CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients with Myeloid Malignancies
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147229
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT04778410
Indication:	Myeloid Malignancies
Protocol ID:	GS-US-546-5920
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 10 December 2020 Amendment 1: 15 June 2021 Amendment 2: 20 September 2021 Amendment 3: 27 January 2022 Amendment 4: 09 May 2022 Amendment 5: 11 November 2022 Amendment 6: 02 November 2023

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, United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

CONFIDENTIALITY STATEMENT

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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<table>
<tr><td>Study Title:</td><td>A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients with Myeloid Malignancies</td></tr>
<tr><td>IND Number:
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<tr><td>Study Centers Planned:</td><td>Approximately 35 centers globally</td></tr>
<tr><td>Primary and Secondary Objectives and Endpoints:</td><td>Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza)
Primary and secondary objectives and endpoints for patients with newly diagnosed, previously untreated acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy are as follows:
<table>
<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
<tr><td>• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine as determined by the complete remission (CR) rate (Phase 2 Cohort 1)
• To evaluate the safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine (Safety Run-in Cohort 1)</td><td>• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 1)
• Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (AEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Safety Run-in Cohort 1)</td></tr>
<tr><th>Secondary Objectives</th><th>Secondary Endpoints</th></tr>
<tr><td>• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine
• To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia</td><td>• Overall response rate (ORR), including CR, complete remission with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), partial remission (PR), and morphologic leukemia-free state (MLFS)</td></tr>
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therapy venetoclax + azacitidine (Phase 2 Cohort 1) • To evaluate the pharmacokinetics (PK) of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine	• CR/CRi rate • Complete remission without minimal residual disease (CR_{MRD-}) rate • Complete remission or complete remission with partial hematologic recovery (CR/CRh) rate • Cytogenetic complete remission (cCR) • Duration of responses (DOR) • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • Event-free survival • Overall survival (OS) • Red blood cell (RBC) transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 1) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)

Primary and secondary objectives and endpoints for patients with relapsed or refractory (R/R) AML are as follows:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy mitoxantrone, etoposide, and cytarabine (MEC) as determined by the CR rate (Phase 2 Cohort 2) • To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy MEC (Safety Run-in Cohort 2)	• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 2) • Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 2)

Secondary Objectives	Secondary Endpoints
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy MEC • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy MEC (Phase 2 Cohort 2) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy MEC • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy MEC	• ORR, including CR, CRi, CRh, PR, and MLFS • CR/CRi rate • CR_{MRD-} rate • CR/CRh rate • cCR • DOR • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • EFS • OS • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 2) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-Chemo Maint Mag+CC-486)

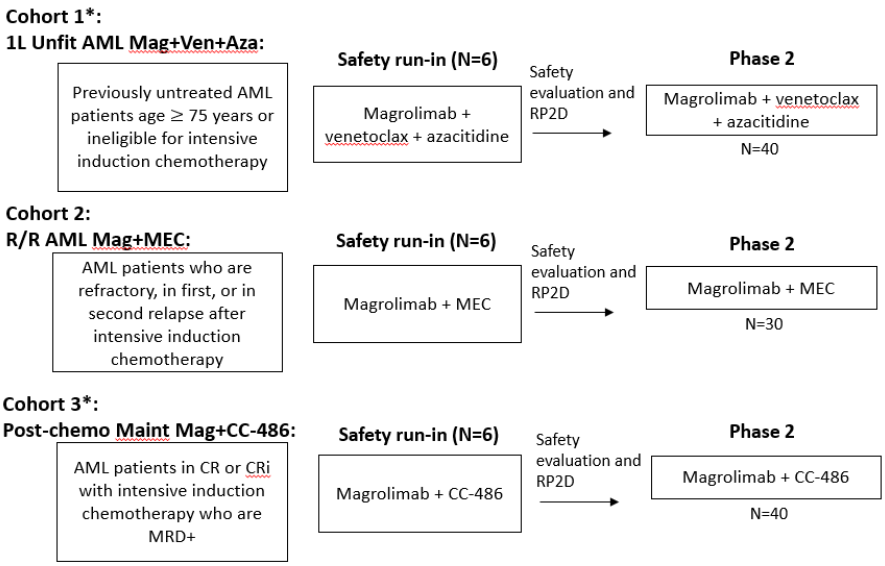
Primary and secondary objectives and endpoints for patients with newly diagnosed AML who are in CR or CRi with minimal residual disease (MRD) positivity following intensive chemotherapy are as follows:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of magrolimab in combination with anti-leukemia therapy CC-486 as determined by the MRD negative CR rate (Phase 2 Cohort 3) • To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy CC-486 (Safety Run-in Cohort 3)	• MRD negative CR rate, defined as the proportion of patients who maintain CR as determined by the investigator based on prespecified criteria and reach MRD negative disease status as determined using multiparameter flow cytometry with a sensitivity of < 0.1% (Phase 2 Cohort 3) • Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 3)

	Secondary Objectives	Secondary Endpoints
	• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy CC-486 (Phase 2 Cohort 3) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy CC-486	• MRD negative CR/CRi rate • Relapse-free survival (RFS) • OS • Duration of MRD negative CR • Duration of MRD negative CR/CRi • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 3) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

Study Design:

This is a Phase 2, open-label, multicenter, multi-arm study to evaluate magrolimab in combination with anti-leukemia therapies in patients with AML. The study schematic is as follows:



** Cohorts 1 and 3 closed to enrollment globally as of Protocol Amendment 5.*

AML = acute myeloid leukemia; MEC = mitoxantrone, etoposide, and cytarabine; MRD = minimal residual disease; RP2D = recommended Phase 2 dose

This study will include the following 3 safety run-in cohorts:

- **Safety Run-in Cohort 1 (1L Unfit AML Mag+Ven+Aza), *closed to enrollment globally as of Protocol Amendment 5***: magrolimab +

	venetoclax + azacitidine in patients with newly diagnosed, previously untreated AML who are ineligible for intensive chemotherapy • **Safety Run-in Cohort 2 (R/R AML Mag+MEC):** magrolimab + MEC in patients with R/R AML • **Safety Run-in Cohort 3 (Post-chemo Maint Mag+CC-486), *closed to enrollment globally as of Protocol Amendment 5*:** magrolimab + CC-486 as maintenance therapy in patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy • **Safety Run-in Cohorts:** Initially, 6 patients will be enrolled into Safety Run-in Cohorts 1, 2, and 3. Initial dose levels are presented in the main protocol. A DLT assessment period of 1 cycle (28 days) will occur. Dose de-escalation decisions will be made as follows: • If no more than 2 patients in a safety run-in cohort experience a DLT in Cycle 1, enrollment into the corresponding Phase 2 cohort will begin at this dose level. • If 3 or more (> 33%) patients in a safety run-in cohort experience a DLT up to the end of Cycle 1, another 6 patients will be enrolled in that cohort at a lower dose and evaluated in the same manner to define the RP2D. Dose de-escalation levels are presented in the main protocol. Any dose de-escalation for Cohorts 1 and 3 will occur with the combination regimen, as there is a lack of dose-dependent toxicities observed with magrolimab in over 500 patients treated to date with magrolimab as monotherapy or in combination, and agents being evaluated in combination with magrolimab have identified or potential dose-related toxicities as cytotoxic agents (ie, venetoclax and CC-486). For Cohort 2, any dose de-escalation will occur with magrolimab, as the combination with chemotherapy (ie, MEC) has not been extensively studied. The selected RP2D for any cohort cannot exceed the identified maximum tolerated dose (MTD) for that cohort. **DLT Assessment Period:** The DLT assessment period is the first cycle (28 days). For patients who are being evaluated for prolonged myelosuppression, the 28 day DLT assessment period will extend to 42 days for Safety Run-in Cohorts 1 and 2. Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT assessment period: • The patient experienced a DLT at any time after initiation of the first dose of study treatment.

	• The patient did not experience a DLT and completed at least 4 infusions of magrolimab and at least 14 doses of venetoclax and 5 doses of azacitidine (Safety Run-in Cohort 1), at least 3 days of dosing with MEC (Safety Run-in Cohort 2), or at least 10 doses of CC-486 (Safety Run-in Cohort 3). If a patient experiences a DLT during the DLT assessment period, the investigator should contact the medical monitor to discuss whether the patient can remain on study drug. Patients who are not evaluable for DLT will be replaced in the safety run-in cohorts. The DLT definition is provided in the main protocol. After completion of each safety run-in cohort and identification of the RP2D for that cohort, the corresponding Phase 2 cohort may be enrolled as follows: • **Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza),** ***closed to enrollment globally as of Protocol Amendment 5*****:** 40 patients with newly diagnosed, previously untreated AML who are ineligible for intensive chemotherapy will be enrolled to receive magrolimab + venetoclax + azacitidine. • **Phase 2 Cohort 2 (R/R AML Mag+MEC):** 30 patients with R/R AML will be enrolled to receive magrolimab + MEC. • **Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486),** ***closed to enrollment globally as of Protocol Amendment 5***: 40 patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy may be enrolled to receive magrolimab + CC-486. Up to 5 to 10 additional patients may be enrolled in each of the Phase 2 cohorts to collect additional safety, efficacy, and/or PK/PD data. Cohort 1 closed to enrollment globally as of Protocol Amendment 5 and no new patients enrolled in Cohort 1 thereafter. Cohort 1 patients enrolled prior to sponsor's notification and implementation of Protocol Amendment 5 will continue on study until end of study or early discontinuation criteria are met as outlined in the main protocol.
Number of Patients Planned:	Up to approximately 164 patients will be enrolled in the study, with up to 54 patients in the safety run-in cohorts and up to 110 patients in the Phase 2 cohorts. A total of 18 patients were enrolled into Cohort 1 (7 patients in safety run-in and 11 patients in Phase 2). No patients were enrolled into Cohort 3 safety run-in and Phase 2.

Target Population:	**Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza),** ***closed to enrollment globally as Protocol Amendment 5***: patients with newly diagnosed, previously untreated AML confirmed 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 chemotherapy **Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)**: patients with confirmation of AML by WHO criteria who are refractory to or have relapsed after the initial intensive chemotherapy **Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486),** ***closed to enrollment globally as of Protocol Amendment 5***: patients with confirmation of AML by WHO criteria who achieved CR or CRi with presence of MRD (MRD positive) after intensive induction chemotherapy with or without consolidation therapy prior to starting maintenance therapy
Duration of Treatment:	Cohorts 1 and 3: treatment until discontinuation criteria is met. Cohort 2: treatment for up to 12 months. Patients in each safety run-in cohort will receive 1 cycle (28 days) of study treatment before being evaluated for DLTs. Patients in the safety run-in cohorts will continue study treatment at the assigned dose level for at least 4 cycles, after which they may continue at the assigned dose level or switch to the RP2D upon agreement between the investigator and the sponsor. Safety run-in cohort patients will continue dosing until Phase 2 cohort end-of-treatment criteria are met. Patients in Phase 2 Cohorts 1 and 3 will receive study treatment until disease progression, unacceptable toxicity, and/or loss of clinical benefit. Patients in Phase 2 Cohort 2 will receive MEC for 2 to 3 cycles. Patients who do not achieve an objective response (OR) (ie, CR, CRi, CRh, PR, or MLFS) after 2 cycles will be discontinued from therapy. For patients achieving a response after 1 to 2 cycles, an additional single MEC cycle will be administered. Magrolimab will be administered in Phase 2 Cohort 2 until disease progression, unacceptable toxicity, and/or loss of clinical benefit for up to 12 months.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** <u>All Patients</u> 1) White blood cell (WBC) count $\leq 20 \times 10^3/\mu L$ prior to first dose of study treatment. If the patient's WBC count is $> 20 \times 10^3/\mu L$ prior to first dose of study treatment, the patient can be enrolled,

	assuming all other eligibility criteria are met. However, ensure that the WBC count is ≤ 20 × 10^3/μL prior to the first dose of study treatment and prior to each magrolimab dose for the first 4 weeks. NOTE: Patients can be treated with hydroxyurea and/or leukapheresis throughout the study or prior to first dose of study treatment to reduce the WBC count to ≤ 20 × 10^3/μL to enable eligibility for magrolimab dosing. 2) Hemoglobin (Hb) must be ≥ 9 g/dL prior to initial dose of study treatment. NOTE: Transfusions are allowed to meet Hb eligibility. 3) Adequate liver function as demonstrated by the following: a. aspartate aminotransferase ≤ 3.0 × upper limit of normal (ULN) b. alanine aminotransferase ≤ 3.0 × ULN c. bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert syndrome or genetic equivalent. 4) Patients must have adequate renal function as demonstrated by a creatinine clearance (CLcr) ≥ 30 mL/min calculated by the Cockcroft-Gault formula. 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, age ≥ 18 years. 8) Pretreatment blood cross-match completed. 9) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception. 10) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines), unless not feasible as determined by the investigator and discussed with the sponsor. <u>Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza), *closed to enrollment globally as of Protocol Amendment 5*</u> 11) Newly diagnosed, previously untreated patients with confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction

	regimen due to age, comorbidity, or other factors. Patients must be considered ineligible for induction therapy defined by the following: a. ≥ 75 years of age b. ≥ 18 to 74 years of age with at least 1 of the following comorbidities: i. 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. LVEF ≤ 50% iv. CLcr < 45 mL/min calculated by the Cockcroft-Gault formula v. Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy that must be approved by the sponsor medical monitor before study enrollment. 12) ECOG performance status: • Of 0 to 2 for subjects ≥ 75 years of age OR • Of 0 to 3 for subjects ≥ 18 to 74 years of age 13) Patients who have not received prior anti-leukemia therapy for AML (excluding hydroxyurea), hypomethylating agent (HMA), low-dose cytarabine, and/or venetoclax. NOTE: Patients with prior myelodysplastic syndrome (MDS) who have not received prior HMA, venetoclax, or a chemotherapeutic agent are eligible. Other prior MDS therapies, including but not limited to lenalidomide, erythroid-stimulating agents, or similar RBC-, WBC-, or platelet direct therapies or growth factors, are allowed. 14) Patients who have not received strong and/or moderate cytochrome P450 enzyme 3A inducers (eg, St John's Wort) within 7 days prior to the initiation of study treatment. 15) Patients who have not consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment or are willing to discontinue consumption of these while receiving study drug.

	16) Patients without malabsorption syndrome or other conditions that preclude enteral route of administration. <u>Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)</u> 17) Patients with confirmation of AML by WHO criteria who are refractory to or have experienced first relapse after initial intensive chemotherapy, which includes 1 or 2 cycles of a 7 + 3-based induction regimen or a purine analogue-based induction therapy, such as fludarabine or cladribine paired with anthracyclines and cytarabine (eg, fludarabine, high-dose cytarabine [ara-C], granulocyte colony-stimulating factor [G-CSF], and idarubicin [FLAG-Ida] or cladribine, ara-C, G-CSF, and mitoxantrone [CLAG-M]) or failed therapy after remission (eg, consolidation) during any number of cycles (maximum of 4) of high- or intermediate-dose cytarabine. For other intensive regimens, please discuss with the medical monitor. NOTE: Patients who are relapsed after or are refractory to more than 1 line of anti-AML treatment are not eligible. Patients who relapsed after undergoing stem cell transplant may be eligible. 18) At least 2 weeks must have elapsed since any prior anti-leukemia agents. NOTE: Localized non-central nervous system (CNS) radiotherapy, hydroxyurea, and erythroid and/or myeloid growth factors are not criteria for exclusion. 19) ECOG performance status of 0 to 2. 20) Patients with LVEF $\geq$ 50%, lack of symptomatic congestive heart failure, or clinically significant cardiac arrhythmias. 21) Patients who have not been treated with trastuzumab within 7 months prior to the initiation of study treatment 22) Patients who have not previously received maximum cumulative doses of anthracyclines and anthracenediones 23) Patients without degenerative or toxic encephalopathies 24) Patients who did not undergo hematopoietic stem cell transplantation (SCT) in the past 100 days, are not on immunosuppressive therapy post SCT in the 2 weeks prior to the first dose of study treatment, or have no active clinically significant graft-versus-host disease. <u>Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486), *closed to enrollment globally as of Protocol Amendment 5*</u>

	25) Patients with confirmation of AML by WHO criteria who achieved a CR or CRi with presence of MRD (MRD positive by local flow cytometry assay, defined as ≥ 0.1% detectable MRD) after intensive induction chemotherapy with or without consolidation therapy, prior to starting maintenance therapy for newly diagnosed AML. 26) ECOG performance status of 0 to 2. 27) Patients without malabsorption syndrome or other conditions that preclude enteral route of administration. **Exclusion Criteria** <u>All Patients</u> 1) Positive serum pregnancy test. 2) Breastfeeding female. 3) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient 4) Patients who received any live vaccine within 4 weeks prior to initiation of study treatments. 5) Prior treatment with cluster of differentiation 47 (CD47) or signal regulatory protein alpha (SIRPα)-targeting agents. 6) Current participation in another interventional clinical trial. 7) Known inherited or acquired bleeding disorders. 8) Clinical suspicion of or documented active CNS involvement with AML. 9) Patients who have acute promyelocytic leukemia. 10) 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 infections, and congestive heart failure New York Heart Association Class III-IV. 11) 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 anticancer therapies and have had no evidence of active malignancy for over 1 year. Previous hormonal therapy with luteinizing hormone-releasing hormone agonists for prostate cancer; and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion.

	NOTE: Patients on maintenance therapy alone who have no evidence of active malignancy for at least ≥ 1 year are eligible. 12) Known medical history of active or chronic hepatitis B or C infection or medical history of human immunodeficiency virus (HIV) infection.
Study Procedures/ Frequency:	Screening assessments include written informed consent; review of medical history; complete physical examination (including vital signs, body weight, and height); serum pregnancy test (females of childbearing potential); complete blood count (CBC) with differential, platelets, reticulocytes; serum or plasma chemistry; prothrombin time, international normalized ratio, and activated partial thromboplastin time or partial thromboplastin time; extended red blood cell phenotyping or genotyping, ABO/Rh type, and screen (any of the 4 blood groups A, B, AB, and O composing the ABO system [ABO]/Rh), direct antiglobulin test; urinalysis; bone marrow biopsy and aspirate for blast evaluation, MRD assessment, cytogenetics, receptor occupancy (RO; to be collected at selected study sites), and correlative studies; peripheral blood smear for blasts; ECOG performance status; 12-lead electrocardiogram; echocardiogram or multigated acquisition (scan) for patients of Cohort 2 only; and recording of all serious AEs and any AEs related to protocol-mandated procedures occurring after signing of the informed consent form and prior and concomitant medications. Eligible patients will return to the study site within 30 days after screening for the following baseline/Day 1 assessments: serum or urine pregnancy test (females of childbearing potential); predose CBC with differential, platelets, reticulocytes and postdose Hb; haptoglobin and lactate dehydrogenase; serum or plasma chemistry; peripheral blood smear for general morphology; peripheral blood sample for RO (to be collected at selected study sites) and correlative studies; buccal swab (may be collected at any visit during the study); PK and antidrug antibody (ADA) sample collection; vital signs, weight, and symptom-directed physical examination; and recording of all AEs and concomitant medications. On-treatment assessments include clinical laboratory evaluations; PK and ADA evaluations; bone marrow aspirate/biopsy for response assessment, MRD assessment, cytogenetics, RO (to be collected at selected study sites), and correlative studies; peripheral blood sample for RO (to be collected at selected study sites) and correlative studies; vital signs and symptom-directed physical examinations; and monitoring for AEs and concomitant medications.

Test Product, Dose, and Mode of Administration:	Study treatment regimens are presented in the main protocol and comprise the following: Safety Run-in Cohort 1 and Phase 2 Cohort 1, *closed to enrollment globally as of Protocol Amendment 5* • Magrolimab 1 mg/kg intravenous (IV) • Magrolimab 15 mg/kg IV • Magrolimab 30 mg/kg IV • Azacitidine 75 mg/m^2 subcutaneous or IV • Venetoclax 10 mg oral tablets • Venetoclax 50 mg oral tablets • Venetoclax 100 mg oral tablets Safety Run-in Cohort 2 and Phase 2 Cohort 2 • Magrolimab 1 mg/kg IV • Magrolimab 15 mg/kg IV • Magrolimab 20 mg/kg IV • Magrolimab 30 mg/kg IV • Mitoxantrone 8 mg/m^2 IV • Etoposide 100 mg/m^2 IV • Cytarabine 1000 mg/m^2 IV Safety Run-in Cohort 3 and Phase 2 Cohort 3, *closed to enrollment globally as of Protocol Amendment 5* • Magrolimab 1 mg/kg IV • Magrolimab 15 mg/kg IV • Magrolimab 30 mg/kg IV • CC-486 200 mg oral tablets • CC-486 300 mg oral tablets
Reference Therapy, Dose, and Mode of Administration:	None

Criteria for Evaluation:	
Safety:	Safety will be evaluated by incidence of AEs, assessment of clinical laboratory test findings, physical examination, 12-lead electrocardiogram, and vital signs measurements. Adverse events will be graded using NCI CTCAE Version 5.0.
Efficacy:	Assessment of leukemia response in patients with AML will be conducted by investigators and determined based on prespecified criteria.
Pharmacokinetics/ Immunogenicity:	Magrolimab concentrations will be evaluated in combination with the following: • Venetoclax and azacitidine • Mitoxantrone, etoposide, and cytarabine • CC-486 Samples will also be collected for the detection of ADAs against magrolimab.
Statistical Methods:	<u>Analysis Data Sets</u> The All Enrolled Analysis Set is the primary analysis set for analyses of patient demographics and baseline characteristics, enrollment, and disposition, and includes all patients who receive a study patient identification number. The Full Analysis Set (FAS) is the primary analysis set for efficacy analyses and includes all enrolled patients who receive at least 1 dose of any study treatment. Treatment assignment in the FAS will be made according to the assigned treatment. The Safety Analysis Set is the primary analysis set for safety analyses and includes all patients who receive at least 1 dose of study treatment. Treatment assignment in the Safety Analysis Set will be made according to the actual treatment received. The DLT Evaluable Analysis Set includes all safety run-in cohort patients in the Safety Analysis Set who have safety assessments through the protocol-specified DLT assessment window and fulfill the protocol-specified criteria for evaluation for DLT. The PK Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab. The Immunogenicity Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

	The Biomarker Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have evaluable baseline and postbaseline measurements to provide interpretable results for the specific parameter of interest. Efficacy Analysis The point estimates of the CR rate, CR/CRi rate, CR/CRh rate, CR_{MRD-} rate, cCR rate, and ORR and the corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method will be provided for Cohorts 1 and 2. The MRD negative CR rate will be summarized similarly for Cohort 3. The analyses of RBC and platelet transfusion independence rates (conversion rate and maintenance rate) will be similar to those of ORR. The CR and MRD negative CR data will also be tested against the historical control rates using 1-group Chi-square test for each cohort separately. Medians, first quartile, and third quartile of the EFS distribution, and the proportion of patients who are event free at Weeks 12, 24, and 48 from the first dosing date will be estimated by cohort using the Kaplan-Meier (KM) method and the corresponding 95% CIs will be reported. Kaplan-Meier plots will be provided. Analyses of OS will be similar to those of EFS. For the time-to-event endpoints of duration of CR, duration of CR/CRi, duration of CR/CRh, DOR, RFS, duration of MRD negative CR, and MRD negative CR/CRi, analyses will be conducted on the subsets for which the outcome measures are defined. Specifically, the duration of CR, duration of CR/CRi, duration of CR/CRh, and DOR will be based on patients in Cohorts 1 and 2 who achieve CR, CR/CRi, CR/CRh, and OR, respectively. The RFS will be analyzed for Cohort 3, duration of MRD negative CR will be based on patients in Cohort 3 who achieve MRD negative status and maintain CR, and the duration of MRD negative CR/CRi will be based on patients in Cohort 3 who achieve MRD negative status and maintain CR/CRi. The KM method will be used to estimate median durations and 95% CIs, and KM plots will be provided. Safety Analysis Extent of exposure to study drugs, AEs, clinical laboratory evaluations, graded laboratory abnormalities, vital signs measurements, and physical examination findings will be summarized by cohort for the Safety Analysis Set using number and percentage of patients for categorical data and number of patients, mean, standard deviation, minimum, quartiles, median, and maximum for continuous data. Study drug administration, study drug compliance, and other safety variables will also be summarized.

	Pharmacokinetic Analysis Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point for the PK Analysis Set. Plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated. Immunogenicity Analysis 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] 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 applicable sample collection time point by treatment cohort, as appropriate. CCI [redacted] Sample Size Sample size calculation is as follows: • For Cohort 2, a sample size of 36 (30 patients in Phase 2 Cohort 2 together with 6 patients in Safety Run-in Cohort 2) provides an 83.1% power for a 1-group Chi-square test at 1-sided alpha of 0.1 level to detect a CR rate of ≥ 35% for the combination compared with a historical control CR rate of 19%. The original protocol for the study included a Cohort 1, for which 46 patients were planned to be enrolled (6 patients in Safety Run-in and 40 patients in Phase 2); however, Cohort 1 was closed to enrollment following enrollment of 18 patients (7 patients in safety run-in and 11 patients in Phase 2), up to implementation of Protocol Amendment 5. The original protocol also included a Cohort 3, for which 46 patients were planned to be enrolled (6 patients in Safety Run-in and 40 patients in Phase 2); however, Cohort 3 was closed to enrollment and no patients were enrolled.

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

LIST 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
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CBC	complete blood count
cCR	cytogenetic complete remission
CD47	cluster of differentiation 47
CI	confidence interval
CLcr	creatinine clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration of drug
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CR/CRh	complete remission or complete remission with partial hematologic recovery
CR/CRi	complete remission or complete remission with incomplete hematologic recovery
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
CSR	clinical study report
CYP	cytochrome P450 enzyme
CTCAE	Common Terminology Criteria for Adverse Events
DAT	direct antiglobulin test
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response

EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
ELN	European Leukemia Net
EOT	end of treatment
EU	European Union
FAS	Full Analysis Set
Fc	crystallizable fragment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Gilead	Gilead Sciences
Hb	hemoglobin
HMA	hypomethylating agent
HR	hazard ratio
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 G 4
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
K_i	inhibitory constant
KM	Kaplan-Meier
LHRH	luteinizing hormone-releasing hormone
LSC	leukemia stem cell
LVEF	left ventricular ejection fraction

mAb	monoclonal antibody
mag	magrolimab
MDACC	MD Anderson Cancer Center
MDS	myelodysplastic syndrome
MEC	mitoxantrone, etoposide, and cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MOA	mechanism of action
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OR	objective response
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial remission
PS	Patient Safety
PT	prothrombin time
PTT	partial thromboplastin time
Q1	first quartile
Q3	third quartile
QW	once weekly
R/R	relapsed/refractory
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RFS	relapse-free survival
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous

SCT	stem cell transplantation
SIRPα	signal regulatory protein alpha
SOC	standard of care
SOP	standard operating procedure
SRT	safety review team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
w/v	weight to volume ratio
WBC	white blood cell
WES	whole exome sequencing
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. Current Treatment Landscape for Acute Myeloid Leukemia

1.1.2.1. Patients Newly Diagnosed with AML Who are Ineligible for Intensive 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, a Bcl-2 inhibitor. 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.

1.1.2.2. Patients with Relapsed or Refractory AML after Induction Chemotherapy

Standard of care treatment for newly diagnosed AML patients who are eligible for induction chemotherapy consists of a combination of cytarabine and an anthracycline. Despite initial CR rates above 50% with induction chemotherapy, a substantial portion will be refractory to initial chemotherapy and a majority of patients will ultimately relapse, particularly those with poor-risk features. Treatment options in the relapsed/refractory (R/R) setting consist of salvage chemotherapy with a goal of undergoing allogeneic stem cell transplantation (SCT) for long-term remission. Various salvage chemotherapies are used in the treatment of R/R AML, including mitoxantrone, etoposide, and cytarabine (MEC); fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (G-CSF); and G-CSF, clofarabine, and cytarabine. With all of these agents, the CR rates range from 15% to 25%, with a median OS of approximately 3 to 5 months {Feldman 2005, Greenberg 2004}.

1.1.2.3. Maintenance Therapy for Patients with AML Remission

Given the high relapse rates with available therapies for newly diagnosed AML, maintenance therapy for patients who are in remission has been explored and is an area of intense clinical interest. Given that induction chemotherapy and consolidation represent a finite treatment course, a high rate of relapse can occur after completion of definitive therapy. Novel therapeutic agents that are well tolerated and that can extend both relapse-free survival (RFS) and OS are needed. Recently, CC-486 (Onureg®, Celgene Corp., Summit, NJ, USA), an oral nucleoside metabolic inhibitor in oral tablet formulation, received US Food and Drug Administration (FDA) approval for use in AML patients who achieved first CR or CRi following intensive induction chemotherapy who are not able to complete intensive curative therapy. This approval was based on the randomized Phase 3 study, QUAZAR, which compared CC-486 versus placebo in patients 55 years and older who were in first CR or CRi following intensive chemotherapy and/or consolidation and were ineligible for hematopoietic SCT. The median OS was significantly longer for patients who received CC-486 compared with those who received placebo (24.7 vs. 14.8 months, HR 0.69) {ONUREG 2020}. Relapse-free survival was also significantly longer in those who received CC-486 compared with those who received placebo (10.2 vs. 4.8 months). The minimal residual disease (MRD) negativity rate for the CC-486 group was 56%, although a high degree of MRD negativity (47%) was also observed in the placebo group {Wei 2019}. In summary, CC-486 has emerged as a SOC option for maintenance therapy in AML patients in first remission who are not candidates for SCT.

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-AML 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).

As described in the 2020 investigator's brochure (IB), magrolimab is being investigated as an anti-AML therapeutic in 6 ongoing clinical studies in the US and United Kingdom, as monotherapy or in combination with other therapeutics, for the treatment of NHL, AML, and MDS. A total of 568 patients have been treated as of the data cut-off dates in the 2020 IB.

While magrolimab has single-agent preclinical and clinical activity, efficacy is best enhanced in combination with other anti-AML 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 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 and completed studies of magrolimab conducted to date. Pharmacokinetic data have been analyzed in a Phase 1 study (SCI-CD47-001) in patients with solid tumor. 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 and completed studies (5F9003, 5F9004, 5F9005, and 5F9006) of magrolimab 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.

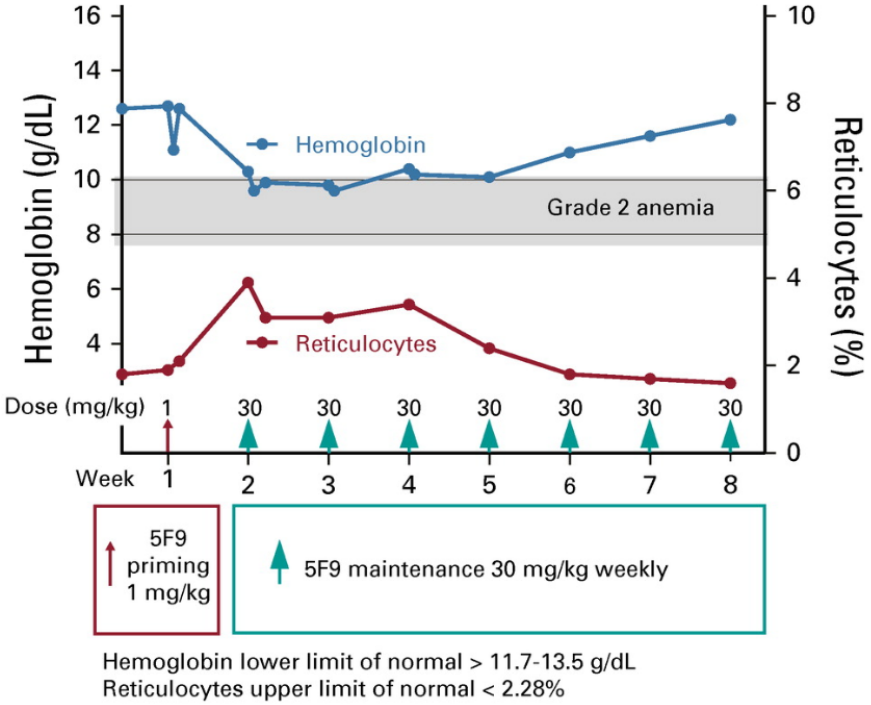
1.2.3.2. Summary of Clinical Safety

Magrolimab is administered as an intravenous (IV) infusion and it is currently being studied in 6 clinical studies. Two completed single-agent Phase 1 studies include Study SCI-CD47-001 in patients with advanced solid tumors and lymphomas, and Study SCI-CD47-002 in patients with R/R AML, along with 2 Phase 1b partnered studies in AML, as well as urothelial carcinoma. Four combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with R/R NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in patients with solid tumors and colorectal cancer; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in patients with AML and MDS; and Study 5F9006, a Phase 1b study of magrolimab with avelumab in patients with solid tumors and ovarian cancer. As of July 2020, over 500 patients have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no maximum tolerated dose (MTD) reached in any study with dosing up to 45 mg/kg. Two anticipated adverse reactions included on-target anemia and infusion-related reactions (IRRs), which are expected with mAbs. Importantly, on-target anemia due to CD47 blockade-mediated red blood cell (RBC) clearance was mitigated with a priming/maintenance dose strategy. The average hemoglobin (Hb) decline with the first (priming) dose was 0.4 g/dL to 1.5 g/dL across indications, with many patients improving their Hb on therapy back to baseline, with a decrease in RBC transfusion requirements for those patients who were transfusion-dependent at baseline.

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 MTD was reached. As described in the 2020 IB, 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 Hb observed within the first 2 weeks of treatment. The initial decrease in Hb after the first dose averages 0.5 to 2 g/dL. In patients with solid tumors, the decrease in Hb was followed by a compensatory reticulocytosis, with many patients experiencing a gradual return to baseline despite continued dosing. The changes in Hb 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



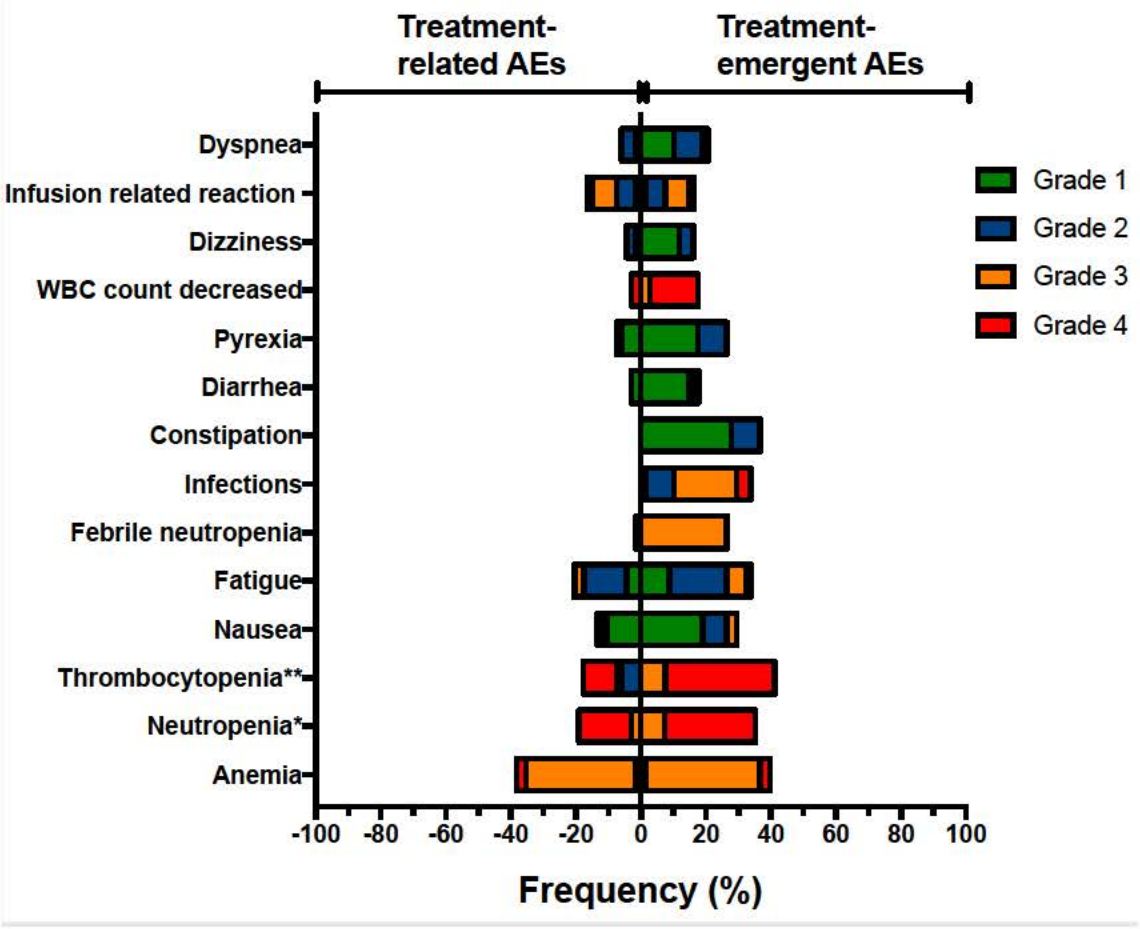
5F9 = magrolimab
The RBC profile of a solid tumor patient treated with magrolimab monotherapy is shown {Sikic 2019}.

Infusion-related reactions 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 5.1.4 and 7.8.1.2. 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 January 2020, 68 patients (39 untreated higher risk MDS patients and 29 untreated induction chemotherapy-ineligible AML patients) have been enrolled in Study 5F9005 with the combination of magrolimab + azacitidine {Sallman 2020b}. The safety profile of magrolimab in combination with azacitidine was acceptable and consistent with azacitidine monotherapy, with no apparent increased toxicities in combination. No MTD was reached with magrolimab dosing of 30 mg/kg weekly. The most common treatment-related AEs with magrolimab were anemia, neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased (Figure 2). Treatment discontinuation due to any AE occurred in 1 of 68 patients (1.47%).

Figure 2. Treatment-Emergent Adverse Events with ≥ 15% Incidence in Study 5F9005



AE = adverse event; WBC = white blood cell
* Includes preferred terms of neutropenia and neutrophil count decreased
** Includes preferred terms of thrombocytopenia and platelet count decreased

1.2.3.3. Summary of Clinical Efficacy

As of July 2020, 52 treatment-naive AML patients who were ineligible for induction chemotherapy have been treated with magrolimab + azacitidine in the Phase 1b study, 5F9005 {Sallman 2020a}. Among 34 patients who were evaluable for efficacy, 65% achieved an objective response (OR), 44% achieved CR, 12% achieved CRi, 3% achieved a partial response, 62% achieved morphologic leukemia-free state (MLFS), 32% achieved stable disease, and 3% had progressive disease as their best response. Time to response was more rapid (median 2.04 months) than that expected for azacitidine alone. For patients with abnormal cytogenetics at baseline, 7 of 15 patients (47%) achieved a cytogenetic CR, and 7 of 19 patients (37%) with CR or CRi achieved MRD negativity as detected by flow cytometry. In 21 patients with mutated *TP53*, 71% achieved an OR, 48% achieved a CR, and 19% achieved CRi. The median OS for patients with *TP53* mutation (N = 34) was 12.9 months and the median OS for patients with wild-type *TP53* (N = 16) was 18.9 months. 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. Additional patients continue to be enrolled on the Phase 1b study. In addition, a randomized Phase 3 study will evaluate magrolimab in combination with azacitidine versus physician's choice of venetoclax plus azacitidine or intensive chemotherapy in previously untreated patients with AML with the *TP53* mutation.

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

1.3. Information About Venetoclax and 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 [K_i] < 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 is approved for the treatment of adult patients with CLL or small lymphocytic leukemia {VENCLEXTA 2020}. 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.

In the European Union, venetoclax is approved as monotherapy for the treatment of adult patients with CLL and in combination with hypomethylating agents for treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

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 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 Revised International Prognostic Scoring System 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.

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.

1.4. Information About Mitoxantrone, Etoposide, and Cytarabine

1.4.1. Description of Mitoxantrone

Mitoxantrone is a cytotoxic chemotherapy and is classified as an anthracenedione antineoplastic agent. It is administered intravenously and is indicated in combination with other chemotherapeutic agents for the treatment of AML.

1.4.2. Description of Etoposide

Etoposide is a cytotoxic chemotherapy and is classified as a topoisomerase II enzyme inhibitor. It is administered intravenously and is indicated in combination with other chemotherapeutic agents for the treatment of AML.

1.4.3. Description of Cytarabine

Cytarabine is a cytotoxic chemotherapy and an antimetabolic agent. It is administered intravenously and is indicated as a single agent or in combination with other chemotherapeutic agents for the treatment of AML.

1.4.4. Clinical Data for Mitoxantrone, Etoposide, and Cytarabine

MEC is considered a long-standing SOC option for AML patients who are relapsed after or refractory to initial induction chemotherapy. Multiple clinical studies have evaluated MEC in the R/R setting and have demonstrated clinical activity, with a CR rate of approximately 20% and a median OS of approximately 3 to 5 months {Greenberg 2004, Roboz 2014}. MEC has a similar safety profile to other salvage chemotherapy regimens used in AML, most notably myelosuppression.

1.5. Information About CC-486

1.5.1. Description of CC-486

CC-486 (Onureg) is an oral HMA indicated for continued treatment of adult patients with AML who achieved first CR or CRi following intensive chemotherapy and who are not able to complete curative therapy {ONUREG 2020}. CC-486 is given orally on a daily dosing regimen.

1.5.2. Clinical Data for CC-486

CC-486 was approved by the US FDA in 2020 for the treatment of AML patients in CR or CRi following intensive chemotherapy. This approval was supported by data from the randomized Phase 3 QUAZAR study comparing CC-486 versus placebo in patients 55 years and older who were in first CR or CRi following intensive chemotherapy and/or consolidation and were ineligible for hematopoietic SCT. The median OS was significantly longer for patients who received CC-486 than for those who received placebo (24.7 vs. 14.8 months, HR 0.69). Relapse-free survival was also significantly longer for patients who received CC-486 than those who received placebo (10.2 vs. 4.8 months) {Abrisqueta 2019}. The MRD negative response rate for CC-486 (CR/CRi MRD positive to CR/CRi MRD negative) was 37%, although a high degree of MRD negativity conversion was also observed in the placebo arm (19%) {Roboz 2020}. In summary, CC-486 has emerged as a SOC option for maintenance therapy in AML patients in first remission who are not candidates for SCT.

1.6. Rationale for This Study

Patients with either newly diagnosed AML who are unfit for intensive chemotherapy or have R/R AML or MRD positive disease require improvements in clinical outcomes. Outside of an allogeneic SCT, there are limited curative therapies available for these patients. Thus, novel treatments that have a strong scientific and clinical rationale are needed to improve clinical outcomes. Magrolimab is being evaluated in each of these patient populations based on the strong scientific rationale for the proposed magrolimab combinations and clinical data supporting these evaluations.

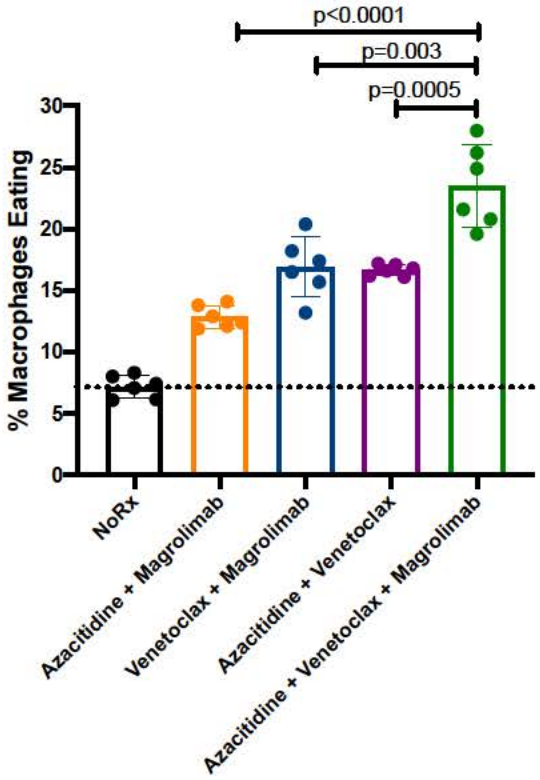
Cohort 1 was closed to enrollment given that sufficient safety and efficacy data have been attained from Study 2020-0027 at MD Anderson Cancer Center (MDACC) to support further testing of the Mag+Ven+Aza combination in the currently active Phase 3 Study GS-US-590-6154 (ENHANCE-3).

Cohort 3 was closed to enrollment due to lack of enrollment.

1.6.1. Cohort 1 (1L Unfit AML Mag+Ven+Aza): Magrolimab in Combination with Azacitidine and Venetoclax in Patients with Newly Diagnosed, Previously Untreated AML Who Are Ineligible for Intensive Chemotherapy

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 (ORR) 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. Furthermore, nonclinical data demonstrate that venetoclax can enhance magrolimab-mediated phagocytosis, which can be further enhanced by azacitidine (Figure 3).

Figure 3. **In Vitro Phagocytosis of AML Cells with Magrolimab, Azacitidine and/or Venetoclax**



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

Based on the nonclinical and clinical data described here, an investigator-initiated study sponsored by the MDACC commenced in the second half of 2020 to evaluate the safety, tolerability, recommended dose, and preliminary efficacy of magrolimab plus azacitidine and venetoclax in R/R AML patients and frontline AML patients who are ineligible for intensive chemotherapy. Emerging data from that study have informed design elements for this study. Venetoclax and azacitidine have overlapping toxicities, particularly myelosuppression and infections. Anemia, neutropenia, thrombocytopenia, and infections have been reported in patients treated with magrolimab.

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.

1.6.2. Cohort 2 (R/R AML Mag+MEC): Magrolimab in Combination with MEC in Patients with AML Who Are Refractory to or Have Relapsed After Initial Induction Chemotherapy

Patients with primary refractory AML or in relapse from AML after induction chemotherapy have a poor prognosis and a median OS of less than 6 months despite receiving SOC therapy with salvage chemotherapy. MEC is a commonly used salvage chemotherapy option in this setting but yields CR rate of approximately 20% and a median OS of approximately 5 months {Greenberg 2004, Roboz 2014}. Thus, combination therapies that can enhance the efficacy of MEC are needed to improve clinical outcomes. Cytotoxic chemotherapies can synergize with magrolimab, which increases prophagocytic signals on tumor cells by blocking the antiphagocytic CD47 signal, thus enhancing phagocytosis. Nonclinical data have demonstrated both in vitro and in vivo that the antitumor activity of magrolimab is enhanced when combined with chemotherapy ({Sikic 2016} and data on file). The combination of mitoxantrone and etoposide (components of MEC chemotherapy) induces high rates of prophagocytic signal expression (specifically calreticulin) and macrophage phagocytosis compared with other chemotherapeutic agents {Obeid 2007}. Given these nonclinical proof-of-concept data and the common usage of MEC as a salvage chemotherapy in R/R AML, the combination of magrolimab with MEC is under evaluation in this study.

1.6.3. Cohort 3 (Post-Chemo Maint Mag+CC-486): Magrolimab in Combination with CC-486 in Patients with AML who Achieve CR or CRi with MRD Positivity after Intensive Induction Chemotherapy

As described above, AML patients who achieve a CR or CRi after induction chemotherapy or consolidation therapy, particularly those who are MRD positive, have a significant risk of relapse prior to starting maintenance therapy. CC-486 is a SOC option for older patients after induction chemotherapy who are ineligible for SCT. Despite the clinical benefit observed, OS and RFS were approximately 14.6 months and 7.1 months for patients who were MRD positive and treated with CC-486 {Roboz 2020}. Thus, novel agents that can be safely combined with CC-486 to extend RFS are needed. Strong nonclinical and clinical rationale exists for treatment of this population with the combination of magrolimab and CC-486. CC-486 is an oral therapy with similarities to azacitidine. Magrolimab, which acts by blocking anti-phagocytic CD47, has been shown in vitro and in vivo to synergize with azacitidine, which upregulates prophagocytic signals on leukemic cells, thus leading to enhanced phagocytosis {Feng 2018}. Clinically, magrolimab enhances azacitidine activity in patients with untreated AML who are unfit to receive intensive chemotherapy. Magrolimab + azacitidine led to a 65% ORR with a 44% CR rate in an ongoing Phase 1b study in this population {Sallman 2020a}. These results compare favorably with historical azacitidine CR rates, which are approximately 10% to 20%. Notably, 37% of patients with CR/CRi achieved MRD negativity, an important outcome measure in this maintenance AML cohort. In addition, the safety profile of magrolimab + azacitidine was well tolerated, with no MTD reached and only 3.8% of patients discontinuing therapy due to a treatment-related AE. Based on these clinical data, the combination of magrolimab with CC-486 is anticipated to be well tolerated and efficacious and lead to higher rates of MRD negativity and RFS, key outcomes for this population.

1.7. 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 dose-limiting toxicity (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. In transfusion-dependent lower-risk MDS patients (Study 5F9005), a magrolimab dosing regimen of 60 mg/kg is being evaluated. This dose was shown to be safe and well tolerated in the initial DLT evaluation period, with no DLTs observed as of October 2020. Furthermore, in these 2 studies, an intrapatient dose escalation approach was followed; after the priming dose, the patients received doses of 15 mg/kg on Day 8 during Week 2, after which the dose was escalated to 30 mg/kg on Day 11 and then weekly thereafter. This schedule was based on nonclinical data indicating enhanced safety of intrapatient dose escalation. 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), 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.

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.

1.8. Risk/Benefit Assessment for the Study

For each of the study cohorts, strong scientific, nonclinical, and clinical data exist that support the rationale to evaluate magrolimab combinations in the selected patient populations.

For the 1L Unfit AML Mag+Ven+Aza cohort (Cohort 1), nonclinical data demonstrate enhanced efficacy when magrolimab is combined with venetoclax and azacitidine. Furthermore, encouraging clinical activity is observed with both the magrolimab plus azacitidine and venetoclax plus azacitidine double combinations, supporting the concept that a triple combination may lead to improved efficacy. Venetoclax and azacitidine have overlapping toxicities, particularly myelosuppression. Anemia, neutropenia, thrombocytopenia, and infections have also been reported in patients treated with magrolimab, and management guidelines for these risks provided in Section 7.8.1. The combination of Mag+Ven+Aza is anticipated to be well tolerated. Specific mitigation measures, including an inclusion criterion requiring Hb $\geq$ 9 g/dL at the initiation of study treatment, magrolimab priming/maintenance dosing regimen, and frequent blood count monitoring, are in place to closely monitor for anemia.

For the R/R AML Mag+MEC cohort (Cohort 2), strong scientific and nonclinical data exist supporting the enhancement of efficacy when magrolimab is added to cytotoxic chemotherapy, including MEC. Furthermore, magrolimab is not anticipated to have overlapping hepatotoxicity.

For the Post-chemo Maint Mag+CC-486 cohort (Cohort 3), strong nonclinical and clinical data exist to support the rationale for combining magrolimab with CC-486. Given that CC-486 shares similar properties with azacitidine, it is anticipated that the combination of magrolimab with CC-486 will be as similarly well tolerated and effective as the combination of magrolimab with azacitidine. Magrolimab plus azacitidine has been well tolerated in AML patients to date, with no MTD reached and a 3.8% AE discontinuation rate in an ongoing study. A CR rate of 44% was observed with the combination, which is substantially higher than azacitidine monotherapy CR rates in historical studies. While CC-486 is not identical to the parenteral form of azacitidine, these agents have the same active substance and share many similarities. Therefore, CC-486 is anticipated to be well tolerated and effective when combined with magrolimab.

For all cohorts, specific safety assessments to monitor for expected toxicities to each of these agents will be implemented, including monitoring for anemia, myelosuppression, tumor lysis syndrome (TLS), hepatotoxicity, IRRs, and other expected toxicities.

During a pandemic, additional potential risks to patients have been identified and may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 3 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 manageable safety profile with the proposed magrolimab combination regimens, this study has an acceptable risk:benefit ratio for patients who participate.

1.9. Compliance

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

2. OBJECTIVES AND ENDPOINTS

Objectives and endpoints for Study GS-US-546-5920 are presented by cohort in Sections 2.1, 2.2, and 2.3. Analysis of the study endpoints is described in Sections 8.1.2, 8.1.3, and 8.1.4.

2.1. Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza)

Primary, secondary, CCI [redacted] objectives and endpoints for patients with newly diagnosed, previously untreated AML who are ineligible for intensive chemotherapy are as follows:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine as determined by the CR rate (Phase 2 Cohort 1) • To evaluate the safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine (Safety Run-in Cohort 1)	• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 1) • Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Safety Run-in Cohort 1)
Secondary Objectives	**Secondary Endpoints**
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine (Phase 2 Cohort 1) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy venetoclax + azacitidine	• ORR, including CR, CRi, CRh, partial remission (PR), and MLFS • CR/CRi rate • Complete remission without minimal residual disease (CR_{MRD-}) rate • Complete remission or complete remission with partial hematologic recovery (CR/CRh) rate • Cytogenetic complete remission (cCR) • Duration of responses (DOR) • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • Event-free survival (EFS) • OS • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 1) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

2.2. Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)

Primary, secondary, CCI objectives and endpoints for patients with R/R AML are as follows:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of magrolimab in combination with the anti-leukemia therapy MEC as determined by the CR rate (Phase 2 Cohort 2) • To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy MEC (Safety Run-in Cohort 2)	• CR rate, defined as the proportion of patients who achieve CR as determined by the investigator based on prespecified criteria (Phase 2 Cohort 2) • Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 2)
Secondary Objectives	**Secondary Endpoints**
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy MEC	• ORR, including CR, CRi, CRh, PR, and MLFS • CR/CRi rate • CR_{MRD-} rate • CR/CRh rate

• To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy MEC (Phase 2 Cohort 2) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy MEC • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy MEC	• cCR • DOR • Duration of CR • Duration of CR/CRi • Duration of CR/CRh • EFS • OS • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 2) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies
CCI	

2.3. Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-Chemo Maint Mag+CC-486)

Primary, secondary, CCI [redacted] objectives and endpoints for patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy are as follows:

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of magrolimab in combination with anti-leukemia therapy CC-486 as determined by the MRD negative CR rate (Phase 2 Cohort 3) • To evaluate the safety and tolerability, and to determine the RP2D of magrolimab in combination with the anti-leukemia therapy CC-486 (Safety Run-in Cohort 3)	• MRD negative CR rate, defined as the proportion of patients who maintain CR as determined by the investigator based on prespecified criteria and reach MRD negative disease status as determined using multiparameter flow cytometry with a sensitivity of < 0.1% (Phase 2 Cohort 3) • Incidence of DLTs, treatment-emergent AEs, and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Safety Run-in Cohort 3)
Secondary Objectives	**Secondary Endpoints**
• To evaluate additional measures of efficacy of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the safety and tolerability of magrolimab in combination with the anti-leukemia therapy CC-486 (Phase 2 Cohort 3) • To evaluate the PK of magrolimab in combination with the anti-leukemia therapy CC-486 • To evaluate the immunogenicity of magrolimab in combination with the anti-leukemia therapy CC-486	• MRD negative CR/CRi rate • RFS • OS • Duration of MRD negative CR • Duration of MRD negative CR/CRi • RBC transfusion independence rate • Platelet transfusion independence rate • Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Phase 2 Cohort 3) • Magrolimab concentrations over time • Rate and magnitude of anti-magrolimab antibodies

CCI [redacted]

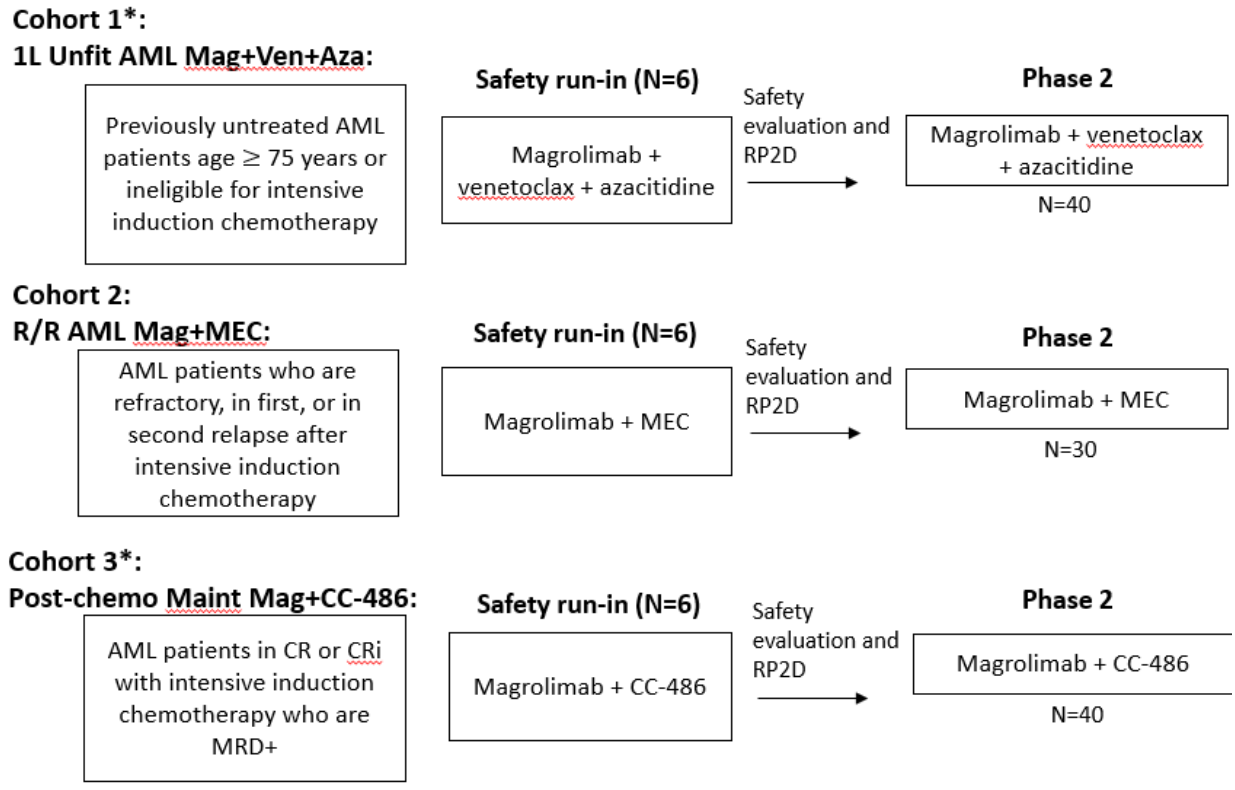
3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, open-label, multicenter, multi-arm study to evaluate magrolimab in combination with anti-leukemia therapies in patients with AML. This trial includes safety run-in cohorts (Section 3.1.1) and Phase 2 cohorts (Section 3.1.2).

The study schematic is presented in Figure 4.

Figure 4. Study Schema



AML = acute myeloid leukemia; MEC = mitoxantrone, etoposide, and cytarabine; MRD = minimal residual disease; RP2D = recommended Phase 2 dose

3.1.1. Safety Run-in Cohorts

This study will include the following 3 safety run-in cohorts:

- **Safety Run-in Cohort 1 (1L Unfit AML Mag+Ven+Aza), *closed to enrollment globally as of Protocol Amendment 5***: magrolimab + venetoclax + azacitidine in patients with newly diagnosed, previously untreated AML who are ineligible for intensive chemotherapy
- **Safety Run-in Cohort 2 (R/R AML Mag+MEC):** magrolimab + MEC in patients with R/R AML
- **Safety Run-in Cohort 3 (Post-chemo Maint Mag+CC-486), *closed to enrollment globally as of Protocol Amendment 5*:** magrolimab + CC-486 as maintenance therapy in patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy

Initially, 6 patients will be enrolled into Safety Run-in Cohorts 1, 2, and 3 to receive study treatment according to the dose levels presented in Table 1, Table 2, or Table 3, respectively. A DLT assessment period of 1 cycle (28 days) will occur. The DLT assessment period and definition are provided in Sections 3.1.1.1 and 3.1.1.2.

Dose de-escalation decisions will be made as follows:

- If no more than 2 patients in a safety run-in cohort experience a DLT in Cycle 1, enrollment into the corresponding Phase 2 cohort will begin at this dose level.
- If 3 or more (> 33%) patients in a safety run-in cohort experience a DLT up to the end of Cycle 1, another 6 patients will be enrolled in that cohort at a lower dose and evaluated in the same manner to define the RP2D.

De-escalation dose levels for each safety run-in cohort are presented in Table 4, Table 5, and Table 6. Any dose de-escalation for Cohorts 1 and 3 will occur with the combination regimen, as there is a lack of dose-dependent toxicities observed with magrolimab in over 500 patients treated to date with magrolimab as monotherapy or in combination, and agents being evaluated in combination with magrolimab have identified or potential dose-related toxicities as cytotoxic agents (ie, venetoclax and CC-486). For Cohort 2, any dose de-escalation will occur with magrolimab, as the combination with chemotherapy (ie, MEC) has not been extensively studied. The selected RP2D for any cohort cannot exceed the identified MTD for that cohort.

3.1.1.1. DLT Assessment Period

The DLT assessment period is the first cycle (28 days). For patients who are being evaluated for prolonged myelosuppression (Section 3.1.1.2), the 28-day DLT assessment period will extend to 42 days for Safety Run-in Cohorts 1 and 2. Patients are considered evaluable for assessment of a DLT if either of the following criteria is met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first dose of study treatment.
- The patient did not experience a DLT and completed at least 4 infusions of magrolimab and at least 14 doses of venetoclax and 5 doses of azacitidine (Safety Run-in Cohort 1), at least 3 days of dosing with MEC (Safety Run-in Cohort 2), or at least 10 doses of CC-486 (Safety Run-in Cohort 3).

If a patient experiences a DLT during the DLT assessment period, the investigator should contact the medical monitor to discuss whether the patient can remain on study drug.

Patients who are not evaluable for DLT will be replaced in the safety run-in cohorts.

3.1.1.2. DLT Definition

All toxicities will be graded according to the NCI CTCAE Version 5.0. A DLT is defined as any Grade 4 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity (that has worsened in severity from pretreatment baseline) during the 4-week DLT assessment period and is related to magrolimab or magrolimab combination.

The following are exceptions to the DLT definition and are NOT considered DLTs:

- Myelosuppression (Grade 4 neutropenia and thrombocytopenia) lasting no longer than 42 days from the start of study treatment for Cohorts 1 and 2, and no longer than 21 days from the start of study treatment for Cohort 3. Complications within the first 4 weeks that are associated with myelosuppression, such as fevers, infections, bleeding, and related hospitalizations, will also not be considered DLTs. However, Grade 4 neutropenia or thrombocytopenia lasting longer than 42 days from the start of study treatment for Cohorts 1 and 2, or 21 days from the start of study treatment for Cohort 3, without evidence of leukemia, will be considered DLTs. Absence of residual disease must be verified by peripheral blood count and bone marrow aspirate and biopsy at Day 43 (+ 10 days) for Cohorts 1 and 2.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 or pretreatment baseline with supportive care within 7 days and is not associated with other clinically significant consequences.
- Grade 3 isolated electrolyte laboratory abnormalities that resolve to ≤ Grade 2 or pretreatment baseline with supportive care within 7 days and are not associated with other clinically significant consequences.

- Grade 3 elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) that resolves to ≤ Grade 2 or pretreatment baseline with supportive care within 7 days and is not associated with other clinically significant consequences.

- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 or pretreatment baseline with supportive care within 7 days.

- Grade 3 fatigue that resolves to ≤ Grade 2 or pretreatment baseline within 2 weeks.

- Grade 3 magrolimab IRRs in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.

- Other single laboratory values out of normal range that have no clinical correlate and resolve to Grade ≤ 2 or to pretreatment baseline within 7 days with adequate medical management.

- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgia, fever, headache, acute pain, or skin toxicity that resolves to ≤ Grade 2 within ≤ 72 hours after medical management (eg, supportive care, including immunosuppressant treatment) has been initiated.

- Grade 3 or 4 TLS or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 14 days.

The recommended dose for the Phase 2 cohorts will be determined by the sponsor based on all relevant clinical and PK data from all patients treated in the safety run-in cohorts.

3.1.1.3. Safety Review Team

A safety review team (SRT) will be established to assess safety of patients across the cohorts.

The SRT will consist of at least 1 investigator, a Gilead safety physician, and the Gilead medical monitor. Others may be invited to participate as members of the SRT if additional expertise is desired. The medical monitor serves as the chair of the SRT. An SRT charter (or similar document) will be agreed on by all SRT members prior to the first SRT meeting. The data reviewed at the SRT meeting to make decisions will be defined in the SRT charter (or similar document). The quality control checks performed on the data reviewed and used for making decisions will be described in the SRT charter (or similar document).

3.1.2. Phase 2 Cohorts

After completion of each safety run-in cohort and identification of the RP2D for that cohort, the corresponding Phase 2 cohort may be enrolled as follows:

- **Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza), *closed to enrollment globally as of Protocol Amendment 5*:** 40 patients with newly diagnosed, previously untreated AML who are ineligible for intensive chemotherapy will be enrolled to receive magrolimab + venetoclax + azacitidine.

- **Phase 2 Cohort 2 (R/R AML Mag+MEC):** 30 patients with R/R AML will be enrolled to receive magrolimab + MEC.

- **Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486), *closed to enrollment globally as of Protocol Amendment 5*:** 40 patients with newly diagnosed AML who are in CR or CRi with MRD positivity following intensive chemotherapy may be enrolled to receive magrolimab + CC-486.

Up to 5 to 10 additional patients may be enrolled in each of the Phase 2 cohorts to collect additional safety, efficacy, and/or PK/PD data.

3.1.3. Closure of Cohorts 1 and 3

Cohort 1 closed to enrollment globally as of Protocol Amendment 5 and no new patients enrolled in Cohort 1 thereafter. A total of 18 patients were enrolled into Cohort 1 (7 patients in safety run-in and 11 patients in Phase 2).

Cohort 1 patients enrolled prior to sponsor's notification and implementation of Protocol Amendment 5 will continue on study, receive study treatment (Sections 3.3, 5.1, and 5.2), and undergo all study assessments (Section 6), until end of study or discontinuation criteria are met (Sections 3.4 and 3.5).

Cohort 3 closed to enrollment globally as of Protocol Amendment 5 and no patients were enrolled.

3.2. Study Treatments

Study treatments for each safety run-in cohort are presented in Table 1, Table 2, and Table 3, respectively. Dose de-escalation plans for each safety run-in cohort are presented in Table 4, Table 5, and Table 6, respectively. Schedules of treatment administration are provided in Appendix Table 6, Appendix Table 7, and Appendix Table 8.

Refer to Section 3.1.3 for information on Cohort 1 patients enrolled prior to implementation of Protocol Amendment 5.

Table 1. Dose Level and Schedule for Safety Run-in Cohort 1 (1L Unfit AML Mag+Ven+Aza)

Drug/Dose/Route	Dose Schedule (Day per 28-Day Cycle)		
	Cycle 1	Cycle 2	Cycle 3+
Azacitidine 75 mg/m^2 SC or IV	Days 1-7 or Days 1-5, 8, 9[a]	Days 1-7 or Days 1-5, 8, 9[a]	Days 1-7 or Days 1-5, 8, 9[a]
Venetoclax PO	100 mg on Day 1 200 mg on Day 2 400 mg on Days 3-28	400 mg on Days 1-28	
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 5th weekly 30 mg/kg dose		

IV = intravenous; PO = orally; Q2W = every 2 weeks; QW = once weekly; SC = subcutaneous
a Or any other alternative schedule, as long as 7 doses of azacitidine of the cycle are administered within 9 consecutive days.

Table 2. Dose Level and Schedule for Safety Run-in Cohort 2 (R/R AML Mag+MEC)

Drug/Dose/Route	Dose Schedule (Day per 28-Day Cycle)	
	Cycle 1	Cycle 2 to 3[a]
Mitoxantrone 8 mg/m^2 IV (over 15-30 min)	Days 1-5	Days 1-5
Etoposide 100 mg/m^2 IV (over 30-60 min)	Days 1-5	Days 1-5
Cytarabine 1000 mg/m^2 IV (over 1 hour)	Days 1-5	Days 1-5
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 5th weekly 30 mg/kg dose, up to 12 months of total magrolimab treatment	

IV = intravenous; MEC = mitoxantrone, etoposide, cytarabine; Q2W= every 2 weeks; QW = once weekly
a If patient achieved blast clearance after Cycle 1, one additional cycle of MEC will be given (total 2 cycles). If patient achieved blast clearance only after Cycle 2, a third cycle of MEC will be given. If no blast clearance at the end of Cycle 2, patient should be discontinued from the study.

Table 3. Dose Level and Schedule for Safety Run-in Cohort 3 (Post-Chemo Maint Mag+CC-486)

Drug/Dose/Route	Dose Schedule (Day per 28-Day Cycle)		
	Cycle 1	**Cycle 2**	**Cycle 3+**
CC-486 300 mg PO	Days 1-14	Days 1-14	Days 1-14
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 5th weekly 30 mg/kg dose		

IV = intravenous; PO = orally; Q2W= every 2 weeks; QW = once weekly

Table 4. Dose De-escalation for Safety Run-in Cohort 1 (1L Unfit AML Mag+Ven+Aza)

Dose Level	Dosing (28-Day Cycle)
Venetoclax starting dose	Cycle 1: 100 mg PO Day 1, 200 mg Day 2, 400 mg Days 3-28, Cycle 2 and later: 400 mg Days 1-28
Level Minus 1	Cycle 1: 100 mg PO Day 1, 200 mg Day 2, 400 mg Days 3-21, Cycle 2 and later: 400 mg Days 1-21
Level Minus 2	Cycle 1: 100 mg PO Day 1, 200 mg Day 2, 400 mg Days 3-14, Cycle 2 and later: 400 mg Days 1-14
Magrolimab and azacitidine (all dose levels)	Will be administered at the starting dose and not dose-reduced for any of the dose minus levels

PO = orally

Table 5. Dose De-escalation for Safety Run-in Cohort 2 (R/R AML Mag+MEC)

	Dosing (28-Day Cycle)	
	MEC	Magrolimab
Dose Level	Cycles 1 and 2 to 3[a]	Up to 12 Months
Starting dose	Mitoxantrone 8 mg/m^2 IV (over 15-30 min) Days 1-5 Etoposide 100 mg/m^2 IV (over 30-60 min) Days 1-5 Cytarabine 1000 mg/m^2 IV (over 1 hour) Days 1-5	Magrolimab: 1 mg/kg IV (over 3 hours) Days 1, 4; 15 mg/kg IV (over 3 hours) Day 8; 30 mg/kg IV (over 2 hours) Days 11 and 15, and then QW × 5 doses 30 mg/kg IV (over 2 hours) Q2W beginning 1 week after the 5th weekly 30 mg/kg dose
Level Minus 1	Mitoxantrone 8 mg/m^2 IV (over 15-30 min) Days 1-5 Etoposide 100 mg/m^2 IV (over 30-60 min) Days 1-5 Cytarabine 1000 mg/m^2 IV (over 1 hour) Days 1-5	Magrolimab: 1 mg/kg IV (over 3 hours) Days 1, 4; 15 mg/kg IV (over 3 hours) Day 8; 20 mg/kg IV (over 2 hours) Days 11 and 15, and then QW × 5 doses 20 mg/kg IV (over 2 hours) Q2W beginning 1 week after the 5th weekly 20 mg/kg dose
Level Minus 2	Mitoxantrone 8 mg/m^2 IV (over 15-30 min) Days 1-5 Etoposide 100 mg/m^2 IV (over 30-60 min) Days 1-5 Cytarabine 1000 mg/m^2 IV (over 1 hour) Days 1-5	Magrolimab: 1 mg/kg IV (over 3 hours) Days 1, 4; 15 mg/kg IV (over 3 hours) Day 8; 15 mg/kg IV (over 2 hours) Days 11 and 15, and then QW × 5 doses 15 mg/kg IV (over 2 hours) Q2W beginning 1 week after the 5th weekly 15 mg/kg dose

IV = intravenous; MEC = mitoxantrone, etoposide, cytarabine; QW = once weekly; Q2W= every 2 weeks

a If patient achieved blast clearance after Cycle 1, one additional cycle of MEC will be given (total 2 cycles). If patient achieved blast clearance only after Cycle 2, a third cycle of MEC will be given. If no blast clearance at the end of Cycle 2, patient should be discontinued from the study.

Table 6. Dose De-escalation for Safety Run-in Cohort 3 (Post-Chemo Maint Mag+CC-486)

Dose Level	Dosing (28-Day Cycle) (Cycles 1, 2, and 3+)
CC-486 Starting dose	300 mg PO Days 1-14
Level Minus 1	200 mg PO Days 1-14
Level Minus 2	200 mg PO Days 1-7
Magrolimab (all dose levels)	Magrolimab will be administered at the starting dose and will not be dose-reduced for any of the dose minus levels

PO = per oral route

3.3. Duration of Treatment

Cohorts 1 and 3: treatment until discontinuation criteria is met.

Cohort 2: treatment for up to 12 months.

Patients in each safety run-in cohort will receive 1 cycle (28 days) of study treatment before being evaluated for DLTs. Patients in the safety run-in cohorts will continue study treatment at the assigned dose level for at least 4 cycles, after which they may continue at the assigned dose level or switch to the RP2D upon agreement between the investigator and the sponsor. Safety run-in cohort patients will continue dosing until Phase 2 cohort end-of-treatment criteria are met.

Patients in Phase 2 Cohorts 1 and 3 will receive study treatment until disease progression, unacceptable toxicity, and/or loss of clinical benefit.

Patients in Phase 2 Cohort 2 will receive MEC for 2 to 3 cycles. Patients who do not achieve an OR (ie, CR, CRi, CRh, PR, or MLFS) after 2 cycles will be discontinued from therapy. For patients achieving a response after 1 to 2 cycles, an additional single MEC cycle will be administered. Magrolimab will be administered in Phase 2 Cohort 2 until disease progression, unacceptable toxicity, and/or loss of clinical benefit for up to 12 months.

3.4. Discontinuation Criteria

Reasons for discontinuation of study treatment must 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)

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 treatments.

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.

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.

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 is recommended prior to SCT.

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.

The assessments to be performed at each of the posttreatment visits are listed in Appendix Table 9.

Refer to Section 3.1.3 for information on Cohort 1 patients enrolled prior to implementation of Protocol Amendment 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 completed study participation altogether when they are no longer followed for safety.

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 AEs as specified in Appendix Table 9.

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 (PK, ADA, and/or PD) laboratory testing, and/or additional biomarker testing.

3.8. Pharmacokinetics/Biomarker Testing

3.8.1. Biomarker and Genomic Samples to Address the Study Objectives

Peripheral blood, bone marrow aspirate and trephine biopsy, and buccal swab samples will be collected from all patients who have provided consent to participate in this study at the time points listed in the schedules of assessments (Appendix Table 1, Appendix Table 2, Appendix Table 3, Appendix Table 4, Appendix Table 5, and Appendix Table 9). The samples may be used to evaluate the association of systemic and/or tissue-based biomarkers with study treatment response, including efficacy and/or AEs, and dosage selection, and to better understand the biological pathways involved in AML pathogenesis and the immune response to AML, as well as the efficacy and MOA for magrolimab combinations. 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.

The blood, bone marrow, and buccal swab samples collected will be used to measure biomarkers, which may include but will not be limited to the frequency of leukemia stem cells or MRD, 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.

The 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 sequences that are cancer specific.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or in accordance with country requirements.

CCI [redacted]

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Up to approximately 164 patients will be enrolled in the study, with up to 54 patients in the safety run-in cohorts and up to 110 patients in the Phase 2 cohorts.

Refer to Section 3.1.3 for information on Cohort 1 patients enrolled prior to implementation of Protocol Amendment 5.

The following patient populations will be enrolled into the study:

- **Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza),** ***closed to enrollment globally as of Protocol Amendment 5***: patients with newly diagnosed, previously untreated AML confirmed 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 chemotherapy

- **Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)**: patients with confirmation of AML by WHO criteria who are refractory to or have relapsed after the initial intensive chemotherapy

- **Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486),** ***closed to enrollment globally as of Protocol Amendment 5***: patients with confirmation of AML by WHO criteria who achieved CR or CRi with presence of MRD (MRD positive) after intensive induction chemotherapy with or without consolidation therapy prior to starting maintenance therapy

4.1.1. Patient Replacement

For the safety run-in cohorts, patients who do not meet the DLT assessment criteria will be replaced. In the Phase 2 cohorts, there will be no patient replacement.

4.2. Inclusion Criteria

All Patients

All patients must meet the following inclusion criteria to be eligible for participation in this study:

1) White blood cell (WBC) count $\leq 20 \times 10^3/\mu L$ prior to first dose of study treatment. If the patient's WBC count is $> 20 \times 10^3/\mu L$ prior to first dose of study treatment, the patient can be enrolled, assuming all other eligibility criteria are met. However, ensure that the WBC count is $\leq 20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each magrolimab dose for the first 4 weeks.

NOTE: Patients can be treated with hydroxyurea and/or leukapheresis throughout the study or prior to first dose of study treatment to reduce the WBC count to $\leq 20 \times 10^3/\mu L$ to enable eligibility for magrolimab dosing.

2) Hb must be ≥9 g/dL prior to initial dose of study treatment

   NOTE: Transfusions are allowed to meet Hb eligibility (see Section 7.8.1.1).

3) Adequate liver function as demonstrated by the following:

   a) AST $\leq$ 3.0 × upper limit of normal (ULN)

   b) ALT $\leq$ 3.0 × ULN

   c) bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert syndrome or genetic equivalent.

4) Patients must have adequate renal function as demonstrated by a creatinine clearance (CLcr) $\geq$ 30 mL/min calculated by the Cockcroft-Gault formula.

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, age $\geq$ 18 years.

8) Pretreatment blood cross-match completed (as detailed in Section 6.5.3).

9) Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.

10) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines), unless not feasible as determined by the investigator and discussed with the sponsor.

Safety Run-in Cohort 1 and Phase 2 Cohort 1 (1L Unfit AML Mag+Ven+Aza), *closed to enrollment globally as of Protocol Amendment 5*

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 1 and Phase 2 Cohort 1 must fulfill the following cohort-specific inclusion criteria:

11) Newly diagnosed, previously untreated patients with confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age, comorbidity, or other factors. Patients must be considered ineligible for induction therapy defined by the following:

    a) ≥ 75 years of age

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

        i. 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. LVEF ≤ 50%

        iv. CLcr < 45 mL/min calculated by the Cockcroft-Gault formula

        v. Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy that must be approved by the sponsor medical monitor before study enrollment.

12) ECOG performance status:

    - Of 0 to 2 for subjects ≥ 75 years of age

    OR

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

13) Patients who have not received prior anti-leukemia therapy for AML (excluding hydroxyurea), HMA, low-dose cytarabine, and/or venetoclax.

    NOTE: Patients with prior MDS who have not received prior HMA, venetoclax, or a chemotherapeutic agent are eligible. Other prior MDS therapies, including but not limited to lenalidomide, erythroid stimulating agents, or similar RBC-, WBC-, or platelet direct therapies or growth factors, are allowed.

14) Patients who have not received strong and/or moderate cytochrome P450 enzyme (CYP) 3A inducers (eg, St. John's Wort) within 7 days prior to the initiation of study treatment.

15) Patients who have not consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment or are willing to discontinue consumption of these while receiving study drug.

16) Patients without malabsorption syndrome or other conditions that preclude enteral route of administration.

Safety Run-in Cohort 2 and Phase 2 Cohort 2 (R/R AML Mag+MEC)

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 2 and Phase 2 Cohort 2 must fulfill the following cohort-specific inclusion criteria:

17) Patients with confirmation of AML by WHO criteria who are refractory to or have experienced first relapse after initial intensive chemotherapy, which includes 1 or 2 cycles of a 7 + 3 based induction regimen or a purine analogue based induction therapy, such as fludarabine or cladribine paired with anthracyclines and cytarabine (eg, fludarabine, high-dose cytarabine [ara-C], G-CSF, and idarubicin [FLAG-Ida] or cladribine, ara-C, G-CSF, and mitoxantrone [CLAG-M]) or failed therapy after remission (eg, consolidation) during any number of cycles (maximum of 4) of high- or intermediate-dose cytarabine. For other intensive regimens, please discuss with the medical monitor.

    NOTE: Patients who are relapsed after or are refractory to more than 1 line of anti-AML treatment are not eligible.

    Patients who relapsed after undergoing stem cell transplant may be eligible.

18) At least 2 weeks must have elapsed since any prior anti-leukemia agents.

    NOTE: Localized non-central nervous system (CNS) radiotherapy, hydroxyurea, and erythroid and/or myeloid growth factors are not criteria for exclusion.

19) ECOG performance status of 0 to 2.

20) Patients with LVEF $\geq$ 50%, lack of symptomatic congestive heart failure, or clinically significant cardiac arrhythmias.

21) Patients who have not been treated with trastuzumab within 7 months prior to the initiation of study treatment

22) Patients who have not previously received maximum cumulative doses of anthracyclines and anthracenediones

23) Patients without degenerative or toxic encephalopathies

24) Patients who did not undergo hematopoietic SCT in the past 100 days, are not on immunosuppressive therapy post SCT in the 2 weeks prior to the first dose of study treatment, or have no active clinically significant graft-versus-host disease.

Safety Run-in Cohort 3 and Phase 2 Cohort 3 (Post-chemo Maint Mag+CC-486), *closed to enrollment globally as of Protocol Amendment 5*

In addition to meeting the inclusion criteria for all patients, patients who are enrolled into Safety Run-in Cohort 3 and Phase 2 Cohort 3 must fulfill the following cohort-specific inclusion criteria:

25) Patients with confirmation of AML by WHO criteria who achieved a CR or CRi with presence of MRD (MRD positive by local flow cytometry assay, defined as ≥ 0.1% detectable MRD) after intensive induction chemotherapy with or without consolidation therapy, prior to starting maintenance therapy for newly diagnosed AML.

26) ECOG performance status of 0 to 2.

27) Patients without malabsorption syndrome or other conditions that preclude enteral route of administration.

4.3. Exclusion Criteria

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

1) Positive serum pregnancy test (Appendix 5).

2) Breastfeeding female.

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

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

5) Prior treatment with CD47 or SIRPα-targeting agents.

6) Current participation in another interventional clinical trial.

7) Known inherited or acquired bleeding disorders.

8) Clinical suspicion of or documented active CNS involvement with AML.

9) Patients who have acute promyelocytic leukemia.

10) 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 infections, and congestive heart failure New York Heart Association Class III-IV.

11) 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 anticancer therapies and have had no evidence of active malignancy for over 1 year. Previous hormonal therapy with luteinizing hormone-releasing hormone (LHRH) agonists for prostate cancer and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion.

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

12) Known medical history of active or chronic hepatitis B or C infection or medical history of human immunodeficiency virus (HIV) infection.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

All study drugs should be prepared as outlined in the Pharmacy Manual for the study.

The first dose of study drugs should be administered within 72 hours after enrollment. Patients should be premedicated in accordance with Sections 5.1.4, 5.2.4, 5.3.5, and 5.4.3.

The dosing regimen for each cohort is presented in Section 3.2.

Refer to Section 3.1.3 for information on Cohort 1 patients enrolled prior to implementation of Protocol Amendment 5.

5.1. All Cohorts (Magrolimab)

5.1.1. Description and Handling of Magrolimab

5.1.1.1. Formulation

Magrolimab is formulated as a sterile, clear to slightly opalescent, colorless to slightly yellow, 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 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.

5.1.1.2. Packaging and Labeling

Magrolimab is 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 FDA, European Union (EU) Guidelines to Good Manufacturing Practice, Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.1.1.3. Storage and Handling

Magrolimab should be stored at 2°C to 8°C (36°F to 46°F). Magrolimab 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.

5.1.2. Dosage and Administration of Magrolimab

The magrolimab dosing regimen for each safety run-in cohort is presented in Table 1, Table 2, and Table 3. The dose de-escalation regimens for magrolimab in Safety Run-in Cohort 2 are presented in Table 5. Treatment schedules are provided in Appendix 2.

Magrolimab will be administered by IV infusion. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. 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 28 days of treatment, WBC count must be $\leq 20 \times 10^3/\mu L$ prior to each magrolimab dose. Patients with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea (up to 4 g/day) 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 2 first doses of magrolimab infusion during initial treatment, all patients must have a documented Hb ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their Hb rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

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 Hb 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 first 28 days of treatment. Patients should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion-related reaction, 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 will be calculated based on actual weight at enrollment (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 may 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 3.4).

Treatment Delay and Repriming/Re-escalation for Magrolimab

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming/re-escalation for magrolimab after a dose delay are provided in Section 5.1.3.

5.1.3. Dose Modification and Delays for Magrolimab

The dose of magrolimab should not be reduced except in Safety Run-in Cohort 2 in the case of dose de-escalation based on DLTs.

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 may be allowed in certain circumstances (eg, with certain AEs), with approval by the sponsor. If a dose reduction is considered, initial 33% dose reduction from the RP2D should be done (from 30 to 20 mg/kg, and from 20 to 15 mg/kg).

When the combination drugs (venetoclax + azacitidine or MEC or CC-486) are delayed due to toxicities, magrolimab should continue independently as per magrolimab administration schedule (Appendix Table 4). Continuous dosing of magrolimab is needed to maintain efficacious exposures as delays of greater than 1 week when magrolimab is dosed every 2 weeks have been seen to result in lower clinical efficacy. Magrolimab may be withheld if treatment-emergent and/or related AEs occur, and will require approval by the sponsor if the delay is longer than 3 days.

The repriming guidelines presented in Table 7 should be followed for patients with magrolimab dose delays. In case of repriming, assessments should follow magrolimab repriming table (Appendix Table 5).

In case of repriming, before the administration of the 2 first doses of magrolimab, Hb should be ≥ 9 g/dL. Transfusions are allowed to meet this Hb level.

Table 7. Repriming Guidelines for Magrolimab

Dose	Dosing Frequency	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	NA – used at initial priming	2 weeks
15 mg/kg	Weekly or more frequent (during first 4 to 8 weeks)	2 weeks
	Every 2 weeks (after 8 weeks of treatment)	4 weeks
20 mg/kg	Weekly or more frequent (during first 4 to 8 weeks)	2 weeks
	Every 2 weeks (after 8 weeks of treatment)	4 weeks
30 mg/kg	Every 2 weeks (after 8 weeks of treatment), weekly or more frequent	4 weeks

NA = not applicable

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

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

Planned Surgical Procedure	Magrolimab Dose Guidance
Minimally invasive procedure (Examples: biopsies [excluding lung/liver], skin/subcutaneous lesion removal, cataract/glaucoma/eye surgery/cystoscopy)	Hold magrolimab 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 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 dose 7 days prior to procedure and restart after 7 days

CNS = central nervous system

5.1.4. Premedication and Prophylaxis for Magrolimab

Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming. Premedication should include 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. For patients who do not experience an IRR with the first 4 doses of magrolimab, corticosteroid pretreatment can be discontinued at the investigators' discretion. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. Premedication decisions for subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior IRRs. Guidance is provided in Table 15.

5.1.5. Prior and Concomitant Medications: Permitted Concomitant Medications for All Cohorts

For the anti-leukemia regimens administered with magrolimab in this study, the current local or regional prescribing information should be consulted regarding permitted and prohibited concomitant medications.

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 5.1.4, 5.2.4, 5.3.5, and 5.4.3, 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 Hb level, and as per investigator 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 the 70-days (± 7 days) safety follow-up visit should be recorded in the eCRF.

5.1.5.1. 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 for patients in Cohort 1 (receiving magrolimab + venetoclax + azacitidine therapy) or Cohort 2 (who are receiving ongoing MEC chemotherapy) 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. For Cohort 2 patients who have completed MEC induction chemotherapy cycles or for Cohort 3 patients, there is no specific recommendation on the timing of a COVID-19 vaccine; individuals may receive the vaccine when available. However, if these patients are neutropenic, investigators may use clinical judgement in determining the timing of the COVID-19 vaccine. 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.

5.2. Cohort 1 (1L Unfit AML Mag+Ven+Aza)

Information for magrolimab is provided in Section 5.1.

The start of the cycle is the first day of azacitidine + venetoclax.

In the event 1 or more components of the study treatment (magrolimab, azacitidine, and/or venetoclax) are discontinued, the following combinations are permitted:

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

The following combinations are not permitted:

- Magrolimab (single agent)
- Venetoclax (single agent)
- Magrolimab + 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.

When both magrolimab and azacitidine are given on the same visit day, magrolimab will be administered at least 1 hour after the completion of azacitidine administration.

5.2.1. Description and Handling of Venetoclax

5.2.1.1. Formulation

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

5.2.1.2. 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.

5.2.1.3. Storage and Handling

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

5.2.2. Description and Handling of Azacitidine

5.2.2.1. Formulation

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

5.2.2.2. 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.

5.2.2.3. Storage and Handling

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

5.2.3. Dosage and Administration of Azacitidine and Venetoclax

The azacitidine and venetoclax dosing regimen for Safety Run-in Cohort 1 is presented in Table 1. The dose de-escalation regimens for venetoclax in Safety Run-in Cohort 1 are presented in Table 4. The treatment schedule is provided in Appendix Table 6.

Azacitidine administration should be completed at least 1 hour before magrolimab 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 the 7 doses of azacitidine of the cycle are administered within 9 consecutive days. 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 height and weight at enrollment (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.

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.

Patients treated with venetoclax may develop TLS. Assess blood chemistry (potassium, uric acid, phosphorous, calcium, and creatinine). Correct pre-existing 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.

For patients taking concomitant CYP3A and P-glycoprotein (P-gp) inhibitors, refer to Table 11 for venetoclax dosing and administration.

5.2.4. Premedication and Prophylaxis for Azacitidine and Venetoclax

Prior to first dose of venetoclax, patients must be provided with prophylactic measures including adequate hydration and antihyperuricemic agents 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.

5.2.5. Dose Modification and Delays for Azacitidine and Venetoclax

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.

5.2.5.1. Venetoclax and Azacitidine Dose Modifications and Delays Due to Hematologic Toxicity

Dose modifications and delays for venetoclax due to AEs should follow Table 9 or the venetoclax local prescribing information. If bone marrow assessment done in Cycle 1 shows blast clearance (< 5%), venetoclax dose for the remainder of the cycle can be omitted to allow for count recovery.

Table 9. Venetoclax and Azacitidine Dose Modifications and Delays Due to Hematological Toxicity

Event	Occurrence	Action Taken[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 same duration (21 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 decrease the duration to 14 days. Resume azacitidine at the same dose.
	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 and duration (14 days) and reduce the azacitidine dose to 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, decrease the duration to 7 days, and continue the azacitidine dose at 50 mg/m^2.
	Sixth 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.
	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, resume venetoclax therapy at the same dose and duration (7 days), and decrease the azacitidine dose to 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 that lasts longer than 7 days from the day blast is noted to be < 5% in the first remission bone marrow.

If per dosing modification 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 patient's clinical condition allows safe resumption of the cycle. If the start of the 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.

5.2.5.2. Venetoclax and Azacitidine Dose Modifications and Delays Due to Nonhematologic Toxicity

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 ≥ 2-fold 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.

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

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 10.

Table 10. Azacitidine Dose Modification 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.

For Grade 3 or higher nonhematologic AEs that are clinically relevant and related to venetoclax, hold venetoclax until toxicity is resolved to Grade 2 or lower, or to baseline grade.

5.2.6. Prior and Concomitant Medications: Prohibited Concomitant Medications for Cohort 1

For the anti-leukemia regimens administered with magrolimab in this study, the current local or regional prescribing information should be consulted regarding permitted and prohibited concomitant medications.

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

Any investigational drugs other than magrolimab are prohibited during study treatment.

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.

Concomitant use of preparations containing St. John's wort is contraindicated during the study.

Conversely, concomitant use of strong and moderate CYP3A inhibitors with venetoclax increases exposure of 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 11. 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 11. 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

5.3. Cohort 2 (R/R AML Mag+MEC)

The start of the cycle is the first day of MEC.

Information for magrolimab is provided in Section 5.1. Magrolimab infusion should be completed at least 1 hour before starting MEC chemotherapy if given on the same day.

5.3.1. Description and Handling of Mitoxantrone

5.3.1.1. Formulation

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

5.3.1.2. 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.

5.3.1.3. Storage and Handling

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

5.3.2. Description and Handling of Etoposide

5.3.2.1. Formulation

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

5.3.2.2. 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.

5.3.2.3. Storage and Handling

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

5.3.3. Description and Handling of Cytarabine

5.3.3.1. Formulation

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

5.3.3.2. 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.

5.3.3.3. Storage and Handling

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

5.3.4. Dosage and Administration of Mitoxantrone, Etoposide, and Cytarabine

The MEC dosing regimen for Safety Run-in Cohort 2 is presented in Table 2. The treatment schedule is provided in Appendix Table 7.

Magrolimab infusion should be completed at least 1 hour before starting MEC chemotherapy if given on the same day.

5.3.5. Premedication and Prophylaxis for Mitoxantrone, Etoposide, and Cytarabine

Premedications for mitoxantrone, etoposide, and cytarabine can be administered per local institutional guidelines.

5.3.6. Dose Modification and Delays for Mitoxantrone, Etoposide, and Cytarabine

MEC is a cytotoxic therapy and causes myelosuppression. Given that patients with AML will also be cytopenic as a result of their leukemia, dose modifications or delays of MEC should only occur if there is no evidence of leukemia, as defined by a bone marrow blast count of < 5% and absence of circulating peripheral blasts.

In the setting of absence of leukemic disease, treatment with MEC should be delayed in instances of ANC < 500/mm^3 or platelets < 50,000/mm^3 until recovery to an ANC ≥ 1000/mm^3 or platelets > 75,000/mm^3 or ANC and platelet values equal to or above the patient's baseline values.

The individual components of the MEC regimen have distinct dose modification considerations and are detailed below.

Mitoxantrone

Mitoxantrone clearance is reduced by hepatic impairment. Patients with total bilirubin > 3.5 mg/dL should reduce the dose of mitoxantrone by 50%. Mitoxantrone can be dosed at the full dose once total bilirubin is ≤ 3.5 mg/dL.

Etoposide

Etoposide is renally metabolized and dose modifications should be made for impaired CLcr. If CLcr is 15 to 50 mL/min, administer 75% of the etoposide dose. If CLcr is < 15 mL/min, consider further dose reductions per institutional guidelines (ie, a 50% dose reduction).

Liver dysfunction may reduce the metabolism and increase the toxicity of etoposide; however, dose adjustment instructions are not provided in the US prescribing information (USPI). For patients with total bilirubin (predominantly direct) > 3 mg/dL or AST > 5 × ULN, administer 50% of the etoposide dose. Etoposide can be dosed at standard levels once total bilirubin is < 3 mg/dL or AST is < 5 × ULN.

Cytarabine

No dose adjustments are required for renal or hepatic impairment.

5.3.7. Prior and Concomitant Medications: Prohibited Concomitant Medications for Cohort 2

For the anti-leukemia regimens administered with magrolimab in this study, the current local or regional prescribing information should be consulted regarding permitted and prohibited concomitant medications.

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

Any investigational drugs other than magrolimab are prohibited during study treatment.

Drugs with cardiotoxic potential are prohibited during the study because of the potential cardiotoxicity with the use of mitoxantrone.

In patients receiving oral anticoagulant therapy, partial thromboplastin time (PTT) or international normalized ratio (INR) should be closely monitored and adjusted as needed with the addition and withdrawal of treatment with mitoxantrone and etoposide.

In patients treated with oral digoxin, monitor plasma digoxin levels during cytarabine treatment.

Gentamycin used against *Klebsiella pneumoniae* and 5-Fluorocytosine are contraindicated during cytarabine treatment.

Co-administration of antiepileptic drugs and etoposide injection can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.

Concomitant phenytoin or phenobarbital therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.

5.4. Cohort 3 (Post-Chemo Maint Mag+CC-486)

The start of the cycle is the first day of CC-486.

Information for magrolimab is provided in Section 5.1. CC-486 is to be administered before magrolimab in Cycle 1.

5.4.1. Description and Handling of CC-486

5.4.1.1. Formulation

Information regarding the formulation of CC-486 can be found in the current prescribing information {ONUREG 2020}.

5.4.1.2. 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.

5.4.1.3. Storage and Handling

Further information regarding storage and handling of CC-486 is available in the local prescribing information {ONUREG 2020}.

5.4.2. Dosing and Administration of CC-486

The CC-486 dosing regimen for Safety Run-in Cohort 3 is presented in Table 3. The dose de-escalation regimens for CC-486 in Safety Run-in Cohort 3 are presented in Table 6. The treatment schedule is provided in Appendix Table 8.

If a patient discontinues CC-486, magrolimab should also be discontinued.

CC-486 (Onureg) will be administered at a dose of 300 mg orally once daily on Days 1 through 14 of each 28-day cycle in accordance with USPI. CC-486 should be taken at the same time each day. If a dose of CC-486 is missed, or not taken at the usual time, the dose should be taken as soon as possible on the same day, and the normal dosing schedule resumed the following day. Two doses should not be taken on the same day. CC-486 should not be substituted with IV or SC azacitidine products. CC-486 treatment will be administered until disease progression, unacceptable toxicity, and/or loss of clinical benefit.

5.4.3. Premedication and Prophylaxis for CC-486

An anti-emetic should be administered 30 minutes prior to each dose of CC-486 for the first 2 cycles. Anti-emetic prophylaxis may be omitted after 2 cycles if there has been no nausea or vomiting. Anti-emetic regimens can be administered by USPI or local institutional guidelines.

5.4.4. Dose Modification and Delays for CC-486

CC-486 can cause myelosuppression, gastrointestinal toxicity, and other toxicities. Dose modifications/reductions of CC-486 will be made in accordance with the US package insert. Dose modifications for these toxicities are described in Table 12.

Table 12. CC-486 Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification[a]
Myelosuppression	Neutrophils less than 0.5 Gi/L on Day 1 of the cycle	Interrupt treatment. Resume at the same dose once neutrophils return to 0.5 Gi/L or higher.
	Neutrophils less than 1 Gi/L with fever at any time	First occurrence: Interrupt treatment. Resume at the same dose once neutrophils return to 1 Gi/L or higher. Occurrence in 2 consecutive cycles: Interrupt treatment. After neutrophils return to 1 Gi/L or higher, resume at reduce dose of 200 mg. If a patient continues to experience febrile neutropenia after dose reduction, reduce the treatment duration by 7 days. If febrile neutropenia reoccurs after dose and schedule reduction, discontinue CC-486.
	Platelets less than 50 Gi/L with bleeding	First occurrence: Interrupt treatment. Resume at the same dose once platelets return to 50 Gi/L or higher. Occurrence in 2 consecutive cycles: Interrupt treatment. After platelets return to 50 Gi/L or higher, resume at reduced dose of 200 mg. If a patient continues to experience thrombocytopenia with bleeding after dose reduction, reduce the treatment duration by 7 days. If thrombocytopenia with bleeding reoccurs after dose and schedule reduction, discontinue CC-486.
Gastrointestinal toxicity	Grade 3 or 4 nausea or vomiting	Interrupt dosing, resume at the same dose once toxicity has resolved to Grade 1 or lower (or baseline). If toxicity recurs, interrupt dosing until resolved to Grade 1 or lower (or baseline). Resume at reduced dose of 200 mg. If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or recurs after dose and schedule reduction, discontinue CC-486.
	Grade 3 or 4 diarrhea	Interrupt dosing, resume at the same dose once toxicity has resolved to Grade 1 or lower (or baseline). If toxicity recurs, interrupt dosing until resolved to Grade 1 or lower (or baseline). Resume at reduced dose of 200 mg. If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or recurs after dose and schedule reduction, discontinue CC-486.

Adverse Reaction	Severity	Dose Modification[a]
Other Adverse Reactions	Grade 3 or 4	Interrupt dosing, resume at the same dose once toxicity has resolved to Grade 1 or lower (or baseline). If toxicity recurs, interrupt dosing until resolved to Grade 1 or lower (or baseline). Resume at reduced dose of 200 mg. If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or recurs after dose and schedule reduction, discontinue CC-486.

Gi = giga per liter; PO = per oral route; RP2D = recommended Phase 2 dose

a If a 200 mg PO dose of CC-486 is selected as the RP2D, then omit further dose reduction and go directly to language "reduce the treatment duration by 7 days".

5.4.5. Prior and Concomitant Medications: Prohibited Concomitant Medications for Cohort 3

For the anti-leukemia regimens administered with magrolimab in this study, the current local or regional prescribing information should be consulted regarding permitted and prohibited concomitant medications.

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

Any investigational drugs other than those used in the study are prohibited during study treatment.

5.5. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (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 following:

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

5.5.1. 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 the 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.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient enrolled in the study are presented in tabular form in Appendix 2 (Appendix Table 1, Appendix Table 2, Appendix Table 3, Appendix Table 4, Appendix Table 5, and Appendix Table 9) and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

Refer to Section 3.1.3 for information on Cohort 1 patients enrolled prior to implementation of Protocol Amendment 5.

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 meet eligibility criteria will be enrolled using an integrated web response system. The first dose of study drugs should be administered within 72 hours after enrollment.

Patients who are determined to be not 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 enrollment to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain demographics and medical history, including cancer history, date of recent RBC and/or platelet transfusions, AML molecular marker results at diagnosis, and echocardiogram/multigated acquisition (scan) (MUGA) or pulmonary function tests if done within the 3 months prior to signing the informed consent form (ICF)
- Complete physical examination, including vital signs, body weight, and height
- Serum pregnancy test (females of childbearing potential)

- Complete blood count (CBC) with differential, platelets, reticulocytes
- Serum or plasma chemistry
- Prothrombin time, INR, and activated partial thromboplastin time or partial thromboplastin time
- Extended red blood cell phenotyping or genotyping, ABO system (ABO)/Rhesus factor (Rh) type, and screen (any of the 4 blood groups A, B, AB, and O composing the ABO/Rh), direct antiglobulin test (DAT)
- Urinalysis
- Bone marrow biopsy and aspirate for blast evaluation, MRD assessment, cytogenetics, and correlative studies
- Bone marrow aspirate for RO (to be collected at selected study sites)
- Peripheral blood smear (for blasts)
- ECOG performance status (Appendix 6)
- Perform 12-lead electrocardiogram (ECG) (single)
- Echocardiogram or MUGA, if not done within the past 30 days prior to consent, for Cohort 2 patients only
- Record all SAEs and any AEs related to protocol-mandated procedures occurring after signing of the ICF
- Record prior and concomitant medications
- Entry criteria

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

6.2.2. Baseline/Day 1 Assessments

Baseline/Day 1 assessments are outlined in Appendix Table 2, Appendix Table 3, Appendix Table 4, and Appendix Table 5.

Patients must return to the study site within 30 days of screening for baseline/Day 1 assessments. The following will be performed and documented at baseline/Day 1:

- Serum or urine pregnancy test (females of childbearing potential)
- Predose CBC with differential, platelets, reticulocytes and postdose Hb
- Haptoglobin and lactate dehydrogenase
- Serum or plasma chemistry
- Vital signs, weight, and symptom-directed physical examination
- Recording of all AEs and concomitant medications
- Peripheral blood smear for general morphology
- Peripheral blood sample for correlative studies
- Peripheral blood sample for RO (to be collected at selected study sites)
- Buccal swab (may be collected on Day 1 or at any time during the study)
- PK and ADA sample collection

6.3. On-Study Treatment Assessments

On-study treatment assessments include evaluations of efficacy (Section 6.4), safety (Section 6.5), PK (Section 6.6), immunogenicity (Section 6.7), and PD and biomarkers (Section 6.8). The schedule for on-treatment assessments is provided in Appendix Table 2, Appendix Table 3, Appendix Table 4, and Appendix Table 5.

6.4. Efficacy Assessments

Clinical response will be assessed by the investigator using prespecified criteria (Appendix 7).

Response assessments will be done in conjunction with bone marrow assessments, according to the schedule of assessments (Appendix Table 2 and Appendix Table 3). Bone marrow assessments (including aspirate and core/trephine biopsy) are required for response assessments and may be used for blast evaluation, MRD assessment, cytogenetics, RO (to be collected at selected study sites), and correlative studies. Peripheral blood smears for blasts should be done on the day of the bone marrow assessments. Details for preparation and distribution of aspirate and biopsy/trephine specimens to the testing laboratories will be provided in the laboratory manual for this study.

If the patient is cytopenic at the time of the bone marrow assessment, CBC is to be monitored at least once per week until optimal count recovery is reached. The best accompanying laboratory CBC result within the ± 2-week window is to be used to support an efficacy response assessment, with the date of response assigned as the date of bone marrow assessment. If a patient achieves a CR, subsequent bone marrow biopsies are still required to be performed in accordance with the schedule of assessments.

Bone marrow aspirate and biopsy slides or blocks for efficacy assessments will be prepared for potential evaluation of response assessments by independent central review.

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.

6.5. Safety Assessments

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

6.5.1. 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 of < 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. A negative serum or urine pregnancy test is required at Cycle 1 Day 1 and every 4 weeks thereafter. 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. For further details, refer to Appendix 5.

6.5.2. Complete Blood Counts

Samples for CBCs should be collected per the schedules of assessments in Appendix 2. White blood cell count must be ≤ 20 x 10^3/μL prior to first dose of study drug and prior to each magrolimab dose for the first 28 days (see Section 5.1.2). 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 Hb monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure WBC level ≤ 20 x 10^3/μL for the first 4 weeks and repriming/re-escalation first 4 weeks.

6.5.3. Type and Screen and Direct Antiglobulin Test

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, ABO/Rh type, antibody screen, RBC phenotyping or genotyping, and DAT need to be performed at screening prior to exposure to magrolimab, as described in Section 7.8.1.1.

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

6.5.4. Vital Signs

Vital signs will 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 2.

6.5.5. Physical Examination

Complete physical examination will 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.

6.5.6. Electrocardiograms

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

6.5.7. 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 (± 7 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.

6.5.8. Laboratory Assessments

Laboratory assessments to be performed at screening are presented in Table 13. Laboratory assessments to be performed during the study are presented in Table 14.

Table 13. 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	Extended RBC phenotyping or genotyping
Chloride	Platelets		
Bicarbonate	WBC differential		Type and screen (ABO/Rh), DAT
Total protein	ANC		Blast evaluation (on CBC)
Albumin	Eosinophils		
Calcium	Basophils		**Bone marrow aspirate and biopsy:**
Magnesium	Lymphocytes		MRD assessment
Phosphorus	Monocytes		Cytogenetics
Glucose	Reticulocytes		Receptor occupancy (to be collected at selected study sites)
BUN or urea	PT		Correlative studies
Creatinine	INR		
Uric acid	aPTT or PTT		**Peripheral blood smear**:
Total bilirubin			Blasts *(with bone marrow assessments)*
Direct bilirubin			
Indirect bilirubin			
Haptoglobin			
LDH			
AST (SGOT)			
ALT (SGPT)			
Alkaline phosphatase			

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; ALT = alanine aminotransferase; ANC = absolute neutrophil count; 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; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell
Refer to Appendix Table 1 for collection time points.

Table 14. 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	Hematocrit	Pharmacokinetics
Calcium	Platelets	Antidrug antibodies
Chloride	WBC differential	Blast evaluation (on CBC)
Bicarbonate	ANC	
Albumin	Lymphocytes	**Bone marrow aspirate and biopsy:**
Glucose	Reticulocytes	MRD assessment
BUN or urea		Cytogenetics
Creatinine		Receptor occupancy (to be collected at selected study sites)
Uric acid (Cohorts 1 and 2)		Correlative studies
Phosphorus (Cohorts 1 and 2)		
Total bilirubin		
Direct bilirubin		**Peripheral blood smear**:
Indirect bilirubin		Blasts *(with bone marrow assessments)*
Haptoglobin		General cell morphology
LDH		
AST (SGOT)		
ALT (SGPT)		
Alkaline phosphatase		

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; 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 the time of bone marrow assessments, CBC to be monitored at least once per week subsequently until optimal count recovery is reached. The best CBC result within the ± 2-weeks window is to be used for the response assessment, with the date of the response being the date of the bone marrow assessment.

Refer to Appendix Table 2, Appendix Table 3, Appendix Table 4, and Appendix Table 5 for collection time points.

6.5.9. 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 (± 7 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 schedule of assessments (Appendix Table 9).

6.6. Pharmacokinetic Assessments

Samples for PK assessment of magrolimab will be collected from all patients in accordance with the schedule of assessments (Appendix Table 4 and Appendix Table 5). Serum magrolimab concentrations will be measured by a validated immunoassay.

CCI [redacted]

6.7. Immunogenicity Assessments

Samples for assessment of anti-magrolimab antibodies will be collected in all patients in accordance with the schedule of assessments (Appendix Table 4 and Appendix Table 5). Antidrug antibody assessment will be performed using a validated assay following a 3-tiered approach: screening, confirmatory, and titer testing.

CCI [redacted]

6.8. Pharmacodynamics and Biomarker Assessments

Peripheral blood samples will be collected for assessment of PD and biomarkers according to the schedule of assessments (Appendix Table 2, Appendix Table 3, Appendix Table 4, and Appendix Table 5). Pharmacodynamic and biomarker assessments provide important information regarding the efficacy and MOA of a drug. They also may identify particular patient subsets likely to respond to a therapy. Leukemia patients in this trial will be assessed by methods including, but not limited to, the studies described below.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

6.9. Posttreatment Assessments

Posttreatment assessments are presented in Appendix Table 9.

6.10. Assessments for Early Discontinuation from Study

Reasons for discontinuation of study treatment are provided in Section 3.4.

6.11. End of Study

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

6.12. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for AEs as specified in Appendix Table 9.

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.
- Pre-existing 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 pre-existing and should be documented as medical history.
- Pre-existing 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 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 Adverse Event/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 or 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 allowed by the protocol or the product labeling (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 the results of which 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 is defined as 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 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, pre-existing 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).

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 4).

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 any 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 (± 7 days) after last administration of study drug and reported on the eCRFs as instructed.

All AEs should be followed up 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 Patient Safety (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 (± 7 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 situations involving a Gilead concomitant therapy (not considered a study drug) that occur after the patient first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.1).

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:	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 Gilead PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

All special situations will be recorded on the SSR 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 concomitant medications manufactured by Gilead 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 SSR 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 study patients that are identified after initiation of study drug and throughout the study, including the protocol-required posttreatment 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 after the 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 EU 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 EU 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, ECG, 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 (eg, decreased Hb).

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 & Human Services (DHHS) 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

7.8.1.1. Anemia, Blood Crossmatching, 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 RBCs 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 Hb of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in Hb 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 (up to 3 g/dL) 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. 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.

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 Hb monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

Patients with low baseline Hb 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 Hb level as per the investigator's clinical judgment. The need for RBC transfusions and anemia from other causes in patients with cancer, means that care has to be taken with RBC cross-matching and packed RBC transfusions.

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. 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 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.

For patients after exposure to magrolimab

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines. For RBC phenotype/genotype matched units are preferred. However, 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, institution can use historical blood group or O type 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}.

7.8.1.2. Management of Infusion-Related Reactions

An IRR is 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 4). 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 use described in Section 5.1.4 will be used to manage IRRs preemptively.

Recommendations for the management of infusion-related reactions are in Table 15:

Table 15. Management of Infusion-related Reactions

CTCAE Grade	Management
Grade 1 Mild transient reaction.	Remain at bedside and monitor patient until recovery from symptoms. Patients who experience IRRs with the first 4 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.	Stop the magrolimab infusion, 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 will be administered at that visit. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. The amount of magrolimab infused must be recorded on the eCRF. Patients who experience a Grade 2 IRR 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.
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. 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 experience Grade 3 IRRs 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 recurrent Grade 3 IRR or patients who experience a Grade 4 IRR at any time should be permanently discontinued from the study treatment. For anaphylaxis, investigators should follow their institutional guidelines for treatment. All patients with a Grade 3 or higher IRR will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AE.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous: SC = subcutaneous

7.8.1.3. Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (Appendix Table 1, Appendix Table 2, Appendix Table 3, Appendix Table 4, Appendix Table 5, and Appendix Table 9) including neutrophils is required for all patients treated with magrolimab. Prophylactic antibiotics and/or antimycotics should be considered. Administer G-CSF if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia:

- Before achieving remission, for Grade 4 neutropenia (ANC < 500/μL) with or without fever or infection, the delay of magrolimab dosing is not recommended. In cases of Grade 4 neutropenia with serious infection, see Section 7.8.1.4 for recommendations on dose delay.

- After achieving remission, for Grade 4 neutropenia (ANC <500/μL) with fever or infection, and lasting at least 7 days, magrolimab dosing delay should be considered. Upon resolution to Grade ≤ 2, resume magrolimab at the same dose should be considered.

7.8.1.4. Serious Infections

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 (eg, fluoroquinolone) or antifungal agents (eg, oral triazoles or parenteral echinocandin) in accordance with current guidelines.

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

7.8.1.5. 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.

7.8.1.6. Management of 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 16 and follows the American Society of Clinical Oncology (ASCO) guidelines for immune-related AEs{Brahmer 2018}. Patients who experience Grade 3 to 4 pneumonitis will be permanently discontinued from study treatment.

Table 16. 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 to 4 weeks as clinically indicated. May resume magrolimab 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 therapy per protocol. Pulmonary and infectious disease consults. Consider empirical antibiotics. Monitor signs and symptoms every 2 to 3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1 to 3 days. If improving to baseline, taper corticosteroids over 4 to 6 weeks and resume magrolimab therapy per protocol. If no clinical improvement after 48 to 72 hours or worsening, treat as Grade 3 to 4.
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening.	Discontinue magrolimab therapy. Hospitalize. Pulmonary and infectious disease consults. 1 to 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 to 6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

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

7.8.2. Venetoclax

Safety management guidelines for venetoclax are described in Section 5.2.5. Additional safety guidelines are provided in the venetoclax local prescribing information {VENCLEXTA 2020}.

7.8.3. Azacitidine

Safety management guidelines for azacitidine are described in Section 5.2.5. Additional safety guidelines are provided in the azacitidine prescribing information {VIDAZA 2018}.

7.8.4. Mitoxantrone

Safety management guidelines for mitoxantrone are in accordance with the prescribing information {MitoXANTRONE 2018}. Key considerations are described here.

Myelosuppression

Mitoxantrone can cause severe myelosuppression when used for AML treatment. Close monitoring of laboratory counts, infectious prophylaxis, and supportive blood products and growth factors is needed. Mitoxantrone should only be administered by physicians experienced with treating AML.

Cardiac Risk

Mitoxantrone can cause congestive heart failure during or after therapy. Cardiotoxicity risk increases with cumulative mitoxantrone use. History of cardiovascular disease, prior therapy with anthracyclines or anthracenediones or use of other cardiotoxic drugs can increase this risk. All patients should be assessed for cardiac signs and symptoms by history, physical examination, and ECG prior to the start of therapy. In addition, all patients should have an echocardiogram to evaluate LVEF prior to starting therapy.

Secondary AML

Secondary AML has been reported in patients treated with mitoxantrone. In 1774 patients with breast cancer who received mitoxantrone concomitantly with other cytotoxic agents and radiotherapy, the cumulative risk of developing treatment-related AML was estimated at 1.1% at 5 years after receiving the therapy.

Hypersensitivity Reactions

Hypersensitivity reactions to mitoxantrone, including anaphylaxis, can occur. If hypersensitivity reactions occur, immediately interrupt treatment with mitoxantrone and institute supportive management per local guidelines. Permanently discontinue mitoxantrone treatment in any patient who experiences a severe hypersensitivity reaction.

7.8.5. Etoposide

Safety management guidelines for etoposide are in accordance with the prescribing information {ETOPOPHOS 2019}. Key considerations are described here.

Myelosuppression

Etoposide when given as an anti-leukemic regimen can cause severe myelosuppression. Close monitoring of laboratory counts, infectious prophylaxis, and supportive blood products and growth factors is needed. Etoposide should only be administered by physicians experienced with treating AML.

Hypersensitivity Reactions

Hypersensitivity reactions to etoposide, including anaphylaxis, can occur. If hypersensitivity reactions occur, immediately interrupt treatment with etoposide and institute supportive management per local guidelines. Permanently discontinue etoposide treatment in any patient who experiences a severe hypersensitivity reaction.

Secondary Leukemias

Secondary leukemias have been observed with etoposide. Further details are provided in the prescribing information {ETOPOPHOS 2019}.

7.8.6. Cytarabine

Safety management guidelines for cytarabine are in accordance with the prescribing information {CYTARABINE 2020}. Key considerations are described here.

Myelosuppression

Cytarabine can cause severe myelosuppression. Close monitoring of laboratory counts, infectious prophylaxis, and supportive blood products and growth factors is needed. Cytarabine should only be administered by physicians experienced with treating AML.

Neurotoxicity

Neurotoxicity has been observed with high-dose cytarabine use. Neurologic symptoms vary but range from somnolence and ataxia to more severe complications such as seizures and even death. Close monitoring for neurologic toxicities, including monitoring for signs and symptoms, neurologic examinations, and imaging (if pertinent) should be conducted. Supportive care measures per institutional guidelines should be instituted for observed neurotoxicities. For severe neurotoxicities, cytarabine should be discontinued.

Hypersensitivity Reactions

Hypersensitivity reactions to cytarabine, including anaphylaxis, can occur. If hypersensitivity reactions occur, immediately interrupt treatment with cytarabine and institute supportive management per local guidelines. Permanently discontinue cytarabine treatment in any patient who experiences a severe hypersensitivity reaction.

7.8.7. CC-486

Safety management guidelines for CC-486 are in accordance with the prescribing information {ONUREG 2020}. Key considerations are described here.

Myelosuppression

CC-486 can cause myelosuppression. Complete blood counts should be performed at least every other week for the first 2 cycles and at least prior to each cycle thereafter.

Hypersensitivity Reactions

CC-486 can cause hypersensitivity reactions. Treatment with CC-486 should be discontinued in any patient who experiences a severe hypersensitivity reaction.

Risk of Substitution with Other Azacitidine Products

CC-486 should not be substituted for IV or SC azacitidine. The indications and dosing of CC-486 differ from those of azacitidine.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Objectives are presented in Section 2.

8.1.2. Primary Endpoints

The primary endpoints for the Phase 2 cohorts are as follows:

- Rate of Complete Remission (Phase 2 Cohorts 1 and 2): The CR rate is defined as the proportion of patients who achieve CR (CR_{MRD-} or complete remission with positive or unknown MRD [$CR_{MRD+/unk}$]) as determined by the investigator based on prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.

- Minimal Residual Disease Negative Complete Remission Rate (Phase 2 Cohort 3): The MRD negative CR rate is defined as the proportion of patients who maintain CR as determined by the investigator based on prespecified criteria (Appendix 7) and reach MRD negative disease status on 2 consecutive bone marrow assessments as determined using multiparameter flow cytometry with a sensitivity of < 0.1% while on study prior to initiation of any new anti-AML therapy. For this cohort, patients will need to have 2 consecutive MRD negative values to be considered MRD negative for analysis.

The primary endpoint for the safety run-in cohorts is as follows:

- Incidence of DLTs, as defined in Section 3.1.1.2, and incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0

8.1.3. Secondary Endpoints

The secondary efficacy endpoints are as follows:

- Overall Response Rate (Cohorts 1 and 2): The ORR is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$), CRi, CRh, PR, or MLFS as determined by the investigator based on prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.

- Complete Remission Rate/Complete Remission with Incomplete Hematologic Recovery (Cohorts 1 and 2): The CR/CRi rate is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRi as determined by the investigator based on prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.

- Minimal Residual Disease Negative Complete Remission Rate (Cohorts 1 and 2): The CR_{MRD-} rate is the proportion of patients who achieve a CR_{MRD-} as determined by the investigator based on prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.
- Complete Remission or Complete Remission with Partial Hematologic Recovery Rate (Cohorts 1 and 2): The CR/CRh rate is the proportion of patients who achieve CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRh as determined by the investigator based on prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.
- Cytogenetic Complete Remission (Cohorts 1 and 2): The cCR rate is the proportion of patients who achieve cCR determined by investigator based on the prespecified criteria (Appendix 7) while on study prior to initiation of any new anti-AML therapy.
- Duration of Response (Cohorts 1 and 2): The DOR is measured from the time assessment criteria are met for CR (CR_{MRD-} or $CR_{MRD+/unk}$), CRi, CRh, PR, or MLFS, whichever is first recorded, until the first date of AML relapse, progressive disease, or death (including assessments post SCT). Those who are not observed to have a relapse, progressive disease, or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of response will be censored at the last response assessment before the initiation of the new anti-AML therapies.
- Duration of Complete Remission (Cohorts 1 and 2): The duration of CR is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of CR will be censored at the last response assessment before the initiation of the new anti-AML therapies.
- Duration of Complete Remission or Complete Remission with Incomplete Hematologic Recovery (Cohorts 1 and 2): The duration of CR/CRi is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRi until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of CR + CRi will be censored at the last response assessment before the initiation of the new anti-AML therapies.
- Duration of Complete Remission or Complete Remission with Partial Hematologic Recovery (Cohorts 1 and 2): The duration of CR/CRh is measured from the time the assessment criteria are first met for CR (CR_{MRD-} or $CR_{MRD+/unk}$) or CRh until the first date of AML relapse or death (including assessments post SCT). Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of CR + CRh will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Event-Free Survival (Cohorts 1 and 2): EFS is defined as the time from the date of the first dose of study treatment to the earliest date of documented relapse from CR, treatment failure (defined as failure to achieve CR before the fifth cycle of magrolimab+venetoclax+azacitidine in Phase 2 Cohort 1 and before the third cycle of magrolimab + MEC in Phase 2 Cohort 2), or death from any cause. Response assessments post SCT will be included in the analysis. Deaths post SCT or new anti-AML therapies (except SCT and post SCT maintenance) will be included. Those who are not observed to have one of these events during the study will be censored at the date of their last response assessment during the study. Day 1 of treatment will be assigned as the event date for patients with treatment failure.

- Minimal Residual Disease Negative Complete Remission or Complete Remission with Incomplete Hematologic Recovery Rate (Cohort 3): The MRD negative CR/CRi rate is defined as the proportion of patients who maintain CR/CRi as determined by the investigator based on prespecified criteria (Appendix 7) and reach MRD negative disease status on 2 consecutive bone marrow assessments as determined using multiparameter flow cytometry with a sensitivity of < 0.1% while on study prior to initiation of any new anti-AML therapy.

- Relapse-Free Survival (Cohort 3): RFS is measured from the time of the first dose of study treatment until the first date of AML relapse or death from any cause, whichever comes first. Those who are not observed to have relapsed disease or death will be censored at the date of their last response assessment during the study.

- Duration of Minimal Residual Disease Negative Complete Remission (Cohort 3): The duration of MRD negative CR is measured from the time the patient achieves MRD negative status (first of the 2 consecutive MRD negative bone marrow assessments) and maintains CR until the first date of AML relapse, loss of MRD negative status, or death (including assessments post SCT). Those who are not observed to have relapsed disease, loss of MRD negative status, or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of MRD negative CR will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Duration of Minimal Residual Disease Negative Complete Remission or Complete Remission with Incomplete Hematologic Recovery (Cohort 3): The duration of MRD negative CR/CRi is measured from the time the patient achieves MRD negative status (first of the 2 consecutive MRD negative bone marrow assessments) and maintains CR/CRi until the first date of AML relapse, loss of MRD negative status, or death (including assessments post SCT). Those who are not observed to have relapsed disease, loss of MRD negative status, or death will be censored at the date of their last response assessment. If patients start taking new anti-AML therapies (except SCT and post SCT maintenance treatment) before relapse, duration of MRD negative CR + CRi will be censored at the last response assessment before the initiation of the new anti-AML therapies.

- Overall Survival: The OS is measured from the date of the first dose of study treatment to the date of death from any cause. Those who are not observed to die during the study will be censored at last date they are known to be alive.

- Red Blood Cell Transfusion Independence Rate: The RBC transfusion independence rate is the proportion of patients who have a 56-day or longer period with no RBC or whole blood transfusion at any time between the date of the first dose and discontinuation of study treatment among all patients who are RBC transfusion-dependent at baseline, defined as having received an RBC or whole blood transfusion within the 28 days prior to the first dose of study treatment (conversion rate), and among all patients who are RBC transfusion-independent at baseline (maintenance rate).

- Platelet Transfusion Independence Rate: The platelet transfusion independence 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 the first dose and discontinuation of study treatment among all patients who are platelet transfusion-dependent at baseline, defined as having received a platelet transfusion within the 28 days prior to the first dose of study treatment (conversion rate), and among all patients who are platelet transfusion independent at baseline (maintenance rate).

The secondary safety endpoint is as follows (Phase 2 cohorts):

- Incidence of treatment-emergent AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0

The secondary PK endpoint is as follows:

- PK concentrations of magrolimab in combination with venetoclax and azacitidine; mitoxantrone, etoposide, and cytarabine; or CC-486

The secondary immunogenicity endpoint is as follows:

- Rate and magnitude of anti-magrolimab antibody incidence and prevalence

CCI [redacted]

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

8.2.2. Primary Analysis

The primary analysis will be conducted after all patients have discontinued the study or have been on study for at least 24 weeks and completed the Week 24 response assessments, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis.

8.2.3. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS). The FAS includes all enrolled patients who receive at least 1 dose of any study treatment, with treatment group designated according to the assigned treatment.

8.3.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set. It includes all patients who receive at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints, as well as study treatment administration. All data collected during treatment up to 70 days (± 7 days) after treatment discontinuation will be included in the safety summaries.

The DLT Evaluable Analysis Set includes all patients in the Safety Analysis Set who are enrolled in the safety run-in cohorts, have safety assessments through the protocol-specified DLT assessment window (first 4 weeks of study dosing, inclusive), and fulfill the criteria for evaluation for DLT specified in Section 3.1.1.

Safety assessments relevant to the DLT Evaluable Analysis Set definition include laboratory serum chemistry tests and hematology tests as specified in Section 3.1.1. The RP2D will be based on the DLT Evaluable Analysis Set.

8.3.1.3. Pharmacokinetics

The PK Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.3.1.4. Immunogenicity

The Immunogenicity Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

8.3.1.5. Biomarker

The Biomarker Analysis Set includes all enrolled patients who receive at least 1 dose of magrolimab and have evaluable baseline and postbaseline measurements to provide interpretable results for the specific parameter of interest.

8.3.1.6. Demographic and Baseline Characteristics

The All Enrolled Analysis Set includes all patients who receive a study patient identification number in the study after screening. This will be the primary analysis set for analyses of patient demographic and baseline characteristics, enrollment, and disposition.

8.3.2. 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 for the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs for 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 cohort.

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 greatest change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative. Analyses will be based on observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of body weight, height, body mass index, WHO AML classification, and ECOG performance status.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The point estimates of the CR rate and the corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method will be provided for Cohorts 1 and 2. The MRD negative CR rate will be summarized similarly for Cohort 3. The CR and MRD negative CR data will also be tested against the historical control rates listed in Section 8.10 using 1-group Chi-square test for each cohort separately.

8.5.2. Secondary Analyses

The point estimates of the ORR, CR rate, CR/CRi rate, CR_{MRD-} rate, cCR rate, and CR/CRh rate and the corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method will be provided for Cohorts 1 and 2. The analyses of RBC and platelet transfusion independence rates (conversion rate and maintenance rate) will be similar to those of ORR.

Medians, first quartile (Q1), and third quartile (Q3) of EFS distribution, and the proportion of patients who are event free at Weeks 12, 24, and 48 from the first dosing date will be estimated by cohort using the KM method and the corresponding 95% CIs will be reported. Kaplan-Meier plots will be provided. Analyses of OS will be similar to those of EFS.

For the time-to-event endpoints of duration of CR, duration of CR/CRi, duration of CR/CRh, DOR, RFS, duration of MRD negative CR, and MRD negative CR/CRi, analyses will be conducted on the subsets for which the outcome measures are defined. Specifically, the duration of CR, duration of CR/CRi, duration of CR/CRh, and DOR will be based on patients in Cohorts 1 and 2 who achieve CR, CR/CRi, CR/CRh, and OR, respectively. The RFS will be analyzed for Cohort 3, duration of MRD negative CR will be based on patients in Cohort 3 who achieve MRD negative status and maintain CR, and the duration of MRD negative CR/CRi will be based on patients in Cohort 3 who achieve MRD negative status and maintain CR/CRi. The KM method will be used to estimate median durations and 95% CIs, and KM plots will be provided.

8.6. Safety Analysis

All safety data collected on or after the date that any drug in a study treatment regimen was first dosed up to the date of the last dose of any drug in a study treatment regimen plus 70 days (± 7 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, the number and percentage 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.

8.6.1. 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 for each drug separately by treatment cohort.

8.6.2. 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 drug up to the date of last dose of study drug plus 70 days (± 7 days).

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

Adverse events that occurred before exposure to study treatment will be reported in data listings and appropriately identified as non-treatment-emergent AEs.

8.6.3. 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 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the patient has been discontinued from treatment for at least 70 days (± 7 days) will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and physical examination findings will be summarized at select time points. Study drug administration, study drug compliance, and other safety variables will also be summarized. Details will be provided in the statistical analysis plan.

8.7. 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 Gilead clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

8.8. 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]

8.9. 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 applicable sample collection time point by treatment cohort, as appropriate. CCI [redacted]

8.10. Sample Size

Sample size calculation is as follows:

1) For Cohort 2, a sample size of 36 (30 patients in Phase 2 Cohort 2 together with 6 patients in Safety Run-in Cohort 2) provides an 83.1% power for a 1-group Chi-square test at 1-sided alpha of 0.1 level to detect a CR rate of ≥ 35% for the combination compared with a historical control CR rate of 19% {Greenberg 2004}.

The original protocol for the study included a Cohort 1, for which 46 patients were planned to be enrolled (6 patients in Safety Run-in and 40 patients in Phase 2); however, Cohort 1 was closed to enrollment following enrollment of 18 patients (7 patients in Safety Run-in and 11 patients in Phase 2).

The original protocol also included a Cohort 3, for which 46 patients were planned to be enrolled (6 patients in Safety Run-in and 40 patients in Phase 2); however, Cohort 3 was closed to enrollment and no patients were enrolled.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP 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. CCI [redacted] The results of the tests performed on the samples will not be given to 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, case report forms (CRFs)/eCRFs, study drug information, and any other study information, remains 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, drug records, staff curricula 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, and including 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

For each patient consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedules of assessments. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only

after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff 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. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log-in credentials 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 by that site. 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 may be made only by the sponsor.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies 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. 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.

9.3.2. 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.

9.3.3. 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.

9.3.4. 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 authority, 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

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A PHASE 2 MULTI-ARM STUDY OF MAGROLIMAB COMBINATIONS IN PATIENTS WITH MYELOID MALIGNANCIES
GS-US-546-5920 Protocol Amendment 6, 02 November 2023

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

PPD	*[See appended electronic signature]*
Name (Printed) Medical Monitor	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. Schedules of Assessment and Treatment Administration

Appendix Table 1. Schedule of Assessments – Screening

Assessment	Study Day -30 to -1
Informed consent	X[a]
Demographics	X
Medical and cancer history, including date of recent RBC and/or platelet transfusions, AML molecular marker results at diagnosis (if available), and echocardiogram/MUGA or pulmonary function tests if done within the 3 months prior	X
Complete physical examination	X
Vital signs, height, and weight	X
Serum pregnancy test[b]	X
CBC with differential, platelets, reticulocytes	X
Serum or plasma chemistry	X
PT, INR, and aPTT (or PTT)	X
Extended RBC phenotyping or genotyping, type, and screen (ABO/Rh), DAT	X
Urinalysis	X
Bone marrow biopsy and aspirate for blast evaluation, MRD assessment, cytogenetics, and correlative studies[c]	X
Peripheral blood smear (for blasts)[d]	X
Bone marrow aspirate for receptor occupancy (to be collected at selected study sites)[c]	X
ECOG performance status	X
12-Lead ECG (single)	X
Echocardiogram or MUGA for Cohort 2 only (if not done in the past 30 days)	X
All SAEs and any AEs related to protocol-mandated procedures	X
Prior and concomitant medications	X
Entry criteria	X

ABO = any of the 4 blood groups A, B, AB, and O composing the ABO system; 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; INR = international normalized ratio; MRD = minimal residual disease; MUGA = multigated acquisition (scan); PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; Rh = Rhesus factor; RO = receptor occupancy; SAE = serious adverse event

a Screening must be completed prior to enrollment. Enrollment must occur within 30 days of signing informed consent. The first dose of study treatment must be given within 72 hours after enrollment.

b Screening pregnancy test may be used as the Cycle 1 Day 1 test if performed within 72 hours of first dose of study treatment and can be performed locally without a requirement to visit the study site; additional guidance is provided in Section 6.5.1. 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.

c A trephine (biopsy) is to be collected for baseline. This procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample will be collected for blast evaluation, MRD assessment, RO (to be collected at selected study sites), and correlative studies. Bone marrow aspirate samples are to be obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics to be tested per institutional standards.

d Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy.

Appendix Table 2. Schedule of Assessments – Treatment Period (Cohorts 1 and 3)

Visit Window (Days)[a]	**Cycle (28-day Cycles)**																		
	1									**2**						**3+**			
	None		**± 3**							**± 3**						**± 3**			
Cycle Day	**1**	**2**	**4**	**8**	**11**	**15**	**22**	**28**	**Weekly for 2 weeks[b]**	**1**	**8**	**15**	**22**	**28**	**Weekly for 2 weeks[b]**	**1**	**15**	**28**	**Weekly for 2 weeks[b]**
Safety																			
Pregnancy test[c]	X	Every 4 weeks following Cycle 1 Day 1																	
CBC with differential, platelets, reticulocytes[d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[d]	X	X	X	X						X									
Peripheral blood smear for general morphology[d,p]	X	X			X														
Serum or plasma chemistry[d]	X	X	X	X		X	X			X		X				X	X		
Vital signs[f]	X	X		X		X	X			X	X	X	X			X	X		
Weight	X									X						X			
Symptom-directed physical examination[d]	X			X		X				X				X					
Adverse events[g]	→																		
Concomitant medications[g]	→																		

Visit Window (Days)[a]	Cycle (28-day Cycles)																		
	1									2						3+			
	None		± 3							± 3						± 3			
Cycle Day	**1**	**2**	**4**	**8**	**11**	**15**	**22**	**28**	**Weekly for 2 weeks[b]**	**1**	**8**	**15**	**22**	**28**	**Weekly for 2 weeks[b]**	**1**	**15**	**28**	**Weekly for 2 weeks[b]**
Efficacy/ Biomarkers																			
Peripheral blood smear for blasts[o]								X						X				Q2C, Q3C[n]	
Peripheral blood sample for correlative studies[h]	X			X				X		X				X				Cycle 6 only	
Bone marrow aspirate/biopsy for correlative studies[i] and receptor occupancy[j]								X						X				X[k]	
Bone marrow aspirate/biopsy for response assessment, cytogenetics, and MRD assessment[l]								X						X				Q2C, Q3C[m]	
Bone marrow slides or blocks for central review								X						X				Q2C, Q3C[m]	
Buccal swab[n]	X																		

CBC = complete blood count; EOT= end of treatment; LDH = lactate dehydrogenase; MRD = minimal residual disease; RO = receptor occupancy; Q2C = every 2 cycles; Q3C = every 3 cycles; WBC = white blood cell

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

b In the absence of count recovery at Day 28, CBC should be collected weekly for 2 weeks or until start of the next cycle, whichever is earlier. 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 does not need to be repeated if the prior CBC (including prior Day 28 CBC) is within 3 days of Day 1.
c The serum pregnancy test collected at screening may be used as the Cycle 1 Day 1 test if performed within 72 hours of first dose of study treatment. Urine or serum pregnancy tests will be conducted every 4 weeks following Cycle 1 Day 1 and can be performed locally without a requirement to visit the study site; additional guidance is provided in Section 6.5.1.
d Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment except for Hb, which must be performed within 24 hours prior to magrolimab dosing. Thereafter, pretreatment assessments are to be collected within 24 hours prior to any intravenous/subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.
e Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ 20 × 103/μL prior to each magrolimab dose during Cycle 1.
f Vital signs will be assessed prior to administration of any study treatment. Details are provided in Section 6.5.4.
g 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.
h Samples will be collected predose within 12 hours prior to study treatment administration. Peripheral blood for correlative studies does not need to be repeated at Cycle 2 Day 1 if done at Cycle 1 Day 28 within 3 days of Cycle 2 Day 1.
i At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for correlative studies.
j Samples for RO will be collected at selected study sites.
k Samples will be collected on Day 28 of Cycles 4, 6, 9, 12, and 15.
l A trephine (biopsy) is to be collected for response assessment. An aspirate sample will be collected for response assessment and MRD assessment. 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. Conventional cytogenetics to be tested per institutional standards.
m Samples will be collected on Day 28 of Cycles 4 and 6, and then every 3 cycles thereafter during study treatment.
n Single sample will be collected on Day 1 or at any time during the study.
o Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy and assessed locally.
p Peripheral blood smears for general morphology will be collected predose and assessed locally.

Appendix Table 3. MEC Administration and Associated Assessment Schedule – Treatment Period (Cohort 2)

	Cycle (28-day Cycles)																
	MEC Cycle 1									MEC Cycle 2 (and 3 if applicable)[a]						Starting at the end of MEC Cycle	
Visit Window (Days)[b]	None		± 3							± 3						± 3	
Cycle Day	**1**	**2**	**4**	**8**	**11**	**15**	**22**	**28**	**Weekly for 2 weeks[l]**	**1**	**8**	**15**	**22**	**28**	**Weekly for 2 weeks[l]**	**Every 4 weeks thereafter (up to 12 months of total treatment)**	**Every 8 weeks x 2 and every 12 weeks thereafter (up to 12 months of total treatment)**
Safety																	
Pregnancy test[c]	X	Every 4 weeks following Cycle 1 Day 1														X	
CBC with differential, platelets, reticulocytes[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haptoglobin and LDH[d]	X	X	X	X						X							
Peripheral blood smear for general morphology[d,n]	X	X			X												
Serum or plasma chemistry[d]	X	X	X	X		X	X			X		X				X	
Vital signs[e]	X	X		X		X	X			X	X	X	X			X	
Weight	X									X						X	
Symptom-directed physical examination[d]	X			X		X				X						X	
Adverse events[f]	→																→
Concomitant medications[f]	→																→
Efficacy/ Biomarkers																	
Peripheral blood smear for blasts[m]								X						X (Cycle 2 only)			X
Peripheral blood sample for correlative studies[g]	X			X				X		X				X (Cycle 2 only)			16 weeks after end of MEC cycle

	Cycle (28-day Cycles)																
	MEC Cycle 1									MEC Cycle 2 (and 3 if applicable)[a]						Starting at the end of MEC Cycle	
Visit Window (Days)[b]	**None**		**± 3**							**± 3**						**± 3**	
Cycle Day	**1**	**2**	**4**	**8**	**11**	**15**	**22**	**28**	**Weekly for 2 weeks[l]**	**1**	**8**	**15**	**22**	**28**	**Weekly for 2 weeks[l]**	**Every 4 weeks thereafter (up to 12 months of total treatment)**	**Every 8 weeks x 2 and every 12 weeks thereafter (up to 12 months of total treatment)**
Bone marrow aspirate/biopsy for correlative studies[i] and receptor occupancy[h]								X						X (Cycle 2 only)			X
Bone marrow aspirate/biopsy for response assessment, cytogenetics, and MRD assessment[j]								X						X (Cycle 2 only)			X
Bone marrow slides or blocks for central review								X						X (Cycle 2 only)			X
Buccal swab[k]	X																

CBC = complete blood count; LDH = lactate dehydrogenase; MEC = mitoxantrone, etoposide, cytarabine; MRD = minimal residual disease

a If patient achieved blast clearance after Cycle 1, one additional cycle of MEC will be given (total 2 cycles). If patient achieved blast clearance only after Cycle 2, a third cycle of MEC will be given. If no blast clearance at the end of Cycle 2, patient should be discontinued from the study.
b Any other visit window specifications for individual assessments should be applied.
c The serum pregnancy test collected at screening may be used as the Cycle 1 Day 1 test if performed within 72 hours of first dose of study treatment. Urine or serum pregnancy tests will be conducted every 4 weeks following Cycle 1 Day 1 and can be performed locally without a requirement to visit the study site; additional guidance is provided in Section 6.5.1.
d Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of any study treatment except for Hb, which must be performed within 24 hours prior to magrolimab dosing. Thereafter, pretreatment assessments are to be collected within 24 hours prior to any intravenous/subcutaneous study drugs during the first 2 weeks and within 72 hours prior to any intravenous or subcutaneous study drugs thereafter.
e Vital signs will be assessed prior to administration of any study treatment. Details are provided in Section 6.5.4.
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 predose within 12 hours prior to study treatment administration.
h Samples for receptor occupancy will be collected at selected study sites.
i At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for correlative studies.
j A trephine (biopsy) is to be collected for response assessment. An aspirate sample will be collected for response assessment and MRD assessment. 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. Conventional cytogenetics to be tested per institutional standards.

k Single sample will be collected on Day 1 or at any time during the study.
l In the absence of count recovery at Day 28, CBC should be collected weekly for 2 weeks or until start of the next cycle, whichever is earlier. 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 does not need to be repeated if the prior CBC (including prior Day 28 CBC) is within 3 days of Day 1.
m Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy and assessed locally.
n Peripheral blood smears for general morphology will be collected predose and assessed locally.

Appendix Table 4. Magrolimab Administration and Associated Assessment Schedule – Treatment Period for All Cohorts

Visit Window (Days)	None[a]			± 3[a]			Weekly x 5 ± 3 days	Every 2 weeks ± 3 days
Day	**1**	**2**	**4**	**8**	**11**	**15**		
Vital signs[b]	X		X	X	X	X	X	X
Hemoglobin[c]	Pre- and postdose		Pre- and postdose					
Peripheral blood sample for receptor occupancy[d,e]	Within 72 hours prior to magrolimab dosing	X		Within 12 hours prior to magrolimab dosing			Within 12 hours prior to magrolimab dosing for 2nd weekly dose	Within 12 hours prior to magrolimab dosing before 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg
Pharmacokinetic								
Antidrug antibodies[f]								
Magrolimab Administration								
Premedication[g]	X		X	X	X			
Magrolimab[h]	X		X	X	X	X	X	X

CBC = complete blood count; PK = pharmacokinetic(s)

a In cases of magrolimab repriming/re-escalation following a treatment delay (Section 5.1.3), follow magrolimab schedule of assessment and administration for repriming (Appendix Table 5).

b Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.5.4.

c Hemoglobin must be performed within 24 hours prior to magrolimab dosing on Days 1 and 4 to ensure hemoglobin is ≥ 9 g/dL. 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. 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. An additional hemoglobin check must be performed 3 to 6 hours after the initiation of the first 2 doses of magrolimab (see Section 5.1.2).

d Samples will be collected predose within 12 hours prior to administration of magrolimab.

e Samples for receptor occupancy will be collected at selected study sites.

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

g Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication should include 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. For patients who do not experience an IRR with the first 4 doses of magrolimab, corticosteroid pretreatment can be discontinued at the investigators' discretion. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. Premedication decisions for subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior infusion related reactions (Section 5.1.4).

h Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, 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 of treatment. For magrolimab dosing, please refer to Table 1.

Appendix Table 5. Magrolimab Repriming Administration and Associated Assessment Schedule – Treatment Period for All Cohorts

Visit Window (Days)[a]	None			± 3				
Day	1	2	4	8	11	15	22[b]	29, then every 2 weeks OR 57, 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		
Peripheral blood smear for general morphology[c,e]	X	X			X			
Vital signs[f]	X		X	X	X	X	X	X
Weight	X							X
Symptom-directed physical examination[c]	X			X		X		
Adverse events[g]	→	→	→	→	→	→	→	→
Concomitant medications[g]	→	→	→	→	→	→	→	→
Efficacy/ Biomarkers								
Peripheral blood sample for receptor occupancy[h,i]	X	X		X			X[j]	X[j]
PK/ Immunogenicity								
PK[j]	X			X			X[j]	X[j]
Antidrug antibodies[k]	X						X[k]	X[k]

Visit Window (Days)[a]	None			± 3				
Day	1	2	4	8	11	15	22[b]	29, then every 2 weeks OR 57, then every 2 weeks
Magrolimab Administration								
Premedication[l]	X		X	X	X			
Magrolimab[m]	X		X	X	X	X	X	X

ADA = antidrug antibody; CBC = complete blood count; EOT = end of treatment; LDH = lactate dehydrogenase; PK = pharmacokinetic(s); RO = receptor occupancy; 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 treatment, patient should receive magrolimab 30 mg/kg weekly × 5 after receiving Day 15 dose. All Day 22 safety assessments should be completed weekly × 5. One week after the 5th weekly dose, dosing will be 30 mg/kg Q2W.

c Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of magrolimab except for Hb, which must be performed within 24 hours prior to magrolimab dosing. Thereafter, pretreatment assessments are to be collected within 24 hours prior to magrolimab dosing during the first 2 weeks and within 72 hours prior to magrolimab thereafter.

d Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level $\leq 20 \times 10^3/\mu L$ prior to each magrolimab dose during first 4 weeks of repriming.

e Peripheral blood smears for general morphology will be collected predose and assessed locally.

f Vital signs will be assessed prior to administration of magrolimab. Details are provided in Section 6.5.4.

g 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.

h Samples will be collected predose within 12 hours prior to study treatment administration.

i Samples for RO will be collected at selected study sites.

j Samples will be collected within 72 hours before the first dose of magrolimab and within 12 hours before subsequent doses of magrolimab. In addition to Day 1, Day 2 (for RO only), and Day 8 , 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 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg, respectively.

k When collected on the day of magrolimab 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 and Day 29 (only applicable if the repriming schedule has 4 additional weekly doses post Day 22), as well as before the 1st, 5th, 9th, 15th and 21st biweekly maintenance doses of 30 mg/kg, respectively.

l Premedication for magrolimab is required prior to the administration of the first 4 doses of study treatment in case of reintroduction with repriming. Premedication should include 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. For patients who do not experience an IRR with the first 4 doses of magrolimab, corticosteroid pretreatment can be discontinued at the investigators' discretion. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. Premedication decisions for subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior infusion related reactions (Section 5.1.4).

m Magrolimab should not be given on consecutive days. The duration of infusion will be 3 hours (± 30 minutes) for the first 3 doses of magrolimab, 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 dosing, please refer to Table 1.

Appendix Table 6. Schedule of Treatment Administration for Venetoclax and Azacitidine – Cohort 1 (1L Unfit AML Mag+Ven+Aza)

	Cycle (28-day Cycles)																										
	1											2									3+						
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**
Visit Window (days)	**0**	**± 3**										**± 3**										**± 3**						
Azacitidine[b]	X	X	X	X	X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X	X
Venetoclax[c]	Daily Days 1-28											Daily Days 1-28										Daily Days 1-28						

AML = acute myeloid leukemia

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 Azacitidine administration should be completed at least 1 hour before magrolimab administration on days when both drugs are administered. 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 the 7 doses of azacitidine of the cycle are administered within 9 consecutive days. Please refer to Table 1.

c Venetoclax is administered daily. Please refer to Table 1. In cases of dose de-escalation, refer to Table 4 for the venetoclax dosing schedule.

Appendix Table 7. Schedule of Treatment Administration for MEC – Cohort 2 (R/R AML Mag+MEC)

	1									2 to 3[b]							
Cycle Day[a]	**1**	**2**	**3**	**4**	**5**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**
Visit Window (days)	**0**	**± 3**								**± 3**							
Mitoxantrone	X	X	X	X	X					X	X	X	X	X			
Etoposide	X	X	X	X	X					X	X	X	X	X			
Cytarabine	X	X	X	X	X					X	X	X	X	X			

AML = acute myeloid leukemia; MEC = mitoxantrone, etoposide, cytarabine; R/R = relapsed/refractory

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 If patient achieved blast clearance after Cycle 1, one additional cycle of MEC will be given (total 2 cycles). If patient achieved blast clearance only after Cycle 2, a third cycle of MEC will be given. If no blast clearance at the end of Cycle 2, patient should be discontinued from the study.

Appendix Table 8. Schedule of Treatment Administration for CC-486 – Cohort 3 (Post-Chemo Maint Mag+CC-486)

	Cycle (28-day Cycles)										
	1						2				3+
Cycle Day[a]	**1**	**4**	**8**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**
Visit Window (days)	**0**	**± 3**					**± 3**				**± 3**
CC-486	Daily Days 1-14						Daily Days 1-14				Daily Days 1-14

CC-486 = Onureg

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.

Appendix Table 9. Schedule of Assessments – Post Treatment

	End-of-treatment Visit	Safety Follow-up Visit/ Telephone Call[a]	Safety Follow-up Visit/ Telephone Call[a]
	Within 7 Days after Last Dose or EOT Decision	30 Days after Last Dose	70 Days after Last Dose
Visit Window (Days)	± 7	± 7	± 7
Serum or urine pregnancy test[b]	Q4W	→	→
CBC with differential, platelets, reticulocytes	X		
Serum or plasma chemistry	X		
Peripheral blood for correlative studies	X		
Pharmacokinetics	X		
Antidrug antibodies	X		
Bone marrow aspirate/biopsy for response assessment[c], cytogenetics[d], and MRD assessment	X		
Bone marrow aspirate/biopsy for correlative studies	X		
Peripheral blood smear (for blasts)[e]	X		
ECOG performance status	X		
Vital signs	X		
Symptom-directed physical examination	X		
Adverse events[f]	X	X	X
Concomitant medications	X	X	X
New anti-AML therapy reporting[g]	X	X	X

AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRD = minimal residual disease; Q4W = every 4 weeks; SAE = serious adverse event

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 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 after 70 days of safety follow-up may be done at home and the result self-reported by the patient.

c Response assessment at EOT visit not required if performed within the last 30 days or progressive disease has been documented.

d Conventional cytogenetics to be tested per institutional standards.

e Peripheral blood smears for blasts are to be collected along with bone marrow aspirate/biopsy.

f Report all AEs through the Safety Follow-up Visit/Call, and any treatment-related SAEs thereafter through the 70-day safety follow-up visit/call.

g Collect data for the first new anti-AML therapy following the last dose of study treatment.

Appendix 3 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.

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) For Cycle 2 and repriming cycles, magrolimab can be administered on Day 7 with azacitidine, with collection of Day 8 assessments (ie, laboratory assessments, PK) on Day 7 in order to minimize an extra patient visit.
      ii) Dosing delays with magrolimab:
         (1) For patients who may have travel restrictions, the 4-week period of magrolimab 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. Magrolimab every-2-week dosing should be encouraged as dosing intervals longer than this will lead to suboptimal efficacy.
      iii) 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 (PI) 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.

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) MRD testing should be collected and shipped in real-time.

iii) 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 patients and sites:

a) Patients may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

Mitigation plan: If permitted by local EC/IRB/Regulatory authority as applicable and with sponsor's approval, study drug supplies may be provided to the patient from the site without a clinic visit. It must be confirmed that the patient may safely continue on study drug as determined by the PI. 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 the study drug from sites to study patients, and a qualified vendor may be utilized to perform infusions in the patients' local vicinity.

b) Shipments of study drug from the sponsor to the investigational site could be delayed because of transportation issues. Without study drug, the patient 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 they foresee shortage in study drug inventory or 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 PI 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 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, confirm that electronic diary questionnaires and patient-reported outcomes have been completed and transmitted

      v) 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); hence, samples may not be sent for central laboratory analyses.

      Mitigation plan: Accredited local laboratory 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. Alternative sample handling and storage may be possible for samples routinely sent to the central laboratory; sites should refer to the study laboratory manual and discuss with the sponsor for further guidance.

   c) Patients may be unable or unwilling to attend the study visit to sign an updated ICF version if there is an update.

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 it 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 patients is important and testing of 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 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 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 if 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 (CSR). 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. 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 study 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 CSR 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 the study drugs 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 4. 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 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

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 post-menopausal, 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 of < 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.

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 to be 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

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in and 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.

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.

Based on its MOA and findings in animals, mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Women treated with mitoxantrone have an increased risk of transitory or persistent amenorrhea. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received mitoxantrone for treatment of cancer.

Based on animal studies and its MOA, etoposide can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.

Cytarabine can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.

Based on the MOA and findings in animals, CC-486 (Onureg) can cause fetal harm when administered to a pregnant woman. Based on animal data, CC-486 (Onureg) may impair female fertility. Studies in vitro have demonstrated that CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information for information on the potential risks of treatment with azacitidine {VIDAZA 2018}, venetoclax {VENCLEXTA 2020}, mitoxantrone {MitoXANTRONE 2018}, etoposide {ETOPOPHOS 2019}, cytarabine {CYTARABINE 2020}, and CC-486 {ONUREG 2020}.

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 (described in the protocol) 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 the latest administered study drug.

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, where local standard of care practices allow:

- 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 6 months after the last dose of the latest administered companion drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive method should also be considered. Based on companion drugs, male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement for the companion drug. 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, post-ovulation 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 6 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. 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 7. Disease Response Criteria Based on European Leukemia Net (ELN) and International Working Group (IWG) Criteria

CCI

[redacted]

Appendix Table 10. Response Criteria in Acute Myeloid Leukemia (Based on 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)	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)	> 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)[a]			< 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% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; 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; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; PR = partial remission; WBC = white blood cell

a Not in the ELN 2017 guidelines. Modification for the purpose of this protocol. 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 11. 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

cCR = cytogenetic complete remission; CR = complete remission; IWG = International Working Group
Source: {Cheson 2003}

Treatment Failure

Treatment failure is defined as failure to achieve complete remission (CR) before the fifth cycle of magrolimab+venetoclax+azacitidine in Cohort 1 and before the third cycle of magrolimab + MEC in Cohort 2.

Appendix 8. 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] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1}{72 \times \text{subject serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 0.85}{72 \times \text{subject serum creatinine [mg/dl]}}$
µM/dL	Males	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.23}{\text{Subject serum creatinine [mg/dl]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140\text{-subject age [years]}) \times \text{subject weight [kilograms]} \times 1.04}{\text{Subject serum creatinine [mg/dl]}}$

eC_{cr}=estimated creatinine clearance
Source: {Cockcroft 1976}

Appendix 9. World Health Organization (WHO) Classification of AML

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 10. 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.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 5 with this amendment will be made available upon the publication of this protocol.

Amendment 6 (02 November 2023)

Rationale for Key Changes Included in Amendment 6	Affected Sections
The rationale and risk/benefit assessment for the study have been updated to align with the information in Edition 12 of the Investigator's Brochure	Sections 1.6.1, 1.6.2, and 1.8
Long-term follow-up and survival follow-up have been removed as collection of efficacy data after the end-of-treatment (EOT) visit is no longer required.	Sections 3.4, 3.5, 3.6, 5.2, 6.4, 6.12, and Appendix Table 9
Guidance for the use of corticosteroids as premedication for the first few infusions of magrolimab has been incorporated to align with the information in Edition 12 of the Investigator's Brochure.	Section 5.1.4, Appendix Table 4, Appendix Table 5
Guidance for the management of infusion-related reactions has been updated to incorporate the use of corticosteroids as premedication during the first few infusions of magrolimab, and to incorporate guidance for discontinuation of magrolimab in certain cases. This was done to align with the information in Edition 12 of the Investigator's Brochure.	Section 7.8.1.2, Table 15
Toxicity management section for magrolimab has been updated to include guidelines for dose delay and discontinuation in case of severe neutropenia and serious infections to align with the information in Edition 12 of the Investigator's Brochure.	Sections 7.8.1.3 and 7.8.1.4
Event-free survival definition has been updated to align with other studies of magrolimab in patients with acute myeloid leukemia (AML).	Section 8.1.3 and Appendix 7
Contraception appendix has been updated to reflect latest nonclinical embryo-fetal development toxicity data.	Appendix 5
Global Patient Safety (GLPS) has been updated to Patient Safety (PS) to reflect the new department name.	Throughout the protocol, as required

Protocol GS-US-546-5920 amd-6

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	02-Nov-2023 20:35:39