counted only once per subject.
Data extracted 20 April 2021

Table 4. 2020-0027: MDACC Investigator Initiated Study: Adverse Events Reported in ≥ 2 Subjects with TP53 mutated AML Treated with Magrolimab + Venetoclax + Azacitidine by Preferred Term

Preferred Term	All Grades n (%) N = 11
Dizziness	8 (72.7)
Hypophosphatemia	7 (63.6)
Constipation	6 (54.5)
Hypokalemia	6 (54.5)
Insomnia	6 (54.5)
Sinus tachycardia	6 (54.5)
Blood bilirubin increased	5 (45.5)
Cough	5 (45.5)
Dyspnea	5 (45.5)
Edema limbs	5 (45.5)
Fatigue	5 (45.5)
Fever	5 (45.5)
Generalized muscle weakness	5 (45.5)
Hyponatremia	5 (45.5)
Hypotension	5 (45.5)
Anorexia	4 (36.4)
Bruising	4 (36.4)
Diarrhea	4 (36.4)
Epistaxis	4 (36.4)
Febrile neutropenia	4 (36.4)
Hypoalbuminemia	4 (36.4)
Hypokalemia	4 (36.4)
Hypomagnesemia	4 (36.4)
Infection	4 (36.4)
Mucositis oral	4 (36.4)
Nausea	4 (36.4)
Alanine aminotransferase increased	3 (27.3)
Anxiety	3 (27.3)
Back pain	3 (27.3)

Preferred Term	All Grades n (%) N = 11
Chills	3 (27.3)
Fall	3 (27.3)
Gait disturbance	3 (27.3)
Headache	3 (27.3)
Lung infection	3 (27.3)
Peripheral motor neuropathy	3 (27.3)
Pruritus	3 (27.3)
Sepsis	3 (27.3)
Vomiting	3 (27.3)
Abdominal pain	2 (18.2)
Alkaline phosphatase increased	2 (18.2)
Anemia	2 (18.2)
Arthralgia	2 (18.2)
Blurred vision	2 (18.2)
Creatinine increased	2 (18.2)
Dental caries	2 (18.2)
Ear pain	2 (18.2)
Erythema multiforme	2 (18.2)
Hematuria	2 (18.2)
Hyperglycemia	2 (18.2)
Pain in extremity	2 (18.2)
Paresthesia	2 (18.2)
Rectal pain	2 (18.2)
Skin infection	2 (18.2)
Spinal cord compression	2 (10.5)

AML = acute myeloid leukemia; MDACC = MD Anderson Cancer Center
Data extracted 20 April 2021

For further clinical efficacy and safety information of magrolimab in other indications, refer to the current magrolimab IB.

1.3. Information About Venetoclax, Azacitidine

1.3.1. Description of Venetoclax

Venetoclax is a selective, orally bioavailable, small-molecule Bcl-2 family inhibitor that binds with high affinity (inhibitory constant < 0.010 nM) {Souers 2013}.

Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance {Fesik 2005}. Overexpression of Bcl-2 has been demonstrated in AML and chronic lymphocytic leukemia (CLL) cells, where it mediates cell survival and resistance to chemotherapeutic agents. Venetoclax restores apoptosis by binding to Bcl-2 protein, thereby displacing pro-apoptotic proteins such as bcl-2–interacting mediator of cell death, triggering mitochondrial outer membrane permeabilization and the activation of caspases. Venetoclax has demonstrated cell-killing activity against patient-derived CLL cells and AML cells and a variety of lymphoma and leukemia cell lines.

In the US, venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine is approved for the treatment of newly diagnosed AML in adults who are ≥ 75 years of age, or who have comorbidities that preclude use of intensive induction chemotherapy {VENCLEXTA 2020}.

In the European Union (EU), venetoclax monotherapy is approved for the treatment of adult patients with CLL and for use in combination with hypomethylating agents for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. For additional information on venetoclax, please refer to the prescribing information.

1.3.2. Description of Azacitidine

Azacitidine is a nucleoside analog, specifically a chemical analog of cytidine. Azacitidine has 2 known primary antineoplastic MOAs: 1) inhibition of DNA methyltransferase leading to hypomethylation of DNA and 2) direct cytotoxicity of malignant hematopoietic cells through cell death via its incorporation into DNA and RNA.

Azacitidine is a SOC and approved in the US for treatment of subtypes of MDS including, but not limited to, MDS with refractory anemia with excess blasts, a subtype that is mostly composed of patients with intermediate- to very high-risk MDS by IPSS-R criteria {VIDAZA 2018}. Azacitidine is also an SOC therapy for previously untreated patients with AML who are ineligible for induction chemotherapy or SCT based on age, comorbidities, or other factors. In Europe, azacitidine is approved for patients with intermediate-2 and high-risk MDS according to International Prognostic Scoring System criteria and for patients with AML who are ineligible for SCT. For additional information on azacitidine, refer to the prescribing information.

1.3.3. Clinical Data for Venetoclax + Azacitidine

Venetoclax in combination with azacitidine or decitabine was studied in M14-358, a non-randomized, open-label clinical study involving patients with newly diagnosed AML {VENCLEXTA 2020}. Sixty-seven of the 84 patients who received venetoclax with azacitidine were ≥ 75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy. Patients received venetoclax after a 5-week ramp-up to a final 400-mg once-daily oral dose and azacitidine at the standard dosing. The median follow-up was 15.9 months (range: 0.4 to 40.3 months). Forty-three percent (29 of 67 patients) achieved a CR (95% CI: 31%, 56%) and 18% (12 of 67 patients) achieved a CR with partial hematologic recovery (CRh) (95% CI: 9.6%, 29%). Median time to first CR or CRh was 1.0 month (range: 0.7 to 8.9 months). The median duration of CR was 23.8 months (95% CI: 15.4, –) and the median duration of CR or CRh was 26.5 months (95% CI: 17.4, –). Of patients treated with venetoclax in combination with azacitidine, 12% (8 of 67) subsequently received SCT. Seventeen of the 84 patients who received venetoclax with azacitidine were 65 to 74 years of age and did not have known comorbidities that precluded the use of intensive induction chemotherapy. For the 17 patients treated with venetoclax in combination with azacitidine, the CR rate was 35% (95% CI: 14%, 62%) and the CRh rate was 41% (95% CI: 18%, 67%). Nine patients (53%) subsequently received SCT. The most common AEs of any grade observed with patients treated with venetoclax and azacitidine or venetoclax and decitabine were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%).

The Phase 3 randomized, double-blind, placebo-controlled study VIALE-A, investigating venetoclax in combination with azacitidine versus azacitidine in combination with placebo in treatment-naive AML patients who are ineligible for intensive chemotherapy, confirms the efficacy of venetoclax + azacitidine with a statistically significant improvement in OS. Median OS with venetoclax + azacitidine was 14.7 months, while the median OS with azacitidine + placebo was 9.6 months (HR 0.66 [95% CI: 0.52, 0.85]; $p < .001$) {DiNardo 2020}. Safety of the combination in VIALE-A was similar to what had been previously reported and can be managed with standard supportive care.

1.3.4. Information About Auxiliary Medicinal Products/Noninvestigational Products

Acetaminophen (also known as paracetamol), diphenhydramine, and corticosteroids (dexamethasone) are considered auxiliary medicinal products (AxMPs) for this clinical study (Appendix 14). Acetaminophen is approved for pain relief and fever reduction. Diphenhydramine is an antihistamine and is used for amelioration of allergic reactions. Corticosteroids are anti-inflammatory medications and are used for the amelioration of allergic reactions. The use of these medications on this study is described in Section 5.5.4.

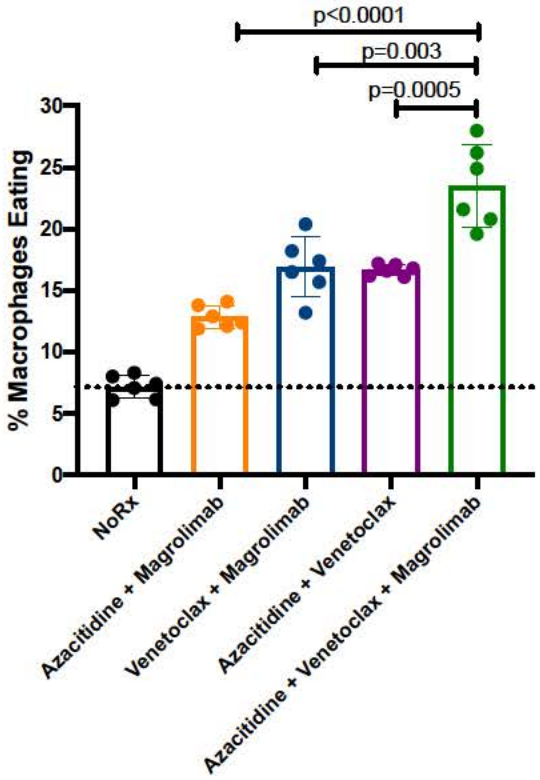
Additional details on acetaminophen, diphenhydramine, and corticosteroids can be found in the prescribing information.

1.4. Rationale for This Study

Magrolimab is under clinical evaluation in combination with azacitidine in the ongoing Phase 1b study, 5F9005, in patients with AML who are previously untreated and ineligible for intensive induction chemotherapy. Among 34 evaluable patients, 65% achieved an OR and 44% achieved a CR. Time to response was rapid (median 2.04 months) {Sallman 2020a}. Clinical activity has also been observed in patients with the *TP53* mutation, a poor-risk subgroup with an overall response rate of 71%. Median OS was 12.9 months in patients with the *TP53* mutation and 18.9 months in patients with wild-type *TP53*. Given the encouraging efficacy data observed with the magrolimab plus azacitidine and venetoclax plus azacitidine double combinations, the triple combination of magrolimab plus azacitidine plus venetoclax is anticipated to show superior activity over either double combination. In terms of safety, the addition of magrolimab to venetoclax and azacitidine is not anticipated to have overlapping toxicities, as magrolimab monotherapy does not cause myelosuppression, which is a key toxicity of venetoclax and azacitidine. These hypotheses are supported by preliminary data from the MD Anderson Cancer Center IIS that have shown no DLT, no deaths within 60 days of the first dose of study drugs, and signs of encouraging early efficacy in patients treated with the combination of magrolimab with azacitidine and venetoclax in frontline AML. Emerging data from this study have informed design elements for the current study.

Furthermore, nonclinical data demonstrate that venetoclax can enhance magrolimab-mediated phagocytosis, which can be further enhanced by azacitidine (Figure 2).

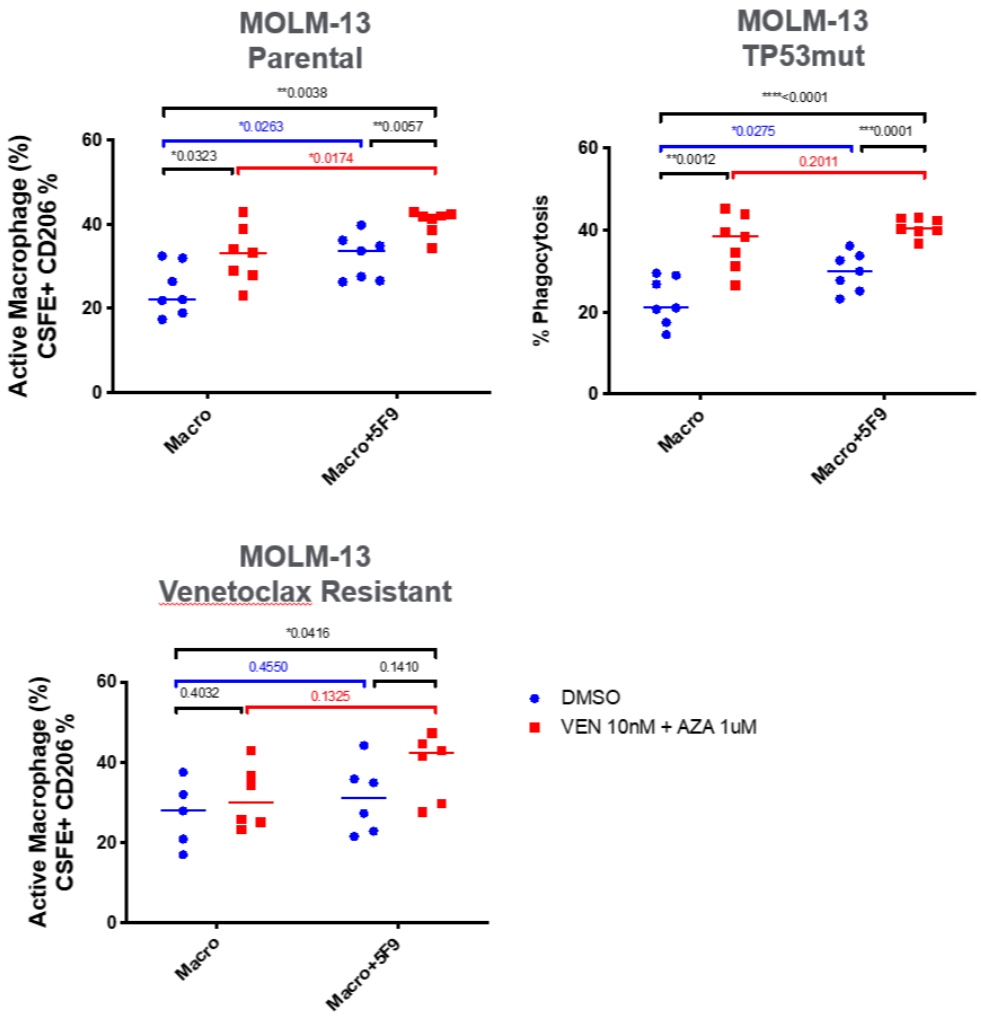
Figure 2. **In Vitro Phagocytosis of AML Cells with Magrolimab, Azacitidine and/or Venetoclax**



AML = acute myeloid leukemia; Rx = treatment
Human macrophages were incubated with AML HL60 cells in the presence of the indicated therapeutic agents with macrophage phagocytosis of AML cells measured.

Additional nonclinical study in vitro suggests that in a variety of AML-derived cell lines, including sub-lines with intrinsic resistance to venetoclax + azacitidine-induced cytotoxicity, these agents can nonetheless increase phagocytosis by macrophages, likely due to upregulation of prophagocytic signals on the cell surface. Furthermore, co-treatment with magrolimab can further increase phagocytosis in combination with venetoclax and azacitidine (Figure 3).

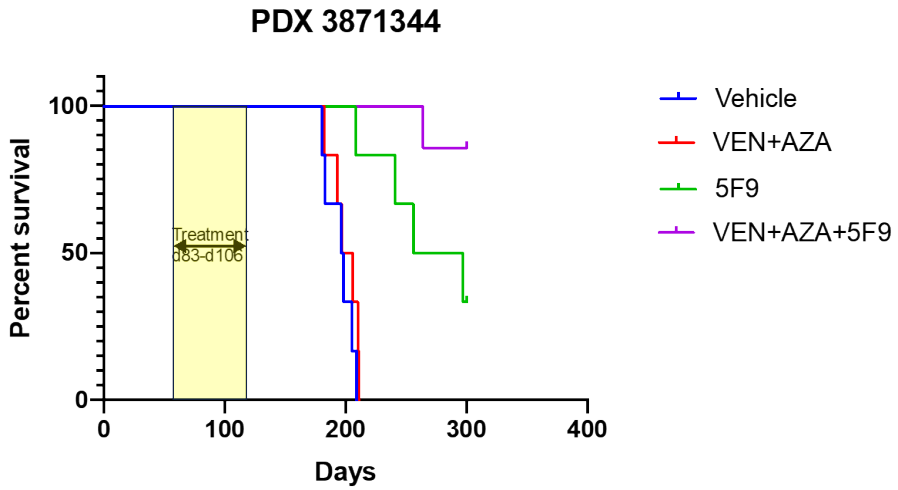
Figure 3. Magrolimab-Induced In Vitro Phagocytosis of AML Cells Resistant to Venetoclax and Azacitidine Cytotoxicity



5F9 = magrolimab; AZA = azacitidine; DMSO = vehicle control; Macro = macrophage; VEN = venetoclax
Human macrophages were incubated with either MOLM-13 AML cells, or VEN + AZA resistant sub-lines in the presence of the indicated therapeutic agents. Phagocytosis indicated on *y* axis was quantified by flow cytometry.
Unpublished data, Marina Konopleva Lab, MD Anderson Cancer Center

Magrolimab, venetoclax, and azacitidine have been tested in combination in an in vivo model of primary human AML engrafted into immunocompromised mice. Following engraftment and detectable disease burden in the peripheral blood, mice were treated with vehicle control, a combination of venetoclax and azacitidine, magrolimab (5F9), or a combination of magrolimab, venetoclax, and azacitidine. In this model, venetoclax plus azacitidine has no efficacy; in contrast, magrolimab monotherapy significantly extends survival. The combination of magrolimab plus venetoclax plus azacitidine shows synergistic efficacy, extending mouse survival to a greater degree than the other therapeutic regimens tested (Figure 4).

Figure 4. Magrolimab Synergistically Increases the Efficacy of Venetoclax Plus Azacitidine in a Patient-Derived Xenograft Model



5F9 = magrolimab; AZA = azacitidine; PDX 3871344 = patient-derived xenograft, VEN + AZA resistant primary AML; VEN = venetoclax
Primary patient AML cells were injected into immunocompromised NSG mice and allowed to engraft until peripheral disease burden was detected. Treatment of the indicated compounds was administered from day 83 to day 106 post engraftment, and mice were followed for survival.
Unpublished data, Marina Konopleva Lab, MD Anderson Cancer Center

In summary, the nonclinical rationale and clinical data support the evaluation of magrolimab in combination with azacitidine and venetoclax in frontline AML patients who are ineligible for intensive chemotherapy.

1.5. Rationale for Dose Selection of Magrolimab

The rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK/pharmacodynamics (PD) data, and modelling and simulation analyses based on data obtained from all ongoing and completed clinical studies with magrolimab in patients with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab (SCI-CD47-001) in patients with solid tumors and lymphomas, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. The use of an initial 1 mg/kg priming dose was integrated into the dosing regimen to mitigate the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged RBCs that are sensitive to CD47 blockade and triggers reticulocytosis of young RBCs that are not affected by CD47 blockade {Chen 2018}. Utilizing a priming dose leads to an initial, transient, and mild anemia that generally normalizes back to baseline over several weeks, even in the presence of repeated therapeutic doses of magrolimab {Advani 2018, Liu 2015a, Sikic 2019}. The maximum weekly dose of 45 mg/kg has an acceptable safety profile, and no MTD was identified in this study.

In studies SCI-CD47-002 and 5F9005 in patients with AML/MDS, magrolimab was administered as a monotherapy at doses of up to 30 mg/kg twice weekly and in combination with azacitidine at doses of up to 30 mg/kg once weekly. In these studies, no significant DLT was observed, and magrolimab had an acceptable safety profile over the tested dose range up to a maximum of 30 mg/kg twice weekly. Furthermore, in these 2 studies, an intrapatient dose escalation approach was followed; after the priming dose, the patients received a dose of 15 mg/kg on Day 8 during Week 2, after which the dose was escalated to 30 mg/kg on Day 11 and weekly thereafter through the end of Cycle 1, and every 2 weeks from Cycle 2 and onward. This schedule was based on nonclinical data indicating enhanced safety of intrapatient dose escalation. The MD Anderson Cancer Center IIS evaluating the combination of magrolimab with venetoclax and azacitidine used the same dosing schedule for magrolimab, with venetoclax and azacitidine dosed per their USPI, and no DLT was observed during the safety run-in.

In studies 5F9003 and 5F9004, magrolimab, in combination with rituximab and cetuximab, respectively, was found to have an acceptable safety profile at doses up to 45 mg/kg every week followed by every other week.

The proposed dosing regimen of magrolimab in this study is expected to have an acceptable safety profile based on the entirety of safety data in multiple oncology populations including the proposed study population, both as a monotherapy and in combination with other tumor-targeted antibodies and chemotherapeutics.

In Study SCI-CD47-002 and Study 5F9005, CD47 RO by magrolimab was tested at baseline and at multiple time points on treatment, on both peripheral blood and bone marrow cells, including leukemic blasts. A PK/PD model linking dose exposure and blood and bone marrow RO was developed and described these data well. Simulations with the model predicted that > 90% RO would be achieved in the bone marrow cells at the magrolimab dosing regimens proposed in this study. This level of RO is typically associated with maximal efficacy for all immune-oncology antibodies. Therefore, the proposed dose regimens are expected to maximize efficacy in the AML patient populations. CCI [redacted]

Based on results from the Phase 1b study of magrolimab in MDS and AML (Study 5F9005) and the MD Anderson Cancer Center IIS, the current study is designed to employ the same intrapatient dose escalation regimen for magrolimab to mitigate on-target toxicities such as anemia and other toxicities observed in nonclinical AML models. Treatment should be continued until disease progression, relapse, loss of clinical benefit, or unacceptable toxicity occur, or other study discontinuation criteria are met. Clinical benefit, as determined by the investigator, can include transfusion independence, adequate blood counts, symptomatic improvement, or other criteria as determined by the investigator.

In summary, the proposed dose regimens have been shown to have acceptable safety profiles in oncology patient populations. Based on PK/PD modeling, the proposed doses are predicted to result in optimal efficacy in myeloid malignancy populations and maximize patient and caregiver convenience.

1.6. Risk/Benefit Assessment for the Study

Nonclinical data demonstrate enhanced efficacy when magrolimab is combined with venetoclax and azacitidine. Furthermore, encouraging clinical activity has been observed with both magrolimab plus azacitidine and venetoclax plus azacitidine double combinations, and supports the concept that a triple combination may lead to improved efficacy. Preliminary data from the MD Anderson Cancer Center IIS suggest encouraging clinical efficacy in frontline AML in patients ineligible for intensive chemotherapy.

Venetoclax and azacitidine have overlapping toxicities, particularly myelosuppression and infections. Anemia, neutropenia, thrombocytopenia, and infections have been reported in patients treated with magrolimab.

Specific safety assessments to monitor for expected toxicities to each of these agents will be implemented. These include monitoring for myelosuppression, tumor lysis syndrome (TLS), hepatotoxicity, IRRs, and other expected toxicities. Detailed guidance on dose modification/dose holds for each study drug, depending on the type of toxicity, is provided in Section 5.5.

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy. Given the risk mitigation measures that are being implemented, the expected benefit-risk assessment to patients remains unchanged.

In summary, based on strong scientific rationale, nonclinical and emerging clinical efficacy data, and the manageable safety profile with the proposed magrolimab combination regimens, this study has an acceptable risk/benefit ratio for patients who participate.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

The endpoints of this study are described in Table 5.

Table 5. Study Objectives and Endpoints

Objective	Endpoint
Primary:	
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in patients with previously untreated AML who are ineligible for intensive chemotherapy as measured by overall survival (OS)	• OS, measured from the date of randomization to the date of death from any cause. Those whose deaths are not observed during the study will be censored at their last known alive date
Secondary:	
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of complete remission (CR) + complete remission with partial hematologic recovery (CRh) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of CR within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by event-free survival (EFS) • To evaluate the duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment • To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRh without minimal residual disease (MRD-) within 6 cycles of treatment • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR without minimal residual disease (CR_{MRD-}) within 6 cycles of treatment	• Rate of CR + CRh within 6 cycles of treatment • Rate of CR within 6 cycles of treatment • EFS • Duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment • DCR in patients who achieved CR within 6 cycles of treatment • Rate of CR/CRh_{MRD-} within 6 cycles of treatment • Rate of CR_{MRD-} within 6 cycles of treatment • Transfusion independence conversion rate • TTD on the GHS/QoL and the physical functioning scales of the EORTC QLQ-C30 • Incidence of treatment-emergent adverse events (AEs) and clinical laboratory abnormalities during the study • Magrolimab serum concentrations over time • Incidence/prevalence rate and magnitude of anti-magrolimab antibodies in serum

Objective	Endpoint
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by conversion rate of transfusion dependence to transfusion independence • To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by time to first deterioration (TTD) on the global health status/quality of life (GHS/QoL) and the physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • To assess the safety and tolerability of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To evaluate the PK and immunogenicity of magrolimab	
[redacted]	

Objective	Endpoint
• To evaluate the duration of response (DOR) and the duration of CR + CRi achieved within 6 cycles of treatment • To evaluate minimal residual disease (MRD) negativity in patients with CR + CRh • To evaluate minimal residual disease (MRD) negativity in patients with CR + CRi • To evaluate minimal MRD negativity by flow cytometry and next generation sequencing (NGS) • To compare the rate of SCT between magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To evaluate 30- and 60-day mortality in patients treated with magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine • To assess biomarkers of immune cell recruitment and immune cell signaling • To assess the mechanism of intrinsic and acquired resistance to magrolimab + venetoclax + azacitidine	• Changes and percentage changes from baseline of biomarkers including biomarkers of immune cell recruitment or of immune cell signaling • Biomarkers related to resistance, including mutational profile of leukemic clones, and immune profile of tumor microenvironment

3. STUDY DESIGN

3.1. Study Design

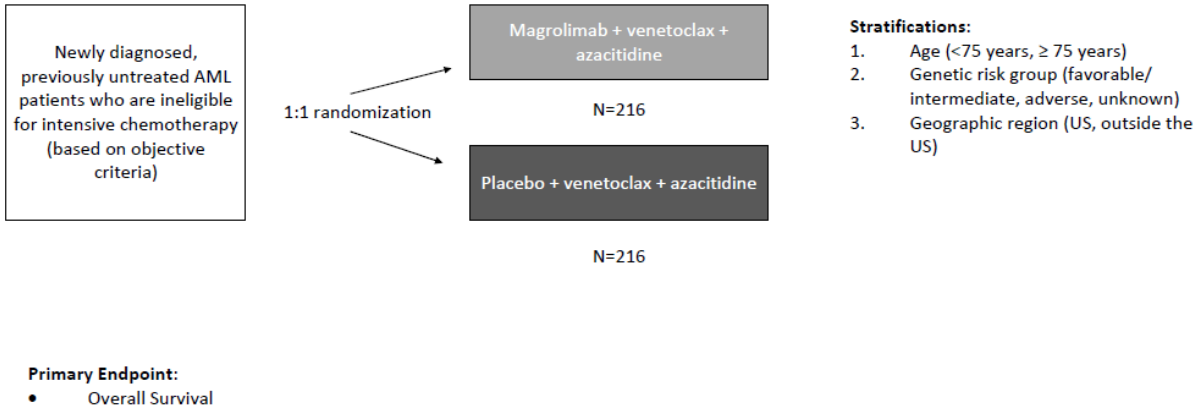
This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in newly diagnosed, previously untreated patients with AML who are ineligible for intensive chemotherapy.

Approximately 432 patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo + venetoclax + azacitidine (control arm). Randomization will be stratified by 3 factors:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown) (Appendix 8)
- geographic region (United States [US], outside the US)

The study schematic is presented in Figure 5.

Figure 5. Study Schema



3.2. Study Treatments

Study treatments are presented in Table 6, and the schedule of treatment administration is provided in Appendix Table 2 and Appendix Table 3.

Table 6. Study Treatments

Treatment Arm	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Experimental arm (magrolimab + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1-7 or Days 1-5 and 8-9
	Magrolimab Administration			
	Magrolimab 1 mg/kg IV (over 3 hours)	Days 1, 4		
	Magrolimab 15 mg/kg IV (over 3 hours)	Day 8		
	Magrolimab 30 mg/kg IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Magrolimab 30 mg/kg IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly 30 mg/kg dose		
Control arm (placebo + venetoclax + azacitidine)	Venetoclax 100 mg oral	Day 1	—	—
	Venetoclax 200 mg oral	Day 2	—	—
	Venetoclax 400 mg oral	Day 3 and daily thereafter	Daily	Daily
	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1-7 or Days 1–5 and 8-9	Days 1-7 or Days 1-5 and 8-9	Days 1–7 or Days 1-5 and 8-9
	Placebo Administration			
	Placebo IV (over 3 hours)	Days 1, 4		
	Placebo IV (over 3 hours)	Day 8		
	Placebo IV (over 2 hours)	Days 11 and 15, and then QW × 5 doses		
	Placebo IV (over 2 hours)	Q2W beginning 1 week after the fifth weekly dose		

IV = intravenous; QW = every week; Q2W = every 2 weeks; SC = subcutaneous
a Azacitidine administered per region-specific labeling or within Days 1-9 of a 28-day cycle per protocol recommendation.

3.3. Duration of Treatment

The cycle length is 28 days. Patients will receive study treatment until disease progression, relapse, loss of clinical benefit, unacceptable toxicities, or until they meet other study treatment discontinuation criteria.

3.4. Protocol-Specific Stopping Criteria

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Disease progression (including treatment failure and relapse)
- Unacceptable toxicity
- Loss of clinical benefit
- Death
- Pregnancy during the study
- Patient request, with or without a stated reason
- Patient noncompliance
- Initiation of anti-AML therapy
- SCT
- Investigator or treating physician decision
- Protocol violation
- Lost to follow-up
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB)/independent ethics committee (IEC)

In the event one or more components of the study treatment (magrolimab/placebo, azacitidine and/or venetoclax) are discontinued, the following combinations are permitted:

- Magrolimab/placebo + azacitidine
- Azacitidine (single agent)
- Venetoclax + azacitidine

The following combinations are not permitted:

- Magrolimab/placebo (single agent)
- Venetoclax (single agent)
- Magrolimab/placebo + venetoclax

If azacitidine is permanently discontinued, the patient must discontinue the remaining study treatment.

Although disease progression is considered a sufficient reason for discontinuing a patient from study treatment, given the delayed treatment benefit commonly seen in immune therapies, the investigator is advised to continue to treat the patient until the investigator considers the study treatment to be no longer clinically beneficial to the patient, or the change of disease state renders the patient unacceptable for further treatment in the judgment of the investigator. All patients must be followed through completion of all study treatment.

If patients remain on study drugs beyond disease progression, a second bone marrow assessment, along with required laboratory tests for response assessment, should be done within 4 weeks. If disease progression is confirmed at the second bone marrow assessment, the patient should be discontinued from the study treatment and participate in long-term follow-up and survival assessment if the patient does not start a new anti-AML therapy.

Patients who discontinue study treatment are to return for an end-of-treatment (EOT) visit for evaluation of safety within 7 days (± 7 days) of their last dose or the decision to end study treatment, whichever is later. In addition, patients are to have a safety follow-up telephone call 30 days and 70 days (± 7 days) after their last dose of study treatment. When a serious adverse event (SAE) or treatment-related AE is reported during the telephone call, the patient should come to the clinic for physical examination and blood tests, if clinically needed. Follow-up for ongoing SAEs or treatment-related AEs after the safety follow-up visit/call will stop if a patient begins another anti-AML therapy – this is only applicable after the 30 day visit/call.

All patients who discontinue study treatment for reasons other than death or start of new anti-AML therapy (except maintenance and SCT) will participate in long-term follow-up for disease response unless the patient withdraws consent for such follow-up and withdraws completely from the study. For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of bone marrow aspirate results will continue until start of new anti-AML therapy (except post SCT maintenance) (Appendix Figure 1). When considering SCT, note that no significant magrolimab-related transplant complications have been observed in patients who have achieved a response and undergone SCT in an ongoing magrolimab study in AML and MDS (Study 5F9005); however, a 4-week wash-out period for magrolimab/placebo is recommended prior to SCT.

All patients will be followed for survival until death, withdrawal of consent, loss to follow-up, completion of survival follow-up, or study termination by the sponsor, whichever occurs first. Duration of survival follow-up will be limited to 5 years from the EOT visit for each patient. If a patient discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the patient's consent. However, an investigator may consult public records to establish survival status. For any patient who dies during this follow-up period, the immediate cause of death must be reported to the sponsor.

If a patient discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study. For patients who discontinue from the study prior to completion of all protocol-required visits for study assessments or survival follow-up as described in the schedule of assessments (Appendix Table 5), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status unless the patient withdraws consent for such follow-up. This ensures reduced risk of missing critical efficacy data.

The assessments to be performed at each of the posttreatment visits are listed in Appendix Table 5.

3.5. End of Study

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual Patients: Patients are considered to have reached the end of study when they are no longer followed for long-term or survival follow-up (up to 5 years from the EOT visit) due to the following reasons: death, loss to follow-up, withdrawal of consent, or sponsor termination of study.

3.6. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for survival, efficacy, and AEs as specified in Appendix Table 5.

3.7. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), local and/or specialty laboratory testing (for PK, ADA and/or PD data), patient-reported outcome (PRO) data, and/or additional biomarker testing.

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 432 patients with newly diagnosed previously untreated AML confirmed by histology based on World Health Organization (WHO) criteria who are age 75 years or older, or who are age 18 years to 74 years and have comorbidities that preclude the use of intensive induction chemotherapy will be enrolled into the study.

Every effort will be made to include patients of any race, gender, and across the age range described in the study inclusion and exclusion criteria provided in Section 4.2 and Section 4.3 of the protocol.

4.1.1. Patient Replacement

Patients who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Previously untreated patients with histological confirmation of AML by 2016 WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age, or comorbidity. Patients must be considered ineligible for intensive chemotherapy, defined by the following:

   a) ≥ 75 years of age;

      Or

   b) ≥ 18 to 74 years of age with at least 1 of the following comorbidities:

      i) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3

      ii) Diffusing capacity of the lung of carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%

      iii) Left ventricular ejection fraction ≤ 50%

      iv) Baseline creatinine clearance ≥ 30 mL/min to < 45 mL/min calculated by the Cockcroft Gault formula or measured by 24-hour urine collection

      v) Hepatic disorder with total bilirubin > 1.5 × upper limit of normal (ULN)

      vi) Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy that must be approved by the sponsor's medical monitor before study enrollment

2) ECOG performance status:

   a) Of 0 to 2 for subjects ≥ 75 years of age

      Or

   b) Of 0 to 3 for subjects ≥ 18 to 74 years of age

3) Patients with white blood cell (WBC) count ≤ $20 \times 10^3/\mu L$ prior to randomization. If the patient's WBC is > $20 \times 10^3/\mu L$ prior to randomization, the patient can be enrolled, assuming all other eligibility criteria are met. However, the WBC should be ≤ $20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each magrolimab/placebo dose during Cycle 1.

   NOTE: Patients can be treated with hydroxyurea and/or leukapheresis prior to randomization and throughout the study to reduce the WBC to ≤ $20 \times 10^{3/}\mu L$ to enable eligibility for study drug dosing.

4) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment based on complete blood count (CBC) result.

   NOTE: Transfusions are allowed to meet hemoglobin eligibility (Section 5.5.3).

5) Patient has provided informed consent.

6) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.

7) Male or female, ≥ 18 years of age

8) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection.

9) Adequate liver function as demonstrated by:

   a) aspartate aminotransferase ≤ 3.0 × ULN

   b) alanine aminotransferase ≤ 3.0 × ULN

   c) total bilirubin ≤ 1.5 × ULN, or primary unconjugated bilirubin ≤ 3.0 × ULN if patient has a documented history of Gilbert's syndrome or genetic equivalent

   d) Patients ≥ 18 to 74 years of age may have total bilirubin ≤ 3.0 × ULN

10) Pretreatment RBC phenotype or genotype completed (Section 7.8.1)

11) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

12) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow assessments (aspirate and trephines). For France-specific requirements regarding bone marrow assessments, please see Appendix 15.

4.3. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Positive serum pregnancy test

2) Breastfeeding female

3) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.

4) Patients receiving any live virus vaccine within 4 weeks prior to initiation of study treatments.

5) Prior treatment with any of the following:

   a) CD47 or SIRPα-targeting agents

   b) Antileukemic therapy for the treatment of AML (eg, HMAs, low-dose cytarabine, and/or venetoclax), excluding hydroxyurea

      NOTE: Patients with prior myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) who have not received prior HMAs or venetoclax or chemotherapeutic agents for MDS/MPN may be enrolled in the study. Prior treatment with MDS/MPN therapies including, but not limited to lenalidomide, erythroid-stimulating agents, or similar RBC-, WBC-, or platelet-direct therapies or growth factors is allowed for these patients.

6) Current participation in another interventional clinical study

7) Known inherited or acquired bleeding disorders

8) Patients who have received treatment with strong and/or moderate CYP3A inducers (eg, such as preparations containing St. John's wort) within 7 days prior to the initiation of study treatments

9) Patients who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment and are unwilling to discontinue consumption of these throughout the receipt of study drug

10) Patients who have malabsorption syndrome or other conditions that preclude enteral route of administration

11) Clinical suspicion of or documented active central nervous system (CNS) involvement with AML

12) Patients who have acute promyelocytic leukemia

13) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infection, and congestive heart failure New York Heart Association Class III to IV.

14) Known history, diagnosis, or suspicion of Hemophagocytic Lymphohistiocytosis (HLH) Syndrome.

15) Second malignancy (except MDS) treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapies and have had no evidence of active malignancy for at least 1 year

    NOTE: Patients on maintenance therapy alone who have no evidence of active malignancy for at least ≥ 1 year are eligible.

    NOTE: Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy for prostate cancer, hormonal therapy or maintenance for breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are also not criteria for exclusion.

16) Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or HIV infection in medical history within 3 months of study entry.

17) Active HBV, and/or active HCV, and/or HIV following testing at screening:

    a) Patients who test positive for hepatitis B surface antigen and patients who test positive for hepatitis B core antibody will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

    b) Patients who test positive for HCV antibody will require HCV RNA quantitative PCR for confirmation of active disease.

    c) Patients who test positive for HIV antibody will require viral load testing; those who have an undetectable viral load in the prior 3 months may be eligible for the study.

5. STUDY DRUGS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Patients who meet randomization eligibility criteria will be randomized in a 1:1 ratio using an interactive response technology (IRT) to either the experimental arm or the control arm. The first dose of study treatment should be administered within 72 hours of randomization.

To achieve balance between treatment arms, randomization will be stratified according to the following factors:

- age (< 75 years, ≥ 75 years)
- genetic risk group (favorable/intermediate, adverse, unknown)
- geographic region (US, outside the US)

The randomization list will be generated with a 3-factor stratified block randomization by Signant Health (https://www.signanthealth.com/) using SAS statistical software.

5.1.2. Blinding

During the randomized phase, the investigators, the study site personnel, the patients, the study management team, and all personnel directly involved with the conduct of the study will remain blinded to treatment assignment until the primary analysis of OS.

Specified personnel may be unblinded based on their study role. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management who facilitates the data transfer of PK files between Gilead and vendors will remain unblinded. Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IRT for purposes of study drug inventory management will remain unblinded. Individuals in Patient Safety (PS) who are responsible for safety signal detection, investigational new drug safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions may be unblinded to individual case data and/or group-level summaries. External (ie, contract research organization [CRO], independent data monitoring committee [DMC]) biostatisticians and programmers responsible for preparing interim tables, listings, and figures for the DMC will be unblinded. The laboratories that will store and/or analyze blood samples for conducting PK and ADA analysis will be unblinded. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting quality assurance activities and/or regulatory agency inspections.

The sponsor study team will remain blinded until the primary analysis of OS.

5.1.3. Planned Interim Unblinding

To assess the safety and efficacy of magrolimab + venetoclax + azacitidine and for the interim analysis planning and program development consideration, a DMC independent of the blinded study team will be assembled. The DMC will be granted access to unblinded clinical data, including treatment assignments, to closely monitor study progress and drug safety. The membership, conduct, and meeting schedule of the DMC will be documented in the DMC charter.

A Gilead internal unblinded team independent of the blinded study team may be assembled, to assess the safety and/or efficacy of magrolimab + venetoclax + azacitidine for planning and development purposes. This group will consist of at least 1 representative from Clinical Research, Biostatistics, and Global Patient Safety, and may include other personnel as necessary. The Gilead medical monitor and clinical research personnel directly interacting with the study center will not be unblinded to the patient treatment assignment. The Gilead internal unblinded team will be granted access to unblinded clinical data at the group summary level including treatment assignments to closely monitor study progress and drug safety.

The membership, conduct, and meeting schedule of the internal unblinded team will be documented in the Gilead Data Review Committee Charter as specified in Gilead procedural documents.

At the time of the second interim analysis, the DMC will review the unblinded analysis results. If the null hypothesis on OS is rejected, and Gilead determines to start the marketing application process, the Gilead study team may remain blinded, and a separate Gilead internal team responsible for the marketing application may be assembled, and unblinded for all enrolled patients and remain blinded for future patients. This group will consist of at least 1 representative from Clinical Research, Biostatistics, and Global Patient Safety, and may include other personnel as necessary.

5.1.4. Procedures for Breaking the Blind on Treatment Codes

In the event of a medical emergency requiring breaking the blind to provide medical care to the patient, the investigator may obtain the patient's treatment assignment directly from the IRT for that patient (IRT vendor may be contacted in case of technology failure). Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine patient emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a patient's treatment assignment is disclosed to the investigator, the patient will have study treatment discontinued. All patients will be followed until study completion unless consent to do so is specifically withdrawn by the patient. During long-term or survival follow-ups, patients can receive new anti-AML therapy as per investigator's judgment.

5.2. Description and Handling of Magrolimab and Placebo

5.2.1. Formulation

Magrolimab is formulated as a sterile, clear, preservative-free liquid intended for IV administration containing 10 mM sodium acetate, 5% (weight-to-volume ratio [w/v]) sorbitol, 0.01% (w/v) polysorbate 20 at a pH of 5.0. Each vial is manufactured to ensure a deliverable volume of 10 mL containing 200 mg of magrolimab at a concentration of 20 mg/mL.

Placebo for magrolimab is formulated as a sterile, clear, preservative-free liquid intended for IV administration containing 10 mM sodium acetate, 5% (weight-to-volume ratio [w/v]) sorbitol, 0.01% (w/v) polysorbate 20 at a pH of 5.0 without magrolimab. Each vial is manufactured to ensure a deliverable volume of 10 mL.

5.2.2. Packaging and Labeling

Magrolimab and placebo are supplied in single-use, 10 mL glass vials with coated elastomeric stoppers and aluminum crimp overseals with a flip-off cap.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guidelines to Good Manufacturing Practice, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

Magrolimab/placebo vials should be stored at 2°C to 8°C (36°F to 46°F). Magrolimab/placebo should not be frozen. Protect from light during storage. Do not shake. Storage conditions are specified on the label. Until dispensed to the patients, study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Venetoclax

5.3.1. Formulation

Information regarding the formulation of venetoclax can be found in the local prescribing information {VENCLEXTA 2020}.

5.3.2. Packaging and Labeling

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Alternatively, in alignment with local regulations, commercial product may be sourced locally by the site.

5.3.3. Storage and Handling

Further information regarding storage and handling of venetoclax is available in the local prescribing information.

5.4. Description and Handling of Azacitidine

5.4.1. Formulation

Information regarding the formulation of azacitidine can be found in the local prescribing information.

5.4.2. Packaging and Labeling

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guidelines to Good Manufacturing Practice, Annex 13 (Investigational Medicinal Products), and/or other local regulations. Alternatively, in alignment with local regulations, commercial product may be sourced locally by the site.

5.4.3. Storage and Handling

Further information regarding storage and handling of azacitidine is available in the local prescribing information.

5.5. Dosage and Administration of Study Drugs

5.5.1. Dose and Administration of Magrolimab/Placebo

The magrolimab/placebo dosing regimen is presented in Table 6. The treatment schedule is provided in Appendix Table 2.

Premedication requirements are provided in Section 5.5.4.

Magrolimab/placebo will be administered by IV infusion. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab/placebo, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Magrolimab/placebo doses should not be given on consecutive days. The reduced infusion time to 2 hours is utilized based on prior data demonstrating majority CD47 RO on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab.

During the first 4 weeks of treatment, WBC count must be $\leq 20 \times 10^3/\mu L$ prior to each magrolimab/placebo dose. Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea and/or leukapheresis throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$.

Within 24 hours prior to each of the first 2 doses of magrolimab/placebo infusion during initial treatment, *all patients* must have a documented hemoglobin ≥ 9 g/dL based on CBC result. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab/placebo (Section 5.5.3.1).

Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab/placebo during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

All patients should be monitored hourly during infusion and for 1 hour after infusion for priming, repriming/re-escalation, and maintenance doses during the 4 first weeks. Patients should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of IRR, which have been observed in previous magrolimab studies. Postinfusion monitoring should begin after the infusion is complete. Postinfusion monitoring is not required for doses after Day 22. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate.

The dose of magrolimab/placebo will be calculated based on actual weight at randomization (using weight obtained either at screening or on Cycle 1 Day 1) and remains constant throughout the study unless there is a > 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a > 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines.

Patients will continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity (further details about treatment discontinuation are provided in Sections 3.3 and 3.5).

5.5.1.1. Treatment Delay and Repriming/Re-escalation for Magrolimab/Placebo

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab/placebo are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming/re-escalation for magrolimab/placebo after a dose delay are provided in Section 5.5.1.2.

5.5.1.2. General Guidance on Dose Modification and Delays for Magrolimab/Placebo

Clinical safety and PK data from dose finding studies in both solid tumor and hematologic malignancies have not demonstrated any dose-dependent toxicities associated with magrolimab. Dose reduction/modification of magrolimab/placebo may be allowed in certain circumstances (eg, with certain AEs), with approval by the sponsor. If treatment-emergent and/or magrolimab/placebo-related AEs occur, magrolimab/placebo may be withheld until clinical resolution or improvement per the treating physician.

When the combination drugs (azacitidine or venetoclax) are delayed due to toxicities, magrolimab/placebo should continue independently as per magrolimab/placebo administration schedule (Appendix Table 3). Continuous dosing of magrolimab is needed to maintain efficacious exposures; prolonged delays of greater than 1 week when magrolimab is dosed every 2 weeks have been seen to result in lower clinical efficacy. Magrolimab/placebo may be withheld for magrolimab-related AEs: if magrolimab is withheld due to toxicities, any delay longer than 3 days should be discussed with the medical monitor.

The repriming guidelines presented in Table 7 should be followed for patients with dose delays. In case of repriming, assessments should follow magrolimab repriming table (Appendix Table 4).

Table 7. Repriming Guidelines for Magrolimab/Placebo

Dose of Magrolimab/Placebo	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	2 weeks
15 mg/kg	2 weeks
30 mg/kg	4 weeks

If planned surgical procedures are needed for patients on study treatment, magrolimab/placebo will be delayed and restarted in accordance with Table 8.

Table 8. Magrolimab/Placebo Dosing Guidance for Planned Surgical Procedures During the Study

Planned Surgical Procedure	Magrolimab/Placebo Dose Guidance
Minimally invasive procedure (Examples: biopsies[a] [excluding lung/liver], skin/subcutaneous lesion removal, cataract/glaucoma/eye surgery/cystoscopy)	Hold magrolimab/placebo dose 3 days prior to procedure and restart after 3 days
Moderately invasive procedure (Examples: lung/liver biopsy, hysterectomy, cholecystectomy, hip/knee replacement, minor laparoscopic procedures, stent/angiopathy)	Hold magrolimab/placebo dose 5 days prior to procedure and restart after 5 days
Highly invasive procedure (Examples: CNS/spine surgery, major vascular surgery, cardiothoracic surgery, major laparoscopic surgery)	Hold magrolimab/placebo dose 7 days prior to procedure and restart after 7 days

CNS = central nervous system
a Study drug should not be held for bone marrow biopsy

5.5.2. Dosage and Administration of Azacitidine and Venetoclax

The azacitidine and venetoclax dosing regimen is presented in Table 6. The treatment schedule is provided in Appendix Table 2.

The start of the cycle is the first day of azacitidine treatment. Venetoclax is to be administered along with azacitidine on Day 1 of each cycle.

Azacitidine administration should be completed at least 1 hour before magrolimab/placebo administration on days when both drugs are administered.

Azacitidine will be administered according to region-specific drug labeling, either subcutaneously (SC) or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle. Azacitidine may be administered on an alternative schedule (such as Days 1 to 5, Day 8, and Day 9 of a 28-day cycle) for flexibility and convenience as long as 7 doses of azacitidine are administered within 9 consecutive days in accordance with local clinical practice guidelines. When administered IV, the total dose of azacitidine (diluted in a 50 to 100 mL infusion bag of either 0.9% sodium chloride injection or lactated Ringer's injection solution) is infused over a period of 10 to 40 minutes (refer to the azacitidine local prescribing information for detailed instructions for preparation and administration).

The dose of azacitidine will be calculated based on actual weight and height obtained either at screening or on Cycle 1 Day 1 and remains constant throughout the study unless there is a > 10% change in body weight from baseline. Modifications to the study treatment doses administered should be made for a > 10% change in body weight from baseline and according to local and regional prescribing standards. Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines.

Once the patient has completed the first cycle of treatment, azacitidine may be administered at home only on days where magrolimab/placebo is not given and azacitidine is administered alone.

Prior to initiation of venetoclax, WBC count must be $\leq 20 \times 10^3/\mu L$. Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea and/or leukapheresis throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$.

Venetoclax should be administered orally once daily with a meal and water, at approximately the same time each day. Patients should be advised to swallow the tablet whole, and not chew, crush, or break the tablets. If a dose is missed and it has been less than 8 hours, patients should be advised to take their dose as soon as possible. If a dose is missed and more than 8 hours has passed, the missed dose should be skipped, and the next dose should be taken at the usual time. If a patient vomits after taking venetoclax, an extra dose should not be taken but rather the next dose should be taken at the usual time.

For patients taking concomitant CYP3A and P-glycoprotein (P-gp) inhibitors, refer to Table 13 for venetoclax dosing and administration.

5.5.2.1. Venetoclax Administration and Tumor Lysis Syndrome

Patients treated with venetoclax may develop tumor lysis syndrome (TLS). Assess blood chemistry (potassium, uric acid, phosphorous, calcium, and creatinine) and correct preexisting abnormalities prior to initiation of treatment with venetoclax. Blood chemistry must be monitored for TLS at predose, 6 to 8 hours after each new dose during ramp-up (Days 1, 2, and 3), and 24 hours after reaching the maintenance dose.

5.5.3. Management of Specific Adverse Events and Dose Modification/Delays of Study Drugs

Dose modification and treatment delay of azacitidine may not occur for patients in the initial 28-day period (Cycle 1).

If ≤ 2 doses of azacitidine are missed during the 7-day dosing period, dosing should continue so that the patient receives the full 7 days of treatment, as long as these additional doses are given within 1 week of the previous dose. If ≥ 3 doses of azacitidine are missed during the 7-day dosing period, the investigator should contact the sponsor, and a dosing decision should be made on an individual case basis.

General guidance about magrolimab/placebo dose modifications is available in Section 5.5.1.2.

5.5.3.1. Management of Hematologic Toxicity

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult, any of the 4 blood groups A, B, AB, and O composing the ABO system (ABO)/Rhesus factor (Rh) type, antibody screen, blood phenotyping or genotyping, and direct antiglobulin test (DAT) need to be performed at screening before exposure to magrolimab, as described in Section 5.5.3.1.1.

Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the patient was transfused since that time.

5.5.3.1.1. Anemia, Blood Cross-Matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBC's membrane. Therefore, when magrolimab binds to CD47, it is likely to interfere with routine blood bank tests needed in case of transfusion. Notify blood transfusion centers/blood banks of this interference with blood bank testing and inform them that a patient will receive magrolimab.

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin of about 0.5 to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in hemoglobin level is acceptable in patients with no other significant diseases or medical conditions. However, for patients with significant diseases or medical

conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life-threatening or fatal. Significant drops (2 g/dL or higher) have been observed in early doses.

Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, *all patients* must have a documented hemoglobin ≥ 9 g/dL based on CBC result. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Patients with a low baseline hemoglobin level, especially those with cardiac history or risk factors, must be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. Red blood cell transfusions are permitted prior to study treatment to ensure adequate hemoglobin level as per the investigator's clinical judgment.

Prior to initiation of magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.

5.5.3.1.1.1. Management in Patients with Cardiac Comorbidities

Patients with cardiac history (e.g. LVEF ≤ 50%), especially those with low baseline hemoglobin levels, must be monitored closely after initial administrations of magrolimab/placebo as pre-existing anemia could be exacerbated. Enhanced monitoring of hemoglobin with extra CBC and careful fluid management, including diuretic administration, during or post transfusion may be required for these patients, as clinically needed.

5.5.3.1.1.2. For Patients After Exposure to Magrolimab/Placebo

Hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

5.5.3.1.1.3. Blood Components for Transfusion

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines.

For RBC transfusions, phenotype/genotype matched units are preferred. However, cytomegalovirus (CMV)-seronegative units for CMV-seronegative patients will not be required for this study.

In case ABO/Rh type cannot be resolved, use pretreatment (historical) phenotype/genotype matched units for minor RBC antigens (CcDEe and Kk, to the feasible extent). Regarding the ABO type, historical blood group or O type can be used as per the institutional guidelines.

For emergency transfusions, the transfusion centers may consider using emergency Group O red cells if phenotype/genotype matched units are not available.

Whenever possible, blood plasma therapy should be blood type specific. Platelets should be blood type compatible whenever possible and, if not, should have been tested and found not to have high titer anti-A or anti-B. Otherwise, plasma and platelet products can be provided as per the institutional policy.

A recent report has suggested that cross-match interference by RBCs due to treatment with magrolimab may be resolved by use of gamma-clone anti-IgG and multiple alloadsorptions with papain-treated RBC samples, pooled single donor apheresis platelets or commercial human platelet concentrate product if required {Troughton 2018, Velliquette 2019}.

5.5.3.1.2. Neutropenia and Thrombocytopenia:

Neutrophil counts may worsen after administration of magrolimab, leading to severe neutropenia. Grade 3 (ANC 500 to < 1000 cells/uL) and Grade 4 (ANC < 500 cells/uL) neutropenia have been reported. Additionally, fatal events of febrile neutropenia have been reported in patients treated with magrolimab. Close hematological monitoring is required for all patients during treatment. In cases of neutropenia, consider antimicrobial prophylaxis and administration of granulocyte-colony stimulating factor (G-CSF) if clinically appropriate. If febrile neutropenia occurs, administer antibiotics and/or antimycotics.

Dose modification guidelines for magrolimab in the case of severe neutropenia or thrombocytopenia are provided below:

- Before achieving remission (ie, bone marrow blast count < 5%), for Grade 4 neutropenia (ANC < 500/uL) with or without fever or infection, delay of magrolimab/placebo dosing is not recommended. In cases of Grade 4 neutropenia with serious infection, recommendations for dose delay are provided in Section 5.5.3.2.2.

- After achieving remission, for Grade 4 neutropenia (ANC < 500/uL) with or without fever or infection, and lasting at least 14 days, magrolimab/placebo dose delay is required. Upon resolution to Grade ≤ 2, resume magrolimab/placebo at the same dose.

- Before achieving remission, for Grade 4 thrombocytopenia, delay of magrolimab/placebo dosing is not recommended.

- After achieving remission, for Grade 4 thrombocytopenia lasting at least 14 days, magrolimab/placebo dose delay is required. Upon resolution to Grade ≤ 2, resume magrolimab/placebo at the same dose.

Dose modifications and delays of venetoclax and/or azacitidine due to neutropenia and thrombocytopenia should follow Table 9.

Table 9. Dose Modifications and Delays of Venetoclax and/or Azacitidine for Neutropenia and Thrombocytopenia

Event	Occurrence	Action Taken for Venetoclax and/or Azacitidine[a]
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission[b]	In most instances, venetoclax and azacitidine cycles should not be interrupted due to cytopenia prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days[c,d]	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and decrease the duration to 21 days. Resume azacitidine at the same dose.
	Second occurrence in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and decrease the duration to 14 days. Resume azacitidine at the same dose.
	Third occurrence in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and duration (14 days) and reduce the azacitidine dose to 50 mg/m^2.
	Fourth occurrence in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose, decrease the duration to 7 days, and continue the azacitidine dose at 50 mg/m^2.
	Fifth occurrence in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and duration (7 days) and decrease the azacitidine dose to 37.5 mg/m^2.
	Sixth occurrence and beyond in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and duration (7 days) and decrease the azacitidine dose to 25 mg/m^2.
	Seventh occurrence and beyond in cycles after achieving remission and lasting 7 days or longer	Delay subsequent treatment cycle of venetoclax and azacitidine and monitor blood counts. Once the toxicity has resolved to Grade 1 or 2, stop venetoclax and resume azacitidine at the same dose of 25 mg/m^2.

a Transfuse blood products and administer prophylactic and treatment anti-infectives as clinically indicated.
b Remission denotes a bone marrow blast count < 5%.
c Administer granulocyte colony-stimulating factor if clinically indicated for Grade 4 neutropenia after remission is achieved.
d Also applies to patients with Grade 4 neutropenia with blast noted to be < 5% in the first remission bone marrow.

If, per dosing modification in Table 9, the patient is eligible to start the cycle but the cycle is delayed, investigator should contact the medical monitor.

The start of the subsequent cycle should not be delayed beyond 2 weeks if the clinical condition allows safe resumption of the cycle. If the start of subsequent cycle is delayed beyond 2 weeks, the investigator should contact the medical monitor.

If after the venetoclax and azacitidine dosing schedule modifications, patients do not experience Grade 4 neutropenia or Grade 4 thrombocytopenia for at least 2 cycles, physicians can consider escalating the venetoclax and azacitidine doses to their immediate previous higher dosing regimens.

5.5.3.2. Management of Nonhematologic Toxicity

5.5.3.2.1. Infusion-related Reactions

Infusion-related reactions are defined by the NCI CTCAE Version 5.0 (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances" (Appendix 6). For the purposes of this study, the time frame for IRR assessment is the 24-hour period beginning from the start of the infusion. Premedication as described in Section 5.5.4 will be used to manage IRRs preemptively.

Recommendations for the management of infusion-related reactions related to magrolimab are provided in Table 10.

Table 10. Management of Infusion-Related Reactions

Infusion-Related Reactions	
CTCAE Grade	**Management**
Grade 1 Mild transient reaction.	Remain at bedside and monitor patient until recovery from symptoms. Patients who experience an IRR with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
Grade 2 Requiring symptomatic treatment and prophylactic medications for ≤ 24 hours.	Interrupt magrolimab/placebo therapy per protocol and begin an IV infusion of normal saline and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg of oral acetaminophen. Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be given at the discretion of the investigator. If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate. If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely. If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab/placebo will be administered at that visit. Patients who experience IRRs with the first (x) doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. The amount of magrolimab/placebo infused must be recorded on the eCRF. Patients who experience a Grade 2 infusion-related reaction during the postinfusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.

Infusion-Related Reactions	
CTCAE Grade	**Management**
Grade 3-4 Grade 3: Prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae. Grade 4: Life-threatening consequences, where urgent intervention is indicated.	Immediately discontinue infusion of magrolimab/placebo. Begin an IV infusion of normal saline, and consider treating the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The patient should be monitored until the investigator is comfortable that the symptoms will not recur. Patients who have Grade 4 infusion-related reactions will be permanently discontinued from study treatment. Patients who experience Grade 3 infusion-related reactions must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician. Patients who receive premedication and still experience a Grade 3 infusion-related reaction will be permanently discontinued from the study treatment. For anaphylaxis, investigators should follow their institutional guidelines for treatment. All patients with ≥ Grade 3 infusion-related reactions will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

AE = adverse event; eCRF = electronic case report form; IV = intravenous

5.5.3.2.2. Serious Infections

Serious infections have been reported in patients treated with magrolimab. Grades 3 and 4 infections have been reported in patients treated with magrolimab, including fatal events of pneumonia and sepsis. Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (e.g. fluoroquinolone) or antifungal agents (e.g. oral triazoles or parenteral echinocandin) in accordance with current guidelines

For serious infections, hold the next dose of magrolimab until the infection has resolved clinically. For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab/placebo.

Dose modification guidelines for delay of azacitidine or venetoclax due to serious infections are provided in Section 5.5.3.2.7.

5.5.3.2.3. Pneumonitis

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its antitumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies.

In instances of suspected pneumonitis, first rule out non-inflammatory causes (eg, infections). If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging (eg, chest x-ray or computed tomography) and pulmonary consultation.

Management of potential pneumonitis is detailed in Table 11 and follows the American Society of Clinical Oncology (ASCO) guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3 - 4 pneumonitis will be permanently discontinued from study treatment.

Table 11. Pneumonitis Management Algorithm

Pneumonitis		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 1 Radiographic changes (CXR or CT) only.	Monitor for signs and symptoms weekly and consider monitoring with CXR. Consider pulmonary and infectious disease consults.	Consider re-imaging with CT in 3-4 weeks as clinically indicated. May resume magrolimab/placebo with radiographic evidence of improvement or resolution. If no clinical improvement or worsening, treat as Grade 2.
Grade 2 Mild to moderate new symptoms.	Interrupt magrolimab/placebo therapy per protocol. Pulmonary and infectious disease consults. Consider empirical antibiotics. Monitor signs and symptoms every 2-3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. If improving to baseline, taper corticosteroids over 4-6 weeks and resume magrolimab/placebo therapy per protocol. If no clinical improvement after 48-72 hours or worsening, treat as Grade 3-4.

Pneumonitis		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 3-4 Severe new symptoms; new/ worsening hypoxia; life-threatening.	Discontinue magrolimab/placebo therapy. Consider interrupting azacitidine Hospitalize. Pulmonary and infectious disease consults. 1-2 mg/kg/day methylprednisolone IV or IV equivalent. Add empirical antibiotics and consider prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improving to baseline, taper corticosteroids over 4-6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).
Venetoclax does not need to be dose modified or delayed for pneumonitis.		

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest x-ray; IV = intravenous.

5.5.3.2.4. Thromboembolic Events

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use. Patients should be closely monitored for the symptoms of thromboembolic events and treated accordingly.

5.5.3.2.5. Renal Abnormalities

Renal abnormalities ranging from elevated serum creatinine to renal failure have been reported with rare frequency in patients treated with azacitidine. In addition, renal tubular acidosis, defined as a decrease in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L), has been rarely observed. If unexplained reductions in serum bicarbonate (< 20 mmol/L) occur, the azacitidine dose should be reduced by 50% on the next cycle. Similarly, if unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2fold above baseline values and above the ULN occur, the next cycle should be delayed until values return to normal or baseline, and the azacitidine dose should be reduced by 50%. The reduced dose should be maintained during subsequent cycles unless toxicity develops. In these cases, magrolimab/placebo and venetoclax should not be dose modified or dose delayed.

5.5.3.2.6. Tumor Lysis Syndrome

Refer to Section 5.5.2.1 for information about TLS.

5.5.3.2.7. Other Non-hematologic Toxicities

For venetoclax related or venetoclax -related nonhematologic toxicities that are ≥ Grade 3 that do not resolve to ≤ Grade 1 or baseline levels with adequate supportive care, and are clinically relevant, venetoclax dosing should be held until resolution to Grade 2 or lower or baseline levels. While venetoclax is held, magrolimab/placebo + azacitidine treatment can be continued.

For other azacitidine only related nonhematologic toxicities or nonhematological toxicities that do not resolve after holding venetoclax that are ≥ Grade 3 that do not resolve to ≤ Grade 2 or baseline levels, azacitidine dosing should be delayed up to 14 days until resolution to ≤ Grade 2 or baseline levels. If ≥ Grade 3 toxicities continue despite this dose delay, dose modification of azacitidine should be performed in accordance with Table 12.

Table 12. Dose Modification of Azacitidine for Nonhematologic Toxicities

Toxicity	Azacitidine Dosing Instructions If Recovery[a] Is Not Achieved Within 14 Days		
	First Occurrence[b]	**Second Occurrence[b]**	**Third Occurrence[b]**
Grade 3 or higher nonhematologic adverse events that are clinically relevant	Reduce azacitidine dose to 50 mg/m^2 administered Days 1–7 per cycle. AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, proceed to second occurrence.	Reduce azacitidine dose to 37.5 mg/m^2 administered Days 1–7 per cycle. AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, proceed to third occurrence.	Reduce azacitidine dose to 25 mg/m^2 administered Days 1–7 per cycle. AND Reassess toxicity on subsequent cycle; if still persistent despite dose delay, then administer azacitidine at 25 mg/m^2 on Days 1–5 per cycle. Reassess toxicity on subsequent cycle. Fourth occurrence and beyond: If toxicity still persists, then contact the medical monitor for azacitidine dosing instructions.

a Recovery is defined as improvement of nonhematologic toxicity to ≤ Grade 2 or baseline value within 14 days of dose delay.
b Azacitidine may be dose-escalated back to the original dose or next higher dose level if there is resolution of the toxicity to ≤ Grade 2 or to baseline grade.

If the other non-hematological toxicities are considered to be related to magrolimab per the investigator requiring dose modifications or hold, the investigator should contact the medical monitor.

5.5.4. Premedication and Prophylaxis

Premedication is required prior to the administration of the first 4 doses of magrolimab/placebo and in case of reintroduction with repriming. Recommended premedication should include oral acetaminophen, an antihistamine (IV or oral) and corticosteroid prophylaxis (IV or oral) before

the initial doses of magrolimab or in the case of repriming of magrolimab. For patients who do not experience an IRR with the first 2 doses of magrolimab, steroid pretreatment can be discontinued at investigators' discretion. Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. Patients who subsequently experience any Grade 4 IRRs or recurrent Grade 3 IRRs after premedication with corticosteroids should be permanently discontinued from magrolimab treatment.

Recommended premedications are oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or comparable regimen. If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted.

Prior to the first dose of venetoclax, provide patients with prophylactic measures including adequate hydration and antihyperuricemic agents per standard of care and continue during the ramp-up phase (Days 1, 2, and 3).

Prophylactic antibiotics for the prevention of neutropenic fever are not required on study but may be administered per local institutional guidelines or investigator discretion.

5.6. Prior and Concomitant Medications: Prohibited Concomitant Medications

Anti-leukemia therapies including chemotherapy (with the exception of hydroxyurea and/or leukapheresis), targeted therapies, and immunotherapy are not permitted while patients are on study treatment.

Live vaccines are prohibited during the study, and for 3 months after the last dose of study treatment {Rubin 2014}.

Premedication, as well as prophylaxis for AEs as described in Sections 5.5.3 and 5.5.4, is permitted while on study treatment.

Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with LHRH agonists for prostate cancer, hormonal maintenance therapy for breast cancers, and treatment with bisphosphonates RANKL inhibitors are permitted.

Red blood cell and platelet transfusions are permitted during screening and prior to enrollment to ensure adequate hemoglobin level according to investigators' clinical judgment. Blood transfusions are also permitted during the study as clinically indicated for management of cytopenias and should be recorded in the electronic case report form (eCRF) dedicated to transfusions during the study.

Hydroxyurea and/or leukapheresis can be used throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$. In nonclinical studies, co-administration of magrolimab and hydroxyurea in human leukemia engrafted immunodeficient mice did not cause phagocytosis of normal bone marrow cells, suggesting limited on-mechanism toxicity in patients. No gross safety

abnormalities were observed in these nonclinical studies. While no formal analyses have been performed, in clinical studies, no significant safety concerns have been observed in patients who have received concomitant magrolimab and hydroxyurea or magrolimab, azacitidine, and hydroxyurea.

All concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 30 days before the first dose of study treatment through 70-day safety follow-up calls/visits should be recorded in the eCRF.

Concomitant use of venetoclax with strong CYP3A inducers or moderate CYP3A inducers should be avoided, as use with a strong CYP3A inducer decreases venetoclax C_{max}, which may decrease venetoclax efficacy.

Conversely, concomitant use of strong and moderate CYP3A inhibitors with venetoclax increases exposure to venetoclax and therefore may increase the risk of venetoclax-related toxicity including TLS. Venetoclax dose modification based on concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor at initiation, during, or after the ramp-up phase, is described in Table 13. Resume the venetoclax dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor. Avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax, as they contain inhibitors of CYP3A.

For additional information about drug interactions with venetoclax, refer to the local prescribing information.

Table 13. Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Co-administered Drug	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)
Posaconazole	Day 1 – 10 mg venetoclax Day 2 – 20 mg venetoclax Day 3 – 50 mg venetoclax Day 4 – 70 mg venetoclax	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor	Day 1 – 10 mg venetoclax Day 2 – 20 mg venetoclax Day 3 – 50 mg venetoclax Day 4 – 100 mg venetoclax	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%	
P-gp inhibitor		

CYP3A = cytochrome P450 enzyme 3A; P-gp = P-glycoprotein

5.6.1. COVID 19 Vaccine

There is no contraindication to the COVID-19 vaccine with magrolimab. Given that immunocompromised individuals on myelosuppressive treatment may have attenuated responses to vaccines, investigators should, after consultation with local guidelines, consider delay of COVID-19 vaccination until recovery of a neutropenic individual's absolute neutrophil count (ANC) and determine the ideal timing of the subsequent dose of vaccine based on count recovery. Investigators should document vaccinations. Investigators should notify patients of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection.

5.7. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug provided by the sponsor (kits, vials, etc.). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to patients must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug (kits, vials, etc.).
- The date, patient number, and the study drug kit and/or lot number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information, in line with local practice.

5.7.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead. If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient in the study are presented in tabular form in Appendix 3 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the CRO.

6.1. Patient Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

Patients who are determined to not be eligible after screening may be rescreened once at the discretion of the investigator. Rescreening must be discussed with and approved by the study medical monitor on a case-by case basis. Patients who are determined to be eligible for rescreening must be reconsented with a new screening number assigned.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Screening assessments are outlined in Appendix Table 1.

Patients will be screened within 30 days before randomization to determine eligibility for participation in the study. Data from assessments performed as part of standard of care prior to informed consent signature may be used if they are within the required screening period. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain demographics and medical history, including AML history, AML molecular marker results at diagnosis, if available, and date of most recent RBC and/or platelet transfusion(s)
- Complete physical examination, including vital signs, body weight, and height
- Serum pregnancy test (females of childbearing potential)
- CBC with differential, platelets, reticulocytes, and blasts
- Serum or plasma chemistry as defined in Table 14
- Serology for HBV, HCV, and HIV
- Prothrombin time (PT) or international normalized ratio (INR), and activated partial thromboplastin time (aPTT) or PTT

- Blood cell ABO genotyping or phenotyping (phenotyping is acceptable only in patients who have not received red blood cell transfusion in the last 3 months) for minor antigens, type, and screen (ABO/Rh), DAT (Section 5.5.3.1.1 Anemia, Blood Cross-Matching, and Packed Red Blood Cell Transfusion Procedures)
- Urinalysis
- Peripheral blood smear (for blasts)
- Bone marrow biopsy and aspirate for blast evaluation (response assessment), cytogenetics, MRD assessment, and biomarker studies. NOTE: Cytogenetic test results from initial diagnosis of AML may be used in lieu of screening cytogenetic assessment. Bone marrow biopsy (blocks) collected within 1 month prior to signing of informed consent may be used in lieu of bone marrow biopsy.
- Bone marrow slides or blocks for central review (bone marrow slides or blocks are optional if aspirate is provided for central review). NOTE: Bone marrow biopsy collected within 1 month prior to signing of informed consent may be used in lieu of bone marrow biopsy for central review.
- ECOG performance status (Appendix 7)
- Perform 12-lead electrocardiogram (ECG) (single)
- Echocardiogram or MUGA (only for patients ≥ 18 to 74 years of age with cardiac disease, if needed to determine eligibility)
- Pulmonary function tests (only for patients ≥ 18 to 74 years of age with respiratory disease, if needed to determine eligibility)
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form (ICF)
- Record prior and concomitant medications
- Eligibility criteria

Assessments performed as part of screening for other magrolimab clinical studies may be acceptable for use on this study with sponsor approval.

From the time of obtaining informed consent through the first administration of study drug, record all serious AEs (SAEs), as well as any AEs related to protocol-mandated procedures on the Adverse Events electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.2.2. Baseline/Day 1 Assessments

Baseline/Day 1 assessments are outlined in Appendix Table 1.

Patients must return to the study site within 30 days of screening for baseline/Day 1 assessments.

The following pretreatment assessments will be performed and documented prior to the initial dose on Cycle 1 Day 1. Laboratory assessments, vital signs, and physical examination may occur up to 72 hours before administration of any study treatment:

- EORTC QLQ-C30, EQ-5D-5L, and PGIS (must complete these questionnaires before any other study procedures at required visits)
- Vital signs, weight, and symptom-directed physical examination
- Serum or urine pregnancy test (females of childbearing potential)
- CBC with differential, platelets, reticulocytes, blasts. Note: Hemoglobin must be ≥ 9 g/dL within 24 hours of Day 1 magrolimab/placebo dose (Section 5.5.3.1)
- Haptoglobin and lactate dehydrogenase
- Serum or plasma chemistry
- Recording of all AEs and concomitant medications
- Peripheral blood sample for biomarker studies
- PK and ADA sample collection

6.3. Randomization

Randomization procedures are described in Section 5.1.1.

6.4. On-Study Treatment Assessments

On-study treatment assessments include evaluations of efficacy (Section 6.5), safety (Section 6.6), PK (Section 6.7), immunogenicity (Section 6.8), and biomarkers (Section 6.9). The schedule for on-treatment assessments is provided in Appendix Table 1.

6.5. Efficacy Assessments

Clinical response will be assessed by the investigator using guidelines based primarily on European LeukemiaNet (ELN) AML recommendations and International Working Group AML response criteria {Cheson 2003, Cheson 2006, Dohner 2017}, with modifications (see Appendix 4).

Response assessments will be done in conjunction with bone marrow assessments, CBC, and peripheral blood smear according to the schedule of assessments (Appendix Table 1, Appendix Table 5). Peripheral blood smear for blasts should be done on the same day as the bone marrow assessment. Complete blood count results used for the response assessment will be derived from the best accompanying laboratory CBC result within the ± 2-week window of the bone marrow assessment used to support the efficacy response assessment. All components (eg, platelets, absolute neutrophils) should come from the same test. The date of the response will be the date of the bone marrow assessment. If disease progression or relapse is assessed based on CBC assessments or new extramedullary disease or both, other than bone marrow blasts assessments, then the date of the corresponding CBC or new extramedullary disease assessment date or the earlier of these 2 dates will be used as the date of response assessment.

6.5.1. Bone Marrow Assessments

Bone marrow assessments (including aspirate and/or core/trephine biopsy) are required for response assessments (eg, blast evaluation), including conventional cytogenetic analysis per institutional standards (Appendix Table 1). In addition, bone marrow specimens may be used for biomarker studies, MRD monitoring, CCI [redacted], and biobanking. Minimal residual disease testing and biomarker studies will be performed by a central laboratory. Details for preparation and distribution of aspirate and/or biopsy/trephine specimens to the testing laboratories will be provided in the laboratory manual for this study. Bone marrow aspirate and/or biopsy slides or blocks for efficacy assessments will be prepared for potential evaluation of response assessments by independent central review.

If the patient is cytopenic at the time of the bone marrow assessments, CBC is to be monitored at least twice per week for 2 weeks or until optimal count recovery is reached (whichever comes first).

Patients responding to initial treatment should be re-evaluated regarding their ability to undergo allogeneic hematopoietic cell transplant, which may cure a proportion of these patients.

Response assessment will be obtained at the EOT visit, unless a prior response assessment has been performed within the last 30 days or progressive disease has been documented. Response assessments should continue during long-term follow-up approximately every 12 weeks until the start of a new anti-AML therapy.

For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of bone marrow aspirate results will continue until start of a new anti-AML therapy (except post SCT maintenance).

If a patient achieves a CR, subsequent bone marrow assessments are still required to be performed in accordance with the schedule of assessments.

6.5.2. Peripheral Blood Smear Assessment

Peripheral blood smears for blasts should be collected on the same day as the bone marrow aspirates for response assessment per the schedules of assessments (Appendix Table 1, Appendix Table 5). These samples should be collected from the arm contralateral to the arm being used for drug infusion/injection, if possible. Peripheral blood smears will be assessed locally.

6.5.3. Patient-Reported Outcomes

Four PRO instruments will be administered in this study: the EORTC QLQ-C30, the EQ-5D-5L, the PGIS, and the PGIC. If the PRO instruments are not available in a patient's language, patients are not required to complete the assessments. Patients with other situations related to PRO instrument completion (eg, visual impairment/blindness, limitation in upper extremity mobility/dexterity) may be exempt from these assessments after discussion with the sponsor.

The patient should complete these questionnaires before any other study procedures at required visits. Please refer to the schedules of assessments (Appendix Table 1, Appendix Table 5) for timing of PRO assessments.

6.5.3.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a reliable and valid measure of PROs and has been widely used among cancer patients. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain) and 6 single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) {Fayers 2001}. The recall period is 1 week (prior week) and it requires approximately 11 minutes to complete. An example is provided in Appendix 9.

6.5.3.2. EQ-5D-5L

The EQ-5D-5L is an instrument for use as a measure of health outcome {EuroQol Research Foundation 2017, Janssen 2013}. The EQ-5D-5L consists of 2 sections: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). An example is provided in Appendix 10.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical VAS, where the endpoints are labeled "the best health you can imagine" and "the worst health you can imagine." The EQ VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

6.5.3.3. PGIS/PGIC

The PGIS and PGIC assessments are both single-item assessments used to demonstrate sensitivity and meaningful change thresholds and bolster the validity of selected PRO assessments {Department for Health and Human Services (DHHS) 2018}. These questionnaires are provided in Appendix 11.

6.6. Safety Assessments

Safety will be evaluated by incidence of AEs, assessment of clinical laboratory test findings (chemistry, hematology), physical examination, 12-lead electrocardiogram, and vital sign measurements.

6.6.1. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age. Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. A negative serum pregnancy test is required at screening, and a negative urine pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Serum or urine pregnancy tests will also be required every 4 weeks thereafter (Appendix Table 1, Appendix Table 5). For further details, refer to Appendix 5.

6.6.2. Complete Blood Counts

Samples for CBC should be collected per the schedules of assessments in Appendix Table 1 and Appendix Table 5. White blood cell counts must be ≤ $20 \times 10^3/\mu L$ prior to first dose of study drug and prior to each magrolimab/placebo dose for the first 4 weeks (Section 5.5). Additional samples for CBC may be collected outside of the protocol-specified time points to ensure WBC level ≤ $20 \times 10^3/\mu L$ for the first cycle and repriming/re-escalation cycle. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

6.6.3. Type and Screen and Direct Antiglobulin Test

Refer to Section 5.5.3 for detailed guidance on type and screen and DAT. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual as applicable.

6.6.4. Vital Signs

Vital signs should include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height should be recorded during screening only. Weight should be recorded during screening and on Day 1 of each cycle. Vital signs are to be recorded prior to dosing of study treatment at the visits specified in the schedules of assessments in Appendix Table 1 and Appendix Table 5.

6.6.5. Physical Examination

Complete physical examination should be performed at screening. Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and neurologic system.

6.6.6. Electrocardiograms

A single 12-lead ECG will be performed at screening.

6.6.7. Echocardiogram or MUGA

An echocardiogram or MUGA will be performed at screening only for patients aged 18 to 74 years with cardiac disease, if needed to determine ineligibility to intensive chemotherapy. Left ventricular ejection fraction (LVEF) is to be reported in the applicable eCRF.

6.6.8. Pulmonary Function Tests

Pulmonary function tests will be performed at screening only for patients aged 18 to 74 years with pulmonary disease, if needed to determine ineligibility to intensive chemotherapy. Diffusion capacity of lung (DLCO) or forced expiratory volume during the first second (FEV1) are to be reported in the applicable eCRF.

6.6.9. Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur after the first dose of study treatment through 70 days after the last dose of study treatment are to be reported using the applicable eCRF (Section 7.1.1). Full details on the definitions, assessment, and reporting instructions for AEs are provided in Section 7.

6.6.10. Laboratory Assessments

Laboratory assessments to be performed at screening are presented in Table 14. Laboratory assessments to be performed during the study are presented in Table 15.

Table 14. Laboratory Analyte Listing (to Be Performed at Screening)

Safety Laboratory Measurements			
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	**Other Laboratory Measurements**
Sodium	Hemoglobin	RBC	Serum pregnancy test
Potassium	Hematocrit	Protein	Blood phenotyping and/or genotyping, type, and screen (ABO/Rh), DAT
Chloride	Platelets		Blasts (peripheral blood smear with bone marrow assessments and with CBC)
Bicarbonate	WBC differential		
Total protein	Absolute neutrophil count		**Hepatitis B and hepatitis C assessments:**
Albumin	Eosinophils		HBsAg, anti-HBc, HCV antibody, HBV DNA, and HCV RNA, as applicable
Calcium	Basophils		
Magnesium	Lymphocytes		**Bone marrow aspirate and biopsy:**
Phosphorus	Monocytes		Response assessment (eg, blast evaluation)
Glucose	Reticulocytes		Cytogenetics
BUN or urea			MRD assessment[a]
Creatinine	**Peripheral Blood Smear**		Biomarker studies[a]
Uric acid			Slides or blocks for independent central review[b]
Total bilirubin			
Direct bilirubin			
Indirect bilirubin			
AST (SGOT)	**Coagulation:**		
ALT (SGPT)	PT/INR		
Alkaline phosphatase	aPTT or PTT		

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; DAT = direct antiglobulin test; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PT = prothrombin time; PTT = partial thromboplastin time; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

a These assays will be performed at a central laboratory.

b Bone marrow biopsy collected within 1 month prior to signing of informed consent may be used in lieu of bone marrow biopsy for central review.

Table 15. Laboratory Analyte Listing (to Be Performed During the Study)

Safety Laboratory Measurements		
Chemistry (Serum or Plasma)	**Hematology[a]**	**Other Laboratory Measurements**
Sodium	Hemoglobin	Serum or urine pregnancy test
Potassium	Platelets	Pharmacokinetics[b]
Calcium	WBC differential	Antidrug antibodies[b]
Chloride	Absolute neutrophil count	Blasts (with CBC)
Bicarbonate	Lymphocytes	
Albumin	Reticulocytes	**Bone marrow aspirate and biopsy**:
Glucose		Response assessment (eg, blast evaluation)
BUN or urea		Cytogenetics
Creatinine		MRD assessment[b]
Uric acid		Biomarker studies[b]
Phosphorus		Slides or blocks for independent central review
Total bilirubin		
Direct bilirubin		
Indirect bilirubin		**Peripheral blood smear**:
Haptoglobin		Blasts *(with bone marrow assessments)*
LDH		
AST (SGOT)		**Peripheral blood:**
ALT (SGPT)		Biomarker studies[b]
Alkaline phosphatase		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = Cycle; CBC = complete blood count; D = Day; LDH = lactate dehydrogenase; MRD = minimal residual disease; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

a If the patient is cytopenic at Day 28, CBC is to be monitored at least twice per week for 2 weeks or until optimal count recovery is reached (whichever comes first). The best CBC result within the ± 2-week window is to be used for the response assessment, with the date of response being the date of the bone marrow assessment. Complete blood count need not be repeated if the prior CBC (including prior Day 28 CBC) is within 3 days of Day 1.

b These assays will be performed at a central laboratory.

Refer to Appendix Table 1 and Appendix Table 5 for collection time points.

6.6.11. Concomitant Medications

All concomitant medications taken by the patient while on study are to be documented. Changes in baseline concomitant medication information are to be collected after informed consent through the study treatment period, and up until 70 days after treatment discontinuation. Concomitant medication associated with procedure related AEs will be captured from the time of informed consent and onward. Information to be collected includes therapy name, indication, dose, unit, frequency, route, start date, and stop date, and must be reported using the applicable eCRF. Note that any anti-AML therapies after the study treatment period should also be collected per the schedules of assessments (Appendix Table 1, Appendix Table 5).

6.7. Pharmacokinetics Assessments

Samples for PK assessment of magrolimab will be collected from all patients predose of magrolimab/placebo (on the first day of the biweekly maintenance dose, an additional sample for postdose PK will be collected at 1 hour [± 15 minutes] after the end of infusion with magrolimab/placebo), in accordance with the schedule of assessments (Appendix Table 1, Appendix Table 5). Serum magrolimab concentrations will be measured by a validated immunoassay.

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6.8. Immunogenicity Assessments

Samples for assessment of anti-magrolimab antibodies will be collected from all patients in accordance with the schedule of assessments (Appendix Table 1, Appendix Table 5). Antidrug antibody assessment will be performed using a validated assay following a 3-tiered approach: screening, confirmatory, and titer testing.

CCI

6.9. Biomarker Assessments

Peripheral blood, bone marrow aspirate, and trephine biopsy samples will be collected from all patients who have provided consent to participate in this study. They may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response, including efficacy and/or AEs, dose optimization, and to better understand the biology of AML in general. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays described below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Blood and bone marrow samples will be collected to measure biomarkers, which may include but will not be limited to the presence of or changes to immune cell populations, secreted protein factors, the expression of cell surface markers on either tumor cells or cells of the tumor microenvironment, and genetic mutations in tumor cells or subclones of tumor cells at the time points listed in the schedules of assessments (Appendix Table 1, Appendix Table 5).

These samples will also be used for genomic research to identify or validate genetic markers that may increase our knowledge and understanding of the biology of the study disease and related diseases, and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may also be used to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. Genomics research may include sequencing of genetic material derived from both cancer cells and normal cells. Sequencing of genetic material derived from cancer cells will be used to better understand the MOA of magrolimab combinations in this patient population, and potentially to identify subsets of patients who are likely to benefit. Sequencing of genetic material derived from normal cells will be used to define differences in sequence that are cancer specific.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual.

6.9.1. Minimal Residual Disease

Sensitive flow cytometry-based assays are capable of identifying phenotypic leukemia cells down to frequencies of less than 1×10^{-3} of total WBCs. These rare leukemia cells are termed MRD, and their presence or absence following treatment is an independent prognostic factor for disease progression and relapse in all AML treatment paradigms. Patients with AML in this trial will be assessed by a flow cytometry-based assay for MRD in their bone marrow at multiple time points before and after treatment during the first 6 cycles, in order to further understand the efficacy and MOA of magrolimab combinations. CCI [redacted] this study, patients will be tested by both methods, and the sensitivity and concordance of the 2 methods may be assessed. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual.

6.9.2. Leukemia Mutation Profiles and Burden

The pathogenesis of all cancers, including leukemias, has a basis in their acquired genetic mutations. The particular genetic mutations present in a patient's cancer may render it sensitive or resistant to anti-cancer therapies, including magrolimab-based combinations. In some cases, if strongly associated with clinical benefit or the MOA of a drug, these genetic mutations can be used to select patients who are eligible for a given treatment. In other cases, the total number of mutations present in the genome of a given cancer (eg, rather than the specific genes mutated) can be correlated with likelihood of response, such as is the case with some T-cell checkpoint therapies. Clonal evolution of leukemia cells will also be tracked while on treatment and at the time of relapse, in order to understand the mechanism of resistance to magrolimab combinations.

6.9.3. Changes in Immune Effector Cell Composition

Activation of the immune system can be associated with changes in immune effector cell frequency or localization to the tumor microenvironment. In order to explore changes in the composition of immune effector cells to inform MOA, patients with AML in this trial will be assessed by methods potentially including, but not limited to, multiplex immunofluorescence and single-cell RNA sequencing at multiple pre- and posttreatment time points.

6.9.4. Changes in Immune Effector Cell Signaling Molecules

Activation of the immune system can be associated with changes in expression or secretion of immune-regulatory molecules, including cytokines, chemokines, and others. Release of such molecules, and their concentration in the peripheral blood or tumor microenvironment can inform MOA. Patients with AML in this trial will be assessed for soluble protein factors in the peripheral plasma and/or bone marrow by methods potentially including, but not limited to, multiplex enzyme-linked immunosorbent assay or aptamer-based measurement.

6.9.5. Expression of Prophagocytic and Antiphagocytic Signals by Leukemia Cells

Preclinical studies suggest that the efficacy of magrolimab depends on the balance of pro- and antiphagocytic signals expressed by cancer cells. Magrolimab combination therapies, including those investigated as part of this clinical trial, may derive their efficacy from the simultaneous blockade of antiphagocytic signals by magrolimab, and the increased expression of prophagocytic signals by the companion drug. In order to better define the efficacy and MOA of magrolimab combinations in AML, the surface profile of known pro- and antiphagocytic signals will be assessed on leukemic cells at multiple pre- and posttreatment time points using methods to include, but not be limited to, flow cytometry, mass cytometry, and multiplex immunofluorescence.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

6.10. Posttreatment Assessments

A schematic of the posttreatment visit schedule is presented in Appendix Figure 1. Posttreatment assessments are presented in Appendix Table 5.

6.11. Assessments for Early Discontinuation from Study Treatment

If a patient discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the patient in the study and continue to perform the required study-related follow-up and procedures (Section 6.11.1). If this is not possible or acceptable to the patient or investigator, the patient may be withdrawn from the study. For patients who discontinue from the study prior to completion of all protocol-required visits for study assessments or survival follow-up (Appendix Table 5), the investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status. This ensures reduced risk of missing critical efficacy data.

6.11.1. Criteria for Discontinuation of Study Treatment

Reasons for discontinuation of study treatment are provided in Section 3.4

6.11.2. End of Study

The end of the entire study for all patients and for individual patients is defined in Section 3.5.

6.12. Post Treatment Discontinuation Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for survival, efficacy and AEs as specified in Appendix Table 5.

For patients who start new anti-AML therapy (other than SCT) before a relapse, efficacy status (done as standard of care) will be collected until relapse.

6.13. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years. If patients provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

Given the primary and secondary endpoints of the study, in order to maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered AEs/SAEs:

- Progression of AML
- Deaths related to progression of AML

Events that are considered to represent progression of the underlying AML should not be recorded as AEs/SAEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE.

Death that is attributed by the investigator as solely due to progression of AML and that occurs during the protocol-specified AE reporting period should be recorded only on the death eCRF (ie, not collected as an SAE on the AE eCRF).

7.1.2.1.1. Deaths not related to AML progression

All other deaths (ie, deaths that are not due to AML progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the AE eCRF and reported within 24 hours of awareness and no later than the next business day.

When recording a death on the eCRF, the event or condition that is considered the primary cause of death should be the AE term, and the outcome should be fatal. A patient can only have 1 AE (SAE) with a fatal outcome and severity of CTCAE Grade 5.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a patient.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the patient has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect of which the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs, Authorized Auxiliary Medical Products, and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

When there is a reasonable possibility that the causality of the AE/SAE can be assigned to the authorized AxMP, the investigator or qualified subinvestigator will need to report the causality assessment for the authorized AxMP(s) in accordance with the eCRF.

7.2.2. Assessment of Severity

The severity of AEs will be graded using the NCI CTCAE Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 6).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, will be collected until 70 days after last administration of study drug and reported on the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 70 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occur after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal patient identification, maintaining the traceability of a document to the patient identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper special situations report form to:

Gilead PS
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female patients that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

  Gilead PS
  Email: Safety_FC@gilead.com
  or
  Fax: 1-650-522-5477

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the Gilead PS.

- The patient should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

- Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs).

In accordance with the European Union Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the NCI CTCAE Version 5.0. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all patients.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, pre-existing or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment if the investigator determines that it is not in the patient's best interest to continue. Discontinuation of treatment should be considered if there is an indication of severe liver injury according to Hy's Law, defined by US FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health and Human Services 2009} as:

- Treatment-emergent ALT or AST elevation (≥ 3 × ULN), AND
- Treatment-emergent total bilirubin elevation (> 2 × ULN), and absence of cholestasis (defined as ALP < 2 × ULN), AND
- No other good explanation for the injury (hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure, worsening liver metastases).

7.8. Toxicity Management

7.8.1. Magrolimab

Safety management guidelines for magrolimab are described in Section 5.5.3.

7.8.2. Venetoclax

Safety management guidelines for venetoclax are described in Section 5.5.3. Additional safety guidelines are provided in the venetoclax local prescribing information.

7.8.3. Azacitidine

Safety management guidelines for azacitidine are described in Section 5.5.3. Additional safety guidelines are provided in the azacitidine local prescribing information.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The study objectives are provided in Section 2.

8.1.1. Definition of Primary Efficacy Endpoint

8.1.1.1. Overall Survival

Overall survival is measured from the date of randomization to the date of death from any cause. Patients whose deaths are not observed during the study will be censored at their last known alive date.

8.1.2. Definition of Secondary Efficacy Endpoints

8.1.2.1. Rate of CR + CRh Within 6 Cycles of Treatment

The CR + CRh rate is the proportion of patients who achieve a CR (including CR_{MRD-} and $CR_{MRD+/unk}$) or CRh as defined by CR with partial platelet and absolute neutrophil count recovery (Appendix 4) within 6 cycles of treatment while on study prior to initiation of any new anti-AML therapy or SCT.

8.1.2.2. Rate of CR Within 6 Cycles of Treatment

The CR rate is the proportion of patients who achieve a CR, including CR_{MRD-} and CR with positive or unknown minimal residual disease ($CR_{MRD+/unk}$) within 6 cycles of treatment, as determined by investigators based on the ELN 2017 for AML {Dohner 2017} with modifications (Appendix 4) while on study prior to initiation of any new anti-AML therapy or SCT.

8.1.2.3. Event-Free Survival

Event-free survival is defined as time from the date of randomization to the earliest date of the documented relapse from CR, treatment failure (defined as failure to achieve CR within 6 cycles of treatment), or death from any cause. Response assessments or death post SCT or new anti-AML therapies will be included in the analysis. The date of randomization will be assigned as the event date for patients with treatment failure.

Patients who are not observed to have one of the specified events on or prior to data cutoff date (the date on which subsequently collected data will not be considered as part of the analysis) will be censored at the date of their last response assessment with clear documentation of no relapse on or prior to the data cutoff date. Patients will be censored at the date of randomization if no response assessment is performed after randomization and the patients do not die.

8.1.2.4. Duration of CR + CRh

The duration of CR + CRh is measured from the time the assessment criteria are first met for CR (including CR_{MRD-} and $CR_{MRD+/unk}$) or CRh within 6 cycles of treatment until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death while on study will be censored at the date of their last response assessment with no evidence of relapse on or prior to the data cutoff date. If patients start taking new anti-AML therapies (excluding post-SCT maintenance therapy) before relapse, duration of CR + CRh will be censored at the last response assessment before the initiation of the new anti-AML therapies.

8.1.2.5. Duration of CR

The DCR is measured from the time the assessment criteria are first met for CR (including CR_{MRD-} and $CR_{MRD+/unk}$) within 6 cycles of treatment until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death while on study will be censored at the date of their last response assessment with no evidence of relapse on or prior to the data cutoff date. If patients start taking new anti-AML therapies (excluding post-SCT maintenance therapy) before relapse, DCR will be censored at the last response assessment before the initiation of the new anti-AML therapies.

8.1.2.6. Rate of CR/CRh_{MRD-} Within 6 Cycles of Treatment

The CR/CRh_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} or CRh_{MRD-} within 6 cycles of treatment while on study prior to initiation of any new anti-AML therapy or SCT. The threshold for MRD negativity in this study is a frequency of less than 1×10^{-3} phenotypic leukemic cells per total WBCs.

8.1.2.7. Rate of CR_{MRD-} Within 6 Cycles of Treatment

The CR_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} within 6 cycles of treatment, as determined by investigators based on the ELN 2017 for AML with modifications (Appendix Table 6), while on study prior to initiation of any new anti-AML therapy or SCT. The threshold for MRD negativity in this study is a frequency of less than 1×10^{-3} phenotypic leukemic cells per total WBCs.

8.1.2.8. Transfusion Independence Conversion Rate

The transfusion independence conversion rate includes both RBC transfusion independence rate and platelet transfusion independence rate.

The RBC transfusion independence conversion rate is the proportion of patients who have a 56-day or longer period with no RBC or whole blood transfusions at any time between the date of first dose of study treatment and discontinuation of study treatment among all patients who are RBC transfusion dependent at baseline. The RBC transfusion dependence at baseline is defined as having received an RBC or whole blood transfusion within the 28 days prior to the first dose of study treatment.

The platelet transfusion independence conversion rate is the proportion of patients who have a 56-day or longer period with no platelet transfusions at any time between the date of first dose of study treatment and discontinuation of study treatment among all patients who are platelet transfusion dependent at baseline. Platelet transfusion dependence at baseline is defined as having received a platelet transfusion within the 28 days prior to the first dose of study treatment.

8.1.2.9. Time to First Deterioration on the EORTC QLQ-C30 GHS/QoL Scale

The TTD on the EORTC QLQ-C30 GHS/QoL scale is defined as time from the date of randomization to the time a patient experienced at least 1 threshold value deterioration from baseline or death, whichever is earlier.

8.1.2.10. Time to First Deterioration on the EORTC QLQ-C30 Physical Functioning Scale

The TTD on the EORTC QLQ-C30 physical functioning scale is defined as time from the date of randomization to the time a patient experienced at least 1 threshold value deterioration from baseline or death, whichever is earlier.

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8.2. Planned Analyses

8.2.1. Interim Analyses

There will be 2 planned interim analyses for OS.

8.2.1.1. First Interim Analysis

The first interim analysis will be performed when approximately 121 deaths (40% of the expected 303 deaths) have occurred, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. An administrative 1-sided alpha = 0.0001 is allocated to this interim analysis. The nonbinding futility analysis with a futility boundary of HR = 1.1 will be performed. A Gamma beta-spending function with parameter -5 is used to obtain the futility boundaries for both interim analysis.

8.2.1.2. Second Interim Analysis

The second interim analysis will be conducted when approximately 227 deaths (75% of the expected 303 deaths) have occurred, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. One-sided $\alpha = 0.0249$ will be allocated to the analysis of OS and key secondary endpoints in the second interim analysis and primary analysis.

The Lan-DeMets approach with O'Brien-Fleming type alpha spending function will be used for the interim analysis and primary analysis for OS. The stopping boundaries at each analysis time are provided in Table 16. If the null hypothesis of OS is not rejected in the second interim analysis, the second nonbinding futility test with a futility boundary of HR = 0.9 will be performed.

Table 16. Stopping Boundaries for Efficacy Superiority Analysis in OS

Planned Analysis	Events (%[a])	Stopping Boundary	
		HR	One-sided P Value
Second interim analysis	227 (75%)	0.733	0.0096
Primary analysis	303 (100%)	0.793	0.022

HR = hazard ratio
a Information fraction = number of events / number of total events × 100

To strongly control the overall type I error across the testing of the primary and key secondary efficacy endpoints, a hierarchical testing strategy will be performed with a predefined order as listed in the protocol and the statistical analysis plan (SAP). The primary efficacy endpoint of OS will be tested for superiority first at the significance level specified in Table 16. If the superiority is established, analysis of key secondary efficacy endpoints for superiority will be performed. For each key secondary endpoint, an O'Brien-Fleming boundary will be derived based on the information fraction defined at the interim analysis and the remaining type I error, respectively, per Table 17.

The information fraction of EFS at the second interim analysis is calculated based on the assumption that median EFS is 9.8 months in patients treated with placebo + venetoclax + azacitidine and HR of 0.7. Approximately 292 and 358 EFS events will be observed at the second interim and primary analysis per efficacy and enrollment assumptions, respectively, so the information fraction is 82% (292/358) at the second interim analysis.

Table 17. Definition of Information Fraction

Endpoint	Information Fraction at the Interim Analysis
Rate of CR + CRh within 6 cycles of treatment	Proportion of patients who have at least 7 months follow-up since randomization
Rate of CR within 6 cycles of treatment	Proportion of patients who have at least 7 months follow-up since randomization
EFS	82%
Rate of CR/CRh$_{MRD-}$ within 6 cycles of treatment	Proportion of patients who have at least 7 months follow-up since randomization
Rate of CR$_{MRD-}$ within 6 cycles of treatment	Proportion of patients who have at least 7 months follow-up since randomization
Transfusion independence conversion rate	Proportion of patients who have at least 9 months follow-up since randomization
TTD on the GHS/QoL and the physical functioning scales	75%, same with that of OS

CR = complete remission; CRh = complete remission with partial hematologic recovery; CR$_{MRD-}$ = complete remission without minimal residual disease; EFS = event-free survival; GHS/QoL = global health status/quality of life; MRD- = without minimal residual disease; OS = overall survival; TTD = time to first deterioration

The key secondary endpoints will be tested in the following order:

- Rate of CR + CRh within 6 cycles of treatment
- Rate of CR within 6 cycles of treatment
- EFS
- Rate of CR/CRh$_{MRD-}$ within 6 cycles of treatment

- Rate of CR_{MRD-} within 6 cycles of treatment
- Transfusion independence conversion rate
- TTD on the EORTC QLQ-C30 GHS/QoL scale
- TTD on the EORTC QLQ-C30 physical functioning scale

A given hypothesis can only be tested and declared statistically significant if all previous hypotheses tested in the hierarchy are also statistically significant.

At the time of each interim analysis, the DMC will review the unblinded analysis results, and provide recommendations. The process details are described in Section 5.1.3 and 8.13.

8.2.1.3. Data Monitoring Committee Analysis

In addition to the 2 planned interim efficacy analyses, the DMC will convene to review safety analysis results periodically.

8.2.2. Interim Analysis Communication Plan

An interim analysis communication plan describing the processes and procedures that will be employed in conducting the prespecified interim efficacy analysis and the controlled dissemination of the resulting interim analysis data will be developed and finalized separately. The unblinding of specific Gilead personnel will be documented in accordance with the appropriate SOPs.

8.2.3. Primary Analysis

If the null hypothesis on OS is not rejected in the second interim analysis, the unblinded primary analysis will be conducted when 303 deaths have occurred. The analysis will be conducted after all outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis of the primary endpoint of OS and key secondary endpoints will serve as the final analysis for these endpoints and will be used to evaluate the efficacy and safety of magrolimab versus placebo in combination with venetoclax and azacitidine.

If the null hypothesis of OS is rejected in the second interim analysis, the primary analysis timing will be determined by the maturity of the key secondary endpoints that have not been rejected in the second interim analysis.

8.2.4. Final Analysis

The final analysis will be performed after all patients have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Unplanned Analysis

After the discontinuation of study 5F9009, a randomized double-blinded phase 3 study evaluating the safety and efficacy of Magrolimab versus Placebo in combination with Azacitidine in newly diagnosed, previously untreated patients with higher risk MDS, Gilead conducted an ad hoc DMC meeting on 31 August 2023, with OS and safety analysis results evaluated by DMC.

8.4. Analysis Conventions

8.4.1. Analysis Sets

8.4.1.1. Efficacy

The primary analysis set for efficacy analysis is the Intent-to-Treat (ITT) analysis set, defined as all randomized patients according to the treatment arm to which the patients are randomized, unless otherwise specified.

The Per-Protocol (PP) Analysis Set will be used in sensitivity analysis of the primary and key secondary efficacy endpoints. The PP Analysis Set includes patients in the ITT Analysis Set who meet the general criteria defining the target population, are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Study drug assignment will be designated according to the actual treatment received. The determination criteria details of the PP Analysis Set will be listed in the SAP.

8.4.1.2. Safety

The primary analysis set for safety analysis is the Safety Analysis Set, defined as all patients who received at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received.

All data collected during treatment period up to the last dose plus 70 days will be included in the safety summaries.

8.4.1.3. Pharmacokinetics

The PK analysis will be conducted on Pharmacokinetic Analysis Set, defined as all randomized patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.4.1.4. Immunogenicity

The Immunogenicity Analysis Set is defined as all randomized patients who received at least 1 dose of magrolimab and had at least 1 evaluable anti-magrolimab antibody test result.

8.4.1.5. Biomarker

The Biomarker Analysis Set includes all randomized patients who received at least 1 dose of any study treatment and have at least 1 evaluable biomarker measurement available.

8.4.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by treatment arm.

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study treatment. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative. Analysis will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analysis may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.5. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include age, sex, race/ethnicity, and randomization stratification group. Baseline data will include a summary of weight, height, body surface area, body mass index, WHO AML classification, and ECOG performance status.

8.6. Efficacy Analysis

8.6.1. Analysis of Primary Endpoint

Formal hypothesis testing will be performed to test the statistical hypothesis that the distribution of OS between the experimental arm and the control arm is the same (null hypothesis) versus that the experimental arm is superior to the control arm in terms of survival function (alternative hypothesis).

A log-rank test stratified by the randomization stratification factors will be used to compare the treatment arms for OS. A stratified Cox proportional hazard regression model will be used to estimate HR and its 2-sided 95% CI. In addition, the Kaplan-Meier method will be used to estimate median OS with its 95% CI, and the Kaplan-Meier plots will be provided.

To assess the robustness of the primary endpoint analysis results, OS will also be compared between treatment arms in the PP Analysis Set.

8.6.2. Analysis of Secondary Endpoints

Analysis will be performed based on the patient populations on which the endpoints are defined. Analysis of EFS will be similar to that of the primary efficacy endpoint OS.

Formal hypothesis testing will be performed to test the statistical hypothesis that the CR + CRh rates of the experimental arm and control arm are the same (null hypothesis) versus that the experimental arm is superior to the control arm in terms of CR + CRh rate (alternative hypothesis).

The Cochran-Mantel-Haenszel test stratified by the randomization stratification factors will be used to test whether CR + CRh rates of the 2 arms are the same. The point estimate of the CR + CRh rate and the corresponding 2-sided exact 95% CI based on Clopper-Pearson method will be provided for each treatment arm.

The CR rate, CR/CRh$_{MRD-}$ rate, CR$_{MRD-}$ rate and transfusion independence conversion rate will be evaluated in a similar manner as CR + CRh rate, except that the transfusion independence conversion rates will be based on the subset of randomized patients who are transfusion-dependent at baseline.

For the time-to-event endpoints of DCR and duration of CR + CRh, analysis will be conducted based on the subsets on which the outcome measures are defined. Specifically, the DCR will be based on patients who achieved CR within 6 cycles of treatment. Duration of CR + CRh will be based on patients who achieved CR or CRh within 6 cycles of treatment. The Kaplan-Meier method will be used to estimate median duration with its 95% CI and Kaplan-Meier plots will be provided.

To assess the robustness of the analysis results, key secondary efficacy endpoints will also be analyzed in the PP Analysis Set.

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8.7. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 70 days will be summarized by treatment group (according to the study drug received). Data for the pretreatment and treatment-free safety follow-up periods will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, count and percent of patients will be summarized. For continuous safety data, including laboratory data, the number of patients, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized by treatment group. Details are noted below.

8.7.1. Extent of Exposure

A patient's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.7.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study treatment up to the date of last dose of study treatment plus 70 days or the day before initiation of new anticancer therapy including SCT, whichever comes first. If the AE onset date is on or before the last dose date, the AE is considered as treatment-emergent AE regardless of the start of new anticancer therapy.

Summaries (number and percentage of patients) of treatment-emergent AEs (by system organ class and preferred term) will be provided by treatment group.

8.7.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized. Graded laboratory abnormalities will be defined using the grading scheme in Appendix 6.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 70 days or the day before initiation of new anticancer therapy including SCT, whichever comes first, will be summarized by treatment group. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study treatment or after the patient has been discontinued from treatment for at least 70 days will be included in a data listing.

8.7.4. Other Safety Evaluations

Vital signs and physical examination findings will be summarized at select time points. Details will be provided in the SAP.

8.8. Pharmacokinetic Analysis

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Due to the sparse nature of PK collection, PK parameters will not be calculated.

Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as zero in summary statistics and reported as is in data listings.

All data from this study may be combined with PK data from other company-sponsored clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

Additional analysis such as exposure-response analysis to evaluate the relationship between magrolimab exposure and efficacy/safety/PD biomarkers endpoints in the study may be performed if data allows and will be reported in a separate report when appropriate.

8.9. Analysis of Patient-Reported Outcome Data

The key PRO endpoints, TTD on the GHS/QoL scale and TTD on the physical functioning scale of the EORTC QLQ-C30, are defined based on the ITT Analysis Set. The TTD will be summarized using the Kaplan-Meier method. The log-rank test stratified by randomization stratification factors will be conducted for the TTD comparison between treatment arms, and the HR estimated using a Cox proportional hazard regression model stratified by randomization stratification factors will be provided.

Additional analysis will be conducted on PRO data, including absolute scores and changes from baseline for scales and single items of the EORTC QLQ-C30 instrument, the EQ-5D-5L instrument, and PGIS/PGIC at each assessment time point for each arm. A linear mixed effect model with treatment, time, treatment by time interaction, stratification factors, and baseline scores as fixed factors may be fitted for analysis of selective PRO endpoints.

8.10. Immunogenicity Analysis

Immunogenicity will be assessed using a 3-tier (screen, confirmatory, and titer) approach on study samples using a validated immunoassay. The rate and magnitude of anti-magrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Titer summaries may also be generated, if relevant. CCI [redacted]

Neutralizing antibody analysis will be conducted using a validated assay on ADA positive samples and results will be summarized.

8.11. Biomarker Analysis

The baseline level, absolute level, and change from baseline level over time will be summarized using descriptive statistics for each biomarker at the sample collection time point by treatment arm, as appropriate. CCI [redacted]

8.12. Sample Size

The study will randomize approximately 432 patients in total into 2 treatment arms at a 1:1 ratio, determined by formal hypothesis testing performed on the primary efficacy endpoint: OS, with family-wise Type I error controlled at 1-sided significance level of 0.025.

It is assumed that administration of magrolimab + venetoclax + azacitidine to study patients will result in a median OS of approximately 21 months, improved from a median OS of 14.7 months in patients treated with placebo + venetoclax + azacitidine. This corresponds to an OS HR of 0.7. Assuming that the duration of OS is exponentially distributed in each of the 2 arms, with an HR equal to 1 under the null hypothesis of no difference between the 2 treatment arms, 303 events are needed to detect an HR of 0.7 with 86.4% power at a 1-sided significance level of 0.025 using a log-rank test, the first interim analysis with futility test when 40% of the information (121 deaths) is available, and the second interim analysis with superiority test together with a futility test when 75% of the information (227 deaths) is available, and one primary analysis. For the second OS interim analysis and the OS primary analysis, the Lan-DeMets alpha spending function with O'Brien-Fleming stopping boundary will be used. The futility boundaries for two interim analyses are obtained using a Gamma beta-spending function with parameter -5.

With an accrual period of 19 months (with approximately 51% of the patients enrolled during the initial 12 months, and the remaining 49% of the patients enrolled during the last 7 months), 24 months of follow up, and an annual 1.43% dropout rate (5% dropout chance by 43 months with time to dropout assuming exponentially distributed time-to-dropout), a total sample size of 432 patients (216 patients per treatment group) is needed to observe the required 303 events.

8.13. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study, perform interim reviews of safety data at regular intervals, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination of the study in the best interests of the patient, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

In addition, the DMC will review the results from the interim analyses. Based on the pre-specified superiority and futility rules, the DMC may make recommendations to Gilead as to whether the study should be terminated for futility or continue as planned. Efficacy superiority boundaries are specified in Section 8.2. The nonbinding futility rule with a futility boundary of HR = 1.1 is used in the first interim analysis, and a futility boundary of HR = 0.9 in used in the second interim analysis if the null hypothesis of OS fails to be rejected at the second interim analysis.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study. If the DMC recommends stopping the study due to efficacy or futility, a Gilead Oversight Committee will be unblinded to confirm the DMC recommendation.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for Good Clinical Practice and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last patient completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform patients about genomic testing and/or planned sample retention. As part of the study-specific ICF to be signed by each patient participating in the study, patients will be asked to document agreement to allow the use of their samples for optional future research, in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to use already collected samples for optional genomic research. The results of the tests done on the samples will not be shared with the patient or the investigator.

9.1.5. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IRB/IEC and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each patient:

- Patient identification
- Documentation that patient meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)

- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An electronic case report form casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture system unless otherwise directed. The electronic case report form casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment electronic case report forms should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form

Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the electronic data capture system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the electronic data capture system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other timepoints (as instructed by Gilead), the investigator apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- The ethical principles of the Declaration of Helsinki
- International Council for Harmonisation (ICH) Good Clinical Practice (GCP)
- Applicable laws and regulatory requirements

9.3.2. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.3. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.4. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.5. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the patients, appropriate regulatory authorities, IRBs, and IECs. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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STUDY ACKNOWLEDGMENT

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

Amendment 7, 20 December 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Medical Monitor

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study. Special pandemic measures can be applied only when in accordance with the current situation and applicable local authority regulations, recommendations, or similar. These potential risks and mitigation plans can be summarized as follows:

1) Schedule of assessments:

    a) Physical examination:

        i) For all assessments where a physical examination is indicated, this portion of the visit can be conducted virtually; however, when samples need to be collected or dosing performed, these activities must occur in the clinic.

        ii) If a virtual visit is conducted for the physical examination assessment portion, in order to limit a patient's time in the clinic, vital signs may be omitted.

    b) Dosing:

        i) Dosing delays with magrolimab/placebo:

            (1) For patients who may have travel restrictions, the 4-week period of magrolimab/placebo dose delay for repriming can be extended to 6 weeks in order to minimize the need for repriming for patients in this scenario. Medical monitor approval is needed for this specific situation.

        ii) Dosing with azacitidine:

            (1) If needed under specific circumstances, sites can allow for administration of azacitidine locally nearer to patient's residence, with proper documentation (eg, name of site, name of physician overseeing transfusion, name of laboratory used, including accreditation certificate). Administration of azacitidine outside the center should be reserved only in cases where patients will not be able to get azacitidine dosing otherwise.

            (2) If treatment administration is given locally, then the patient should be evaluated by a local hematologist on Day 1 of that treatment cycle and have all laboratory assessments required on the Day 1 treatment cycle performed as per the protocol. The site should procure the clinical notes and laboratory reports for the principal investigator review and signature. The site is to ensure that all of these documents are filed in the patient's source records.

            (3) The treating physician at the study site should speak to the local hematologist and review protocol guidelines/dosing of azacitidine/reporting of reactions and document this information in the medical records.

iii) Venetoclax supply to patients:

(1) Patients may be unable to return to the site for a number of visits to get venetoclax, or the site may be unable to accept any patient visits.

Mitigation plan: Venetoclax may be provided to the patient from the site without a clinic visit, once it is confirmed that the patient may safely continue on venetoclax as determined by the principal investigator. A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship venetoclax from sites to study patients if permitted by local ethic committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

c) Sample collection:

i) While it is preferred to collect all protocol-specified laboratory samples, if resources are limited, PK/ADA samples may be collected and stored (frozen) and not shipped in real time if staff are not available to do so.

ii) For correlative peripheral blood or bone marrow aspirate samples, if they cannot be shipped according to their corresponding standard procedures same day, or refrigerated overnight for shipment the next day, please isolate the mononuclear cells (eg, by Ficoll gradient) and cryopreserve according to local best practices. If it is not possible to either ship samples or preserve and store according to the guidance above, then collection of these samples may be omitted until normal operations can resume.

d) General patient selection guidance:

i) To minimize patients receiving RBC transfusions given the current transfusion product shortage, we recommend selecting patients with higher hemoglobin thresholds at baseline and use IV iron and/or erythropoietin where clinically indicated.

2) Study drug supplies to sites:

a) Shipments of study drug could be delayed because of transportation issues. Without study drug patients would not be able to stay on the study drug as planned per protocol.

Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

3) Patient safety monitoring and follow-up:

a) Patients may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For patients who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the patient within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if patient has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm patient's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (2).

iv) If applicable, remind patient to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws);

Mitigation plan: Local laboratories may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Patients may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

d) The safety of trial participants is important and testing of coronavirus disease 2019 (COVID-19) infection will be based on local clinical guidelines for testing based on signs/symptoms and or suspected exposure to COVID-19.

Mitigation plan: If a patient has a diagnosis of COVID-19 while on this clinical study, study drugs may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general magrolimab/azacitidine/venetoclax dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in a clinical trial will have this event documented as an adverse event in the clinical database.

4) Protocol and monitoring compliance:

   a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with Gilead policy, a remote SDV should not be arranged. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on site must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

   a) There may be an increased amount of missing data due to patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of magrolimab in study patients remains unchanged. In the event that these potential risks cannot be mitigated due to the escalation of a pandemic, randomization of new patients will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

Appendix 3. Schedules of Assessment and Treatment Administration

Appendix Table 1. Schedule of Assessments for Azacitidine and Venetoclax – Screening and Treatment Period

Visit Window (Days)[a]	Screen-ing	Cycle (28-day Cycles)																			
		1										2						3+			
		None		± 3								± 3						± 3			
Cycle Day	-30 to -1	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]
Informed consent[c]	X																				
Demographics	X																				
Medical and cancer history, AML molecular marker results at diagnosis (if available), including date of most recent RBC and/or platelet transfusion(s)	X																				
Physical examination[d,e]	X	X				X		X				X						X			
HBV, HCV, and HIV	X																				
Vital signs, height, and weight[e,f]	X	X	X	X	X	X	X	X	X			X	X	X	X			X			
Pregnancy test[e,g]	X	Q4W →																			
CBC with differential, platelets, reticulocytes, blasts[e,h]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[e]		X	X		X	X						X									
Serum or plasma chemistry[e]	X	X[i]	X[i]	X[i]	X[i]	X		X	X			X		X				X			

Visit Window (Days)[a]	**Screen-ing**	**Cycle (28-day Cycles)**																			
		1										**2**						**3+**			
		None		**± 3**								**± 3**						**± 3**			
Cycle Day	**-30 to -1**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[b]**	**1**	**8**	**15**	**22**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[b]**	**1**	**15**	**28**	**Twice Weekly Until Count Recovery (Max = 14 Days)[b]**
PT/INR, and aPTT (or PTT)	X																				
Blood phenotyping or genotyping, type, and screen (ABO/Rh), DAT[j]	X																				
Urinalysis	X																				
ECOG performance status	X																				
12 Lead ECG (single)	X																				
Echocardiogram or MUGA[k]	X																				
Pulmonary function tests[l]	X																				
Adverse events[m]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications[n]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Eligibility criteria	X																				
Randomization[c]		X																			
Efficacy/Biomarkers																					
PRO assessment[o]		X										X						X			
Peripheral blood smear (for blasts)[p]	X									X						X				C4D28, C6D28, then Q3C	

Visit Window (Days)[a]	Screen-ing	Cycle (28-day Cycles)																			
		1										2						3+			
		None		± 3								± 3						± 3			
Cycle Day	-30 to -1	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]
Peripheral blood sample for biomarker studies[q]		X				X				X		X[r]				X		X[r]		C3D28, C6D28, C12D28	
Bone marrow aspirate for biomarker studies[s]	X									X						X				C6D28, C12D28	
Bone marrow biopsy for biomarker studies	X									X										C12D28	
Bone marrow aspirate for response assessment and cytogenetics[s,t]	X									X						X				C4D28, C6D28, then Q3C	
Bone marrow aspirate for flow based MRD assessment[t]	X									X						X				C4D28, C6D28	
Bone marrow aspirate ± biopsy slides or blocks[u] for independent central review[s]	X									X						X				C4D28, C6D28, then Q3C	

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; ADA = antidrug antibodies; AE = adverse event; AML = acute myeloid leukemia; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT= end of treatment; EQ-5D = EuroQoL (5 dimensions, 5 levels); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PGIS/PGIC = Patient Global Impression of Severity/Patient Global Impression of Change; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; Q3C = every 3 cycles; RBC = red blood cell; Rh = Rhesus factor; SAE = serious adverse event; WBC = white blood cell

a Any other visit window specifications for individual assessments should be applied.
b If the patient is cytopenic at Day 28, CBC is to be monitored at least twice per week for 2 weeks or until optimal count recovery is reached (whichever comes first). The best CBC result within the ± 2-week window is to be used for the response assessment, with the date of response being the date of the bone marrow assessment. Complete blood count need not be repeated if the prior CBC (including prior Day 28 CBC) is within 3 days of Day 1.
c Screening must be completed prior to randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 72 hours after randomization.
d Complete physical examination is to be performed at screening and symptom-directed physical examination is to be performed from Cycle 1 Day 1.
e Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to any study treatment administration.
f Vital signs will be assessed prior to administration of any study treatment. Details are provided in Section 6.6.4. Height will be collected at screening only. Weight will be collected at screening and Day 1 of each cycle.
g A serum pregnancy test will be conducted at screening and serum or urine pregnancy tests will be conducted every 4 weeks thereafter and can be performed locally without a requirement to visit the study site. A follicle-stimulating hormone test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Additional guidance is provided in Section 6.6.1.
h Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ $20 \times 10^3/\mu L$ prior to each magrolimab/placebo dose during Cycle 1.
i To monitor the risk of tumor lysis syndrome during venetoclax ramp-up, blood chemistry is to be collected predose and 6 to 8 hours postdose of venetoclax administration on Cycle 1 Day 1, Cycle 1 Day 2, and Cycle 1 Day 3. An additional blood chemistry is to be collected 24 hours (±3 hours) after the Cycle 1 Day 3 administration.
j ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) must be performed for each participant. Red blood cell genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a participant received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for participants with a recent transfusion). Results must be available before the first dose of magrolimab.
k Only for patients ≥ 18 to 74 years of age with cardiac disease, if needed to determine ineligibility to intensive chemotherapy
l Only for patients ≥ 18 to 74 years of age with pulmonary disease, if needed to determine ineligibility to intensive chemotherapy
m All SAEs and any AEs related to protocol-mandated procedures should be collected at screening. Adverse events should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.
n Prior and concomitant medications should be collected at screening. Concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.
o Four PRO instruments will be administered in this study: the EORTC QLQ-C30 questionnaire, the EQ-5D-5L, the PGIS, and the PGIC. The patient should complete these questionnaires before any other study procedures at required visits. EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC. PGIC is not required at Cycle 1 Day 1. If the PRO instruments are not available in a patient's language, patients are not required to complete the assessments. Patients with other situations related to PRO instrument completion (eg, visual impairment/blindness, limitation in upper extremity mobility/dexterity) may be exempt from these assessments after discussion with the sponsor.
p Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy.
q Samples will be collected predose within 12 hours prior to study treatment administration.
r Starting at Cycle 2 Day 1, peripheral blood samples for biomarker studies on Cycle X Day 1 do not need to be repeated at Day 1 of the cycle if they have been collected within the past 7 days.
s A trephine (biopsy) is to be collected if the aspirate sample is dry (not obtainable). If a bone marrow aspirate sample is not evaluable, another aspirate sample must be performed within 7 days. At screening, this procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for response assessment (eg, blast evaluation), cytogenetics, MRD assessment (performed during the first 6 cycles only), biomarker studies, and biobanking. When done on the same day, bone marrow aspirate samples are to be obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics are to be tested per institutional standards.

t Response assessments may be adjusted by ± 1 week for Day 28 of Cycles 1 and 2. After Cycle 2 Day 28, the window is ± 14 days. Bone marrow response information from Day 28 may be required to decide start of the next cycle per dosing modification guidelines in the protocol.
u Bone marrow biopsy (blocks) collected within 1 month prior to the signing of informed consent may be used in lieu of bone marrow biopsy at screening.

Appendix Table 2. Schedule of Treatment Administration for Azacitidine and Venetoclax

	Cycle (28-day Cycles)																										
	1[b]											2[b]										3+[b]						
Cycle Day[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Azacitidine[c]	X	X	X	X	X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X	X
Venetoclax[d]	Daily Days 1-28											Daily Days 1-28										Daily Days 1-28						

a Adverse events and concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.

b Visit window: Cycle 1 Days 3-15, ± 3 days; Cycle 2 onward, ± 3 days.

c Azacitidine administration should be completed at least 1 hour before magrolimab/placebo administration on days when both drugs are administered. Azacitidine may be administered on an alternative schedule of Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience. Please refer to Table 6. Once the patient has completed the first cycle of treatment, azacitidine may be administered at home only on days where magrolimab/placebo is not given and azacitidine is administered alone. Study drug should not be held for bone marrow biopsy.

d Venetoclax is administered daily. Please refer to Table 6. Study drug should not be held for bone marrow biopsy.

Appendix Table 3. Magrolimab/Placebo Administration and Associated Assessment Schedule-Treatment Period

Visit Window (Days)	None[a]		± 3[a]			Weekly x 5 ± 3 days	Every 2 weeks ± 3 days[b]
Day	**1**	**4**	**8**	**11**	**15**		
Vital signs[c]	X	X	X	X	X	X	X
CBC (hemoglobin)[d]	pre and postdose	pre and postdose	X	X	X		
PK[e]	Within 72 hours prior to magrolimab/placebo dosing		Within 12 hours prior to magrolimab/placebo dosing		Within 12 hours prior to magrolimab/placebo dosing	Within 12 hours prior to magrolimab/placebo dosing for 2nd week dose	Within 12 hours prior to magrolimab/placebo dosing before 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg[f]
Antidrug antibodies[f]							
Magrolimab/Placebo Administration							
Premedication[g]	X	X	X	X			
Magrolimab/Placebo[h]	X	X	X	X	X	X	X

ADA = antidrug antibodies; CBC = complete blood count; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PK = pharmacokinetic(s); RDW = red blood cell distribution width;

a In cases of magrolimab/placebo repriming/re-escalation following a treatment delay (Section 5.5.1.1), follow magrolimab/placebo schedule of assessment and administration for repriming (Appendix Table 4).

b On the first day of the biweekly maintenance dose, an additional sample for postdose PK will be collected at 1 hour (± 15 minutes) after the end of infusion of magrolimab/placebo.

c Vital signs will be assessed prior to administration of magrolimab/placebo. Details are provided in Section 6.6.4.

d Hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab/placebo during initial treatment, as described in Section 5.5.3.1. For CBC collection schedule beyond Day 15, please refer to Appendix Table 1.

e Samples will be collected predose within 12 hours prior to administration of magrolimab/placebo.

f When collected on the day of study treatment dosing, the blood sample for ADA must be collected at the same time as the PK sample.

g Premedication for magrolimab/placebo is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication for subsequent cycles may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion related reactions. In the case of a Grade 3 infusion related reaction, a premedication regimen for subsequent cycles is required (Section 5.5.1.2).

h Magrolimab/placebo doses should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab/placebo, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion for priming, repriming/re-escalation, and maintenance doses during the first 4 weeks. For magrolimab/placebo dosing, please refer to Table 6.

Appendix Table 4. Magrolimab/Placebo Repriming Administration and Associated Assessment Schedule – Treatment Period

Visit Window (Days)[a]	None			± 3				
Day	**1**	**2**	**4**	**8**	**11**	**15**	**22[b]**	**29, then every 2 weeks**
Safety								
CBC with differential, platelets, reticulocytes[c,d]	X	X	X	X	X	X	X	
Haptoglobin and LDH[c]	X	X	X	X				
Chemistry[c]	X	X	X	X		X		
Vital signs[e]	X		X	X	X	X	X	X
Weight	X							
Symptom-directed physical examination[c]	X			X		X		
Adverse events[f]	→	→	→	→	→	→	→	→
Concomitant medications[f]	→	→	→	→	→	→	→	→
PK/ Immunogenicity								
PK[g]	X			X		X[g]		X[g]
Antidrug antibodies[h]	X					X[h]		X[h]
Magrolimab/Placebo Administration								
Premedication[i]	X		X	X	X			
Magrolimab/Placebo[j]	X		X	X	X	X	X	X[j]

CBC = complete blood count; LDH = lactate dehydrogenase; PK = pharmacokinetic(s);-Q4W = every 4 weeks; WBC = white blood cell

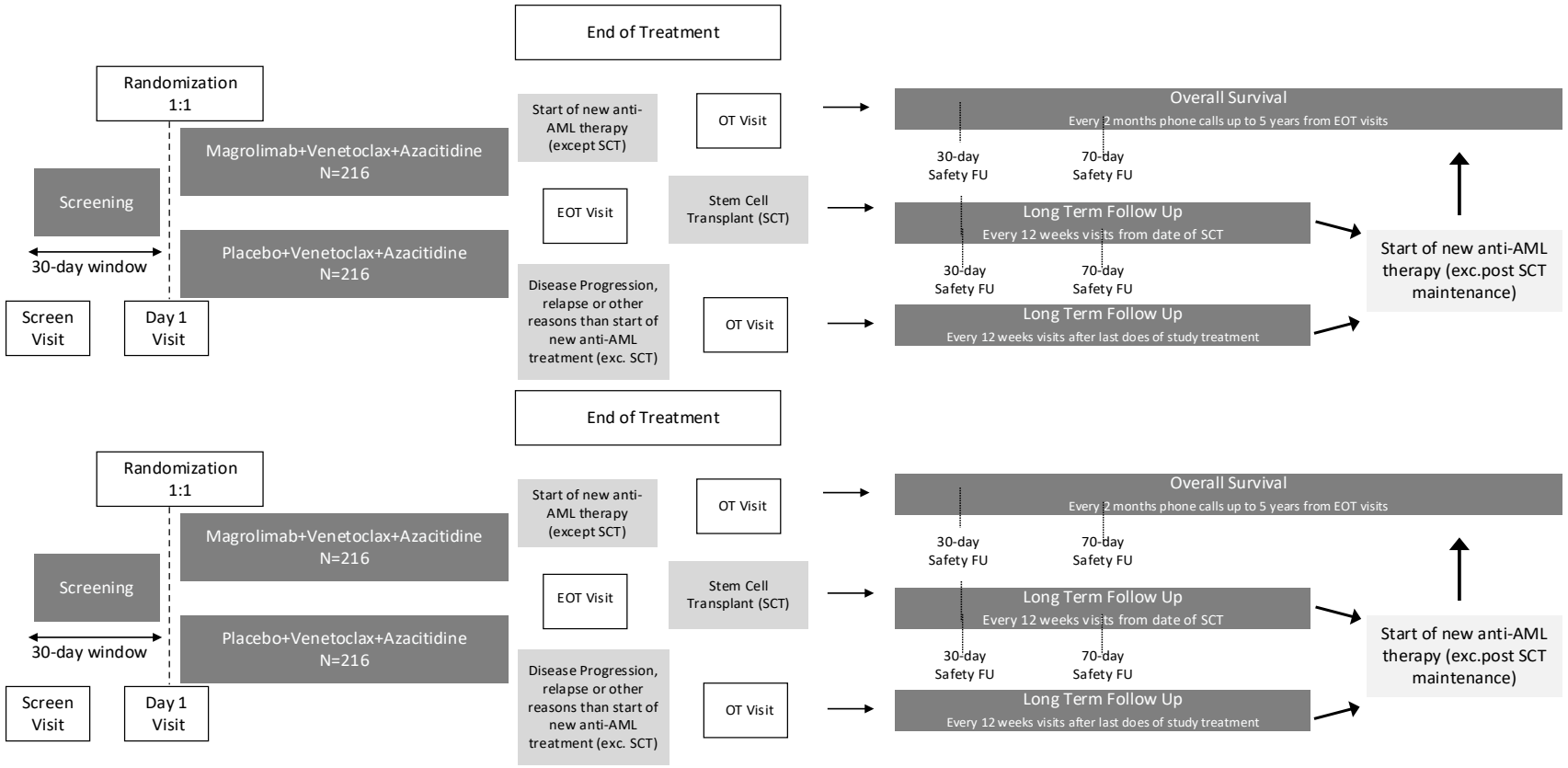
a Any other visit window specifications for individual assessments should be applied.

b In case the repriming occurs during the first 4 weeks of magrolimab/placebo treatment, patient should receive magrolimab 30 mg/kg or placebo weekly x 5 after receiving Day 15 dose. All Day 22 safety assessments should be completed weekly x 5. One week after the fifth weekly dose, dosing of magrolimab/placebo will be 30 mg/kg Q2W.

c Pretreatment assessments for the initial dose may be collected up to 72 hours before administration of any study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to any study treatment administration.

d Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ 20 × 10^3/μL prior to each magrolimab/placebo dose during first 4 weeks of repriming.
e Vital signs will be assessed prior to administration of magrolimab/placebo. Details are provided in Section 6.6.4.
f Adverse events and concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.
g Samples will be collected within 72 hours before the first dose of magrolimab/placebo and within 12 hours before subsequent doses of magrolimab/placebo. In addition to Day 1, Day 8, and Day 15, predose samples will also be collected before the Day 29 dose (only applicable if the repriming schedule has 4 additional weekly doses post Day 22), as well as before the first, fifth, ninth, 15th, and 21st biweekly maintenance doses of 30 mg/kg, respectively, and at EOT. On the first day of the biweekly maintenance dose, an additional sample for postdose PK will be collected at 1 hour (± 15 minutes) after the end of infusion of magrolimab/placebo.
h When collected on the day of magrolimab/placebo dosing, the blood sample for ADA must be collected at the same time as the predose PK sample. ADA samples will be collected at predose on Day 1, Day 15, and Day 29 (only applicable if the repriming schedule has 4 additional weekly doses post Day 22), as well as before the first, fifth, ninth, 15th, and 21st biweekly maintenance doses of 30 mg/kg, respectively, and at EOT.
i Premedication for magrolimab/placebo is required prior to the administration of the first 4 doses of study treatment in case of reintroduction with repriming. Premedication for subsequent cycles may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion related reactions. In the case of a Grade 3 infusion related reaction, a premedication regimen for subsequent cycles is required (Section 5.5.4 and Section 5.5.3.2.1).
j Magrolimab/placebo doses should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab/placebo, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. Monitor patients for 1 hour post infusion, during first 4 weeks for repriming. For magrolimab/placebo dosing, please refer to Table 6.

Appendix Figure 1. Posttreatment Visit Schedule



AML = acute myeloid leukemia; EOT = end of treatment; FU = follow-up; SCT = stem cell transplant

Appendix Table 5. Schedule of Assessments – Posttreatment

	End-of-Treatment Visit	Safety Follow-up Visit/Telephone Call[a]	Safety Follow-up Visit/Telephone Call[a]	Long-term Follow-up	Long-term Follow-up after SCT	Survival Follow-up
	Within 7 Days after Last Dose or EOT Decision, whichever occurs later	30 Days after Last Dose	70 Days after Last Dose	Until Start of a New Anti-AML Therapy[b]	Until Start of a New Anti-AML Therapy[b]	Every 2 Months (up to 5 years from EOT visit) Until Death or End of Study, whichever occurs first
Visit Window	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 14 days**	**± 14 days**	—
Symptom-directed physical examination	X					
Vital signs	X					
Serum or urine pregnancy test[c]	Q4W	→	→	→	→	→
CBC with differential, platelets, reticulocytes, blasts	X			Q12W	Q12W	
Serum or plasma chemistry	X					
ECOG performance status	X					
Adverse events[d]	X	X	X			
Concomitant medications	X	X	X			
New anti-AML therapy reporting[e]	X	X	X	X	X	X
PRO assessment[f]	X			Q12W	Q12W	
Peripheral blood smear (for blasts)	X			Q12W	Q12W	
Peripheral blood sample for biomarker studies	X					
Bone marrow aspirate for biomarker studies	X					

	End-of-Treatment Visit	Safety Follow-up Visit/Telephone Call[a]	Safety Follow-up Visit/Telephone Call[a]	Long-term Follow-up	Long-term Follow-up after SCT	Survival Follow-up
	Within 7 Days after Last Dose or EOT Decision, whichever occurs later	30 Days after Last Dose	70 Days after Last Dose	Until Start of a New Anti-AML Therapy[b]	Until Start of a New Anti-AML Therapy[b]	Every 2 Months (up to 5 years from EOT visit) Until Death or End of Study, whichever occurs first
Visit Window	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 14 days**	**± 14 days**	—
Bone marrow aspirate for response assessment, and cytogenetics[g,h]	X			Q12W	Q12W	
Pharmacokinetics	X					
Antidrug antibodies	X					
Survival follow-up						X

AE = adverse event; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; EQ-5D = EuroQoL (5 dimensions, 5 levels); PGIS/PGIC = Patient Global Impression of Severity/Patient Global Impression of Change; PRO = patient-reported outcome; Q4W = every 4 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SCT = stem cell transplant

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site.
b For patients who start new anti-AML therapy (other than SCT) before a relapse, efficacy status (done as standard of care) will be collected until relapse.
c Pregnancy testing will be continued monthly up to 6 months after the end of treatment per the duration of contraception requirement as discussed in Appendix 5. Testing during survival follow-up may be done at home and the result self-reported by the patient.
d Report all AEs through the Safety Follow-up Visit/Call, and any treatment-related SAEs thereafter.
e Collect data for the first new anti-AML therapy following the last dose of study treatment or following SCT.
f Four PRO instruments will be administered in this study: the EORTC QLQ-C30 questionnaire, the EQ-5D-5L, the PGIS, and the PGIC. The patient should complete these questionnaires before any other study procedures at required visits. EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC. If the PRO instruments are not available in a patient's language, patients are not required to complete the assessments. Patients with other situations related to PRO instrument completion (eg, visual impairment/blindness, limitation in upper extremity mobility/dexterity) may be exempt from these assessments after discussion with the sponsor.
g Response assessment at EOT visit not required if performed within the last 30 days or documented disease progression/relapse or start of new anti-AML therapy, whichever occurs first. (SCT and maintenance therapy are not considered new anti-AML therapy.)
h Conventional cytogenetic testing (per institutional standards) is required for all patients.

Appendix 4. Disease Response Criteria Based on European LeukemiaNet (ELN) and International Working Group (IWG) Criteria

Assessment of leukemia response in AML patients will be conducted using the European LeukemiaNet (ELN) 2017 recommendations for AML with modifications {Dohner 2017} (Appendix Table 6). Response classifications include complete remission without minimal residual disease (CR_{MRD-}), complete remission with positive or unknown minimal residual disease ($CR_{MRD+/unk}$), CR with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), and stable disease (SD).

In addition, CR with partial hematologic recovery (CRh) will be assessed for AML, as defined as patients who achieve a CR per AML ELN 2017 recommendations {Dohner 2017}, but with only partial recovery of peripheral blood counts (platelets > 50×10^9/L and absolute neutrophil count (ANC) > 0.5×10^9/L).

Cytogenetic CR (cCR) will be assessed by 2003 IWG criteria as CR with normal cytogenetics (Appendix Table 7) {Cheson 2003}.

Hematologic improvement will be assessed by 2006 IWG criteria {Cheson 2006} to compare with disease response assessed by 2017 ELN criteria (Appendix Table 8) {Dohner 2017}.

The date of the bone marrow assessment should be used as the date of response assessment. Complete blood count results used for the response assessment will be derived from the best accompanying laboratory CBC result within the ± 2-week window of the bone marrow assessment used to support the efficacy response assessment. All components (eg, platelets, absolute neutrophils) should come from the same test. If disease progression or relapse is assessed based on CBC assessments or new extramedullary disease or both, other than bone marrow blast assessments, then the date of the corresponding CBC or new extramedullary disease assessment or the earlier of these 2 dates will be used as the date of response assessment.

Appendix Table 6. Response Criteria in Acute Myeloid Leukemia (ELN 2017 Recommendations with Modifications)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Complete remission without minimal residual disease (CR_{MRD-})	> 1.0×10^9/L	> 100×10^9/L	< 5%	MRD negative (determined using multiparameter flow cytometry with a sensitivity of < 0.1%). Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
Complete remission with positive or unknown minimal residual disease ($CR_{MRD+/unk}$)	> 1.0×10^9/L	> 100×10^9/L	< 5%	MRD positive (determined using multiparameter flow cytometry with a sensitivity of < 0.1%) or unknown. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
Complete remission with incomplete hematologic recovery (CRi)[a]	Neutrophils > 1.0×10^9/L OR Platelets > 100×10^9/L		< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease. (All CR criteria except residual neutropenia [<1.0×10^9/L] or thrombocytopenia [<100×10^9/L]).
Complete remission with partial hematologic recovery (CRh)[a]	> 0.5×10^9/L	> 50×10^9/L	< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
Morphologic leukemia-free state (MLFS)			< 5%	Absence of circulating blasts and 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)	> 1.0×10^9/L	> 100×10^9/L	Decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Blasts < 5% with Auer rods may also be considered a PR
Stable disease	Absence of CR_{MRD-}, $CR_{MRD+/unk}$, CRi, CRh, PR, MLFS; and criteria for progressive disease not met			

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Progressive disease	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • ≥ 50% increase in marrow blasts over baseline (a minimum 15% increase is required in cases with < 30% blasts at baseline); or persistent marrow blast percentage of > 70% over at least 3 months, and without at least a 100% improvement in ANC to an absolute level > 0.5×10^9/L [500/μL], and/or platelet count to > 50×10^9/L [50,000/μL] non-transfused); or • ≥ 50% increase in peripheral blasts (WBC × % blasts) to> 25×10^9/L (> 25,000/μL) (in the absence of differentiation syndrome); or • New extramedullary disease.			
Hematologic relapse (after CR_{MRD-}, $CR_{MRD+/unk}$, CRi, CRh)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease			

ANC = absolute neutrophil count; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CR_{MRD-} = complete remission without minimal residual disease; $CR_{MRD+/unk}$ = complete remission with positive or unknown minimal residual disease; ELN = European LeukemiaNet; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PR = partial remission; WBC = white blood cell
a A response could be classified as both CRh and CRi if both criteria are met.
Source: Based on ELN 2017 guidelines {Dohner 2017} with modifications for the purposes of this protocol.

Appendix Table 7. Additional Response Definitions Used in This Study (2003 IWG Criteria)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Cytogenetic CR (cCR)	> 1.0×10^9/L	> 100×10^9/L	< 5%	Cytogenetics normal and no evidence of extramedullary disease
Treatment Failure[a]	Failure to achieve CR within 6 cycles of treatment			

cCR = cytogenetic complete remission; CR = complete remission; IWG = International Working Group
a. Treatment failure defined for this protocol.
Source: {Cheson 2003}

Appendix Table 8. Response Criteria for Hematologic Improvement

Hematologic Improvement (HI) Category[a]	Response Criteria
Erythroid Response (HI-E) (pretreatment < 110 g/L)	Pretransfusion increase in hemoglobin by 15 g/L or Compared to an 8-week pretreatment period, a reduction in transfusion requirements by 4 units in an 8-week posttreatment period
Platelet Response (HI-P) (pretreatment < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patient starting with a platelet count > 20×10^9/L pretreatment or Increase from < 20×10^9/L pretreatment to > 20×10^9/L post-treatment and by at least 100%
Neutrophil Response (HI-N) (pretreatment < 1.0×10^9/L)	At least 100% increase and an absolute increase of > 0.5×10^9/L
Progression/relapse after Hematological Improvement[b]	One or more of the following ≥ 50% decrement from maximum response in neutrophils or platelets Reduction in hemoglobin by ≥ 15 g/L Transfusion dependence

a Pretreatment counts should be an average of at least 2 measurements (not influenced by transfusions) performed ≥ 1 week apart.
b In the absence of another explanation. For example, including, but not restricted to, acute infection, gastrointestinal bleeding and hemolysis.
Source: {Cheson 2006}

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in an embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

For the purposes of this study, a female-born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Patients

a. Study Drug Effects on Pregnancy and Hormonal Contraception

There are no adequate and well-controlled studies of magrolimab in pregnant women. Magrolimab when dosed to pregnant monkeys was not teratogenic, but resulted in stillbirth and neonate deaths, secondary to fetal anemia. Based on these data, magrolimab should not administered to pregnant women. Advise females with reproductive potential to avoid pregnancy during treatment with magrolimab and for at least 3 months after treatment.

For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the mechanism of action (MOA) and findings in animals, azacitidine may cause fetal harm when administered to a pregnant woman. Advise females with reproductive potential to avoid pregnancy during treatment with azacitidine. Studies in vitro have demonstrated that CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Based on its MOA and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. Advise females with reproductive potential to avoid pregnancy during treatment with venetoclax. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information for additional information on the potential risks of treatment with azacitidine, and venetoclax.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. Pregnancy tests will be performed every 4 weeks thereafter until the end of contraception requirement. Duration of required contraception for female patients in this clinical trial should start from screening visit until 6 months after the last dose of study drug administered. Female patients must agree to one of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Non-hormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
  - Subdermal contraceptive implant
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

3) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 3 months (6 months in Canada only) after the last dose of study drug administered. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive method should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to Be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months post last study drug dose. Study drug must be discontinued immediately.

Male patients whose partner has become pregnant or suspects she is pregnant from start of study to 3 months post last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 7. Eastern Cooperative Oncology Group Performance Status

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Available online: http://ecog-acrin.org/resources/ecog-performance-status. Accessed 18 February 2020.

Appendix 8. 2017 European LeukemiaNet Risk Stratification by Genetics

Risk Category[a]	Genetic Abnormality
Favorable	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*-ITD or with *FLT3*-ITD[low,b]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high,b]
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low,b] (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[c]
	Cytogenetic abnormalities are not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KM2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EV11)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype[d], monosomal karyotype[e]
	Wild-type *NPM1* and *FLT3*-ITD[high,b]
	Mutated *RUNX1*[f]
	Mutated *ASXL1*[f]
	Mutated *TP53*[g]

AML = acute myeloid leukemia; DNA = deoxyribonucleic acid; HCT = hematopoietic cell transplant; WHO = World Health Organization

a Prognostic impact of a marker is treatment-dependent and may change with new therapies.

b Low, low allelic ratio (< 0.5); high, high allelic ratio (≥ 0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild-type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.

c The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

d Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1.*

e Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

f These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

g *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

Table adapted from {Dohner 2017}.

Appendix 9. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 10. EuroQol (5 Dimensions, 5 levels) Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

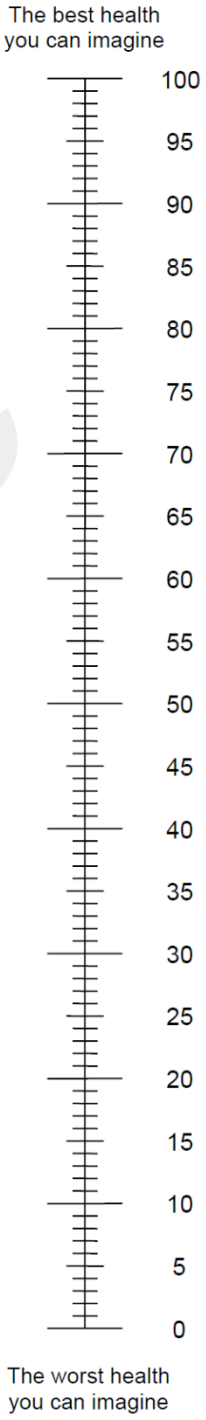
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 11. Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

HEALTH-RELATED QUALITY OF LIFE

Patient Global Impression Status: health-related quality of life

Please choose the response below that best describes your health-related quality of life (physical, social and psychological wellbeing) during the past week.

- Excellent
- Good
- Moderate
- Poor
- Very Poor

Patient Global Impression of Change: health-related quality of life

All things considered, how did your health-related quality of life (physical, social and psychological wellbeing) change since you started taking the study medication?

- Much improved
- A little improved
- No change
- A little worsened
- Much worsened

PHYSICAL FUNCTION

Patient Global Impression of Status: physical function

Please choose the response below that best describes your physical function*

- Excellent
- Good
- Moderate
- Poor
- Very Poor

* Physical function includes activities like eating, dressing, washing yourself, or using the toilet, carrying a heavy shopping bag or a suitcase, taking a long walk, taking a short walk outside of the house, and not having to stay in bed or chair during the day.

Patient Global Impression of Change: physical function

All things considered, how did your physical function change since you started taking the study medication?*

- Much improved
- A little improved
- No change
- A little worsened
- Much worsened

* Physical function includes activities like eating, dressing, washing yourself, or using the toilet, carrying a heavy shopping bag or a suitcase, taking a long walk, taking a short walk outside of the house, and not having to stay in bed or chair during the day.

Appendix 12. Cockcroft Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided in the table below. The formula appropriate to the units in which serum creatinine was measured and the patient's gender should be used.

Serum Creatinine Units	Gender	Formula
mg/dL	Males	eC_{cr} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1}{72 \times \text{patient serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{- patient age [years]}) \times \text{patient weight [kilograms]} \times 0.85}{72 \times \text{patient serum creatinine [mg/dl]}}$
µM/dL	Males	eC_{cr} [mL/min] = $\frac{(140\text{- patient age [years]}) \times \text{patient weight [kilograms]} \times 1.23}{\text{Patient serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{- patient age [years]}) \times \text{patient weight [kilograms]} \times 1.04}{\text{Patient serum creatinine [mg/dl]}}$

Abbreviation: eCcr=estimated creatinine clearance
Source: {Cockcroft 1976}

Appendix 13. World Health Organization (WHO) Classification of AML (2016)

AML with recurrent genetic abnormalities

- AML with a translocation between chromosomes 8 and 21 [t(8;21)]
- AML with a translocation or inversion in chromosome 16 [t(16;16) or inv(16)]
- APL with the *PML-RARA* fusion gene
- AML with a translocation between chromosomes 9 and 11 [t(9;11)]
- AML with a translocation between chromosomes 6 and 9 [t(6;9)]
- AML with a translocation or inversion in chromosome 3 [t(3;3) or inv(3)]
- AML (megakaryoblastic) with a translocation between chromosomes 1 and 22 [t(1;22)]
- AML with the *BCR-ABL1* (*BCR-ABL*) fusion gene
- AML with mutated *NPM1* gene
- AML with biallelic mutations of the *CEBPA* gene (that is, mutations in both copies of the gene)
- AML with mutated *RUNX1* gene

AML with myelodysplasia-related changes

AML related to previous chemotherapy or radiation

AML not otherwise specified (This includes cases of AML that do not fall into one of the above groups.)

Appendix 14. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country	Authorized by Swissmedic
Magrolimab	Study drug	No	No[a]	No
Azacitidine	Study drug	Yes	Yes[a]	Yes
Venetoclax	Study drug	Yes	Yes[a]	Yes
Acetaminophen	AxMP	Yes	Yes	Yes
Diphenhydramine	AxMP	Yes	Yes	Yes
Dexamethasone	AxMP	Yes	Yes	Yes

AxMP = auxiliary medicinal product; EU = European Union; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

a Rationale described in Section 1.

Appendix 15. Country-Specific Requirements

Additional Country-Specific Requirements for France

Country-specific Requirements	Protocol Section
F#12: Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow assessments.	Section 4.2
Bone marrow aspirate for blast evaluation (response assessment), cytogenetics, MRD assessment, and biomarker studies. A trephine (biopsy) is required if the aspirate sample is dry (not obtainable).	Section 6.2.1
Bone marrow assessments (aspirate and/trephine biopsy if the aspirate sample is dry [not obtainable]) are required for response assessments (eg, blast evaluation), including conventional cytogenetic analysis per institutional standards (Appendix Table 1). In addition, bone marrow specimens may be used for biomarker studies, MRD monitoring, CCI [redacted], and biobanking. Bone marrow biopsy for biomarker studies will be optional. Minimal residual disease testing and biomarker studies will be performed by a central laboratory. Details for preparation and distribution of aspirate and/or biopsy/trephine specimens to the testing laboratories will be provided in the laboratory manual for this study. Bone marrow aspirate and/or biopsy slides or blocks for efficacy assessments will be prepared for potential evaluation of response assessments by independent central review.	Section 6.5.1
Peripheral blood, bone marrow aspirate, and trephine biopsy samples will be collected from all patients who have provided consent to participate in this study. Bone marrow trephine biopsy for biomarker studies are optional. However, for patients whose bone marrow aspirate is dry (not obtainable), trephine biopsy samples will be required for biomarker studies. On-treatment CCI [redacted] Biomarker samples may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response, including efficacy and/or AEs, dose optimization, and to better understand the biology of AML in general. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays described below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.	Section 6.9

Appendix Table 1. Schedule of Assessments for Azacitidine and Venetoclax – Screening and Treatment Period

Visit Window (Days)[a]	Screen-ing	Cycle (28-day Cycles)																			
		1										2						3+			
		None		± 3								± 3						± 3			
Cycle Day	-30 to -1	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]
Informed consent[c]	X																				
Demographics	X																				
Medical and cancer history, AML molecular marker results at diagnosis (if available), including date of most recent RBC and/or platelet transfusion(s)	X																				
Physical examination[d,e]	X	X				X		X				X						X			
HBV, HCV, and HIV	X																				
Vital signs, height, and weight[e,f]	X	X	X	X	X	X	X	X	X			X	X	X	X			X			
Pregnancy test[e,g]	X	Q4W →																			
CBC with differential, platelets, reticulocytes, blasts[e,h]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[e]		X	X		X	X						X									
Serum or plasma chemistry[e]	X	X[i]	X[i]	X[i]	X[i]	X		X	X			X		X				X			
PT/INR, and aPTT (or PTT)	X																				

Visit Window (Days)[a]	Screen-ing	Cycle (28-day Cycles)																			
		1										2						3+			
		None		± 3								± 3						± 3			
Cycle Day	-30 to -1	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]
Blood phenotyping or genotyping, type, and screen (ABO/Rh), DAT[j]	X																				
Urinalysis	X																				
ECOG performance status	X																				
12 Lead ECG (single)	X																				
Echocardiogram or MUGA[k]	X																				
Pulmonary function tests[l]	X																				
Adverse events[m]	→																				→
Concomitant medications[n]	→																				→
Eligibility criteria	X																				
Randomization[c]		X																			
Efficacy/Biomarkers																					
PRO assessment[o]		X										X						X			
Peripheral blood smear (for blasts)[p]	X									X						X				C4D28, C6D28, then Q3C	
Peripheral blood sample for biomarker studies[q]		X				X				X		X[r]				X		X[r]		C3D28, C6D28, C12D28	

Visit Window (Days)[a]	Screen-ing	Cycle (28-day Cycles)																			
		1										2						3+			
		None		± 3								± 3						± 3			
Cycle Day	-30 to -1	1	2	3	4	8	11	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	8	15	22	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]	1	15	28	Twice Weekly Until Count Recovery (Max = 14 Days)[b]
Bone marrow aspirate for biomarker studies[s]	X									X						X				C6D28, C12D28	
CCI																					
Bone marrow aspirate for response assessment and cytogenetics[s,t]	X									X						X				C4D28, C6D28, then Q3C	
Bone marrow aspirate for flow based MRD assessment[t]	X									X						X				C4D28, C6D28	
Bone marrow aspirate ± biopsy slides or blocks[u] for independent central review[s]	X									X						X				C4D28, C6D28, then Q3C	

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; ADA = antidrug antibodies; AE = adverse event; AML = acute myeloid leukemia; aPTT = activated partial thromboplastin time; CBC = complete blood count; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT= end of treatment; EQ-5D = EuroQoL (5 dimensions, 5 levels); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; PGIS/PGIC = Patient Global Impression of Severity/Patient Global Impression of Change; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; Q3C = every 3 cycles; RBC = red blood cell; Rh = Rhesus factor; SAE = serious adverse event; WBC = white blood cell

a Any other visit window specifications for individual assessments should be applied.

b If the patient is cytopenic at Day 28, CBC is to be monitored at least twice per week for 2 weeks or until optimal count recovery is reached (whichever comes first). The best CBC result within the ± 2-week window is to be used for the response assessment, with the date of response being the date of the bone marrow assessment. Complete blood count need not be repeated if the prior CBC (including prior Day 28 CBC) is within 3 days of Day 1.

c Screening must be completed prior to randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 72 hours after randomization.
d Complete physical examination is to be performed at screening and symptom-directed physical examination is to be performed from Cycle 1 Day 1.
e Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to any study treatment administration.
f Vital signs will be assessed prior to administration of any study treatment. Details are provided in Section 6.6.4. Height will be collected at screening only. Weight will be collected at screening and Day 1 of each cycle.
g A serum pregnancy test will be conducted at screening and serum or urine pregnancy tests will be conducted every 4 weeks thereafter and can be performed locally without a requirement to visit the study site. A follicle-stimulating hormone test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Additional guidance is provided in Section 6.6.1.
h Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ $20 \times 10^3/\mu L$ prior to each magrolimab/placebo dose during Cycle 1.
i To monitor the risk of tumor lysis syndrome during venetoclax ramp-up, blood chemistry is to be collected predose and 6 to 8 hours postdose of venetoclax administration on Cycle 1 Day 1, Cycle 1 Day 2, and Cycle 1 Day 3. An additional blood chemistry is to be collected 24 hours (±3 hours) after the Cycle 1 Day 3 administration.
j ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) must be performed for each participant. Red blood cell genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a participant received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for participants with a recent transfusion). Results must be available before the first dose of magrolimab.
k Only for patients ≥ 18 to 74 years of age with cardiac disease, if needed to determine ineligibility to intensive chemotherapy
l Only for patients ≥ 18 to 74 years of age with pulmonary disease, if needed to determine ineligibility to intensive chemotherapy
m All SAEs and any AEs related to protocol-mandated procedures should be collected at screening. Adverse events should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.
n Prior and concomitant medications should be collected at screening. Concomitant medications should be recorded at all scheduled and unscheduled assessment visits, and at all treatment visits, even when other assessments are not scheduled.
o Four PRO instruments will be administered in this study: the EORTC QLQ-C30 questionnaire, the EQ-5D-5L, the PGIS, and the PGIC. The patient should complete these questionnaires before any other study procedures at required visits. EORTC QLQ-C30 and EQ-5D-5L questionnaires should be performed prior to PGIS/PGIC. PGIC is not required at Cycle 1 Day 1. If the PRO instruments are not available in a patient's language, patients are not required to complete the assessments. Patients with other situations related to PRO instrument completion (eg, visual impairment/blindness, limitation in upper extremity mobility/dexterity) may be exempt from these assessments after discussion with the sponsor.
p Peripheral blood smears for blasts are to be collected along with bone marrow aspirate.
q Samples will be collected predose within 12 hours prior to study treatment administration.
r Starting at Cycle 2 Day 1, peripheral blood samples for biomarker studies on Cycle X Day 1 do not need to be repeated at Day 1 of the cycle if they have been collected within the past 7 days.
s If a bone marrow aspirate sample is not evaluable, another aspirate sample must be performed within 7 days. At screening, this procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for response assessment (eg, blast evaluation), cytogenetics, MRD assessment (performed during the first 6 cycles only), biomarker studies, and biobanking. For patients whose bone marrow aspirate is dry (not obtainable), a trephine biopsy sample is required. If an CCI [redacted] Conventional cytogenetics are to be tested per institutional standards.
t Response assessments may be adjusted by ± 1 week for Day 28 of Cycles 1 and 2. After Cycle 2 Day 28, the window is ± 14 days. Bone marrow response information from Day 28 may be required to decide start of the next cycle per dosing modification guidelines in the protocol. For patients whose bone marrow aspirate is dry (not obtainable), a trephine biopsy sample is required.
u Bone marrow biopsy (blocks) collected within 1 month prior to the signing of informed consent may be used in lieu of bone marrow biopsy at screening.

Appendix 16. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing Amendment 6 to this amendment will be made available upon the publication of this protocol.

Amendment 7 (15 December 2023)

Rationale for Key Changes Included in Amendment 7	Affected Sections
Specific information regarding the Gilead internal unblinded team was added to the planned interim unblinding section.	Section 5.1.3
Additional clarification was provided for azacitidine administration per local clinical practice guidelines.	Section 5.5.2
Magrolimab/placebo dose modification guidelines were revised for patients in remission with Grade 4 neutropenia or Grade 4 thrombocytopenia.	Section 5.5.3.1.2
Minor changes to correct typographic errors were applied.	Throughout, as needed

Prot GS-US-590-6154 amd-7

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	20-Dec-2023 20:13:15