ENHANCE: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome

Short title: Magrolimab + Azacitidine versus Azacitidine + Placebo in Untreated MDS

Investigational Product(s)	Magrolimab (Hu5F9-G4) (GS-4721)
Protocol Number	5F9009
Version Date	Original protocol: 26 February 2020 Protocol Amendment 1: 18 September 2020 Protocol Amendment 2: 09 October 2020 Protocol Amendment 2.1 (UK): 23 December 2020 Protocol Amendment 3: 07 January 2021 Protocol Amendment 4: 04 February 2021 Protocol Amendment 5: 18 August 2021 Protocol Amendment 6: 01 April 2022 Protocol Amendment 7: 27 July 2022 Protocol Amendment 8: 11 October 2022
EudraCT Number **NCT Number**	2020-004287-26 NCT04313881
Sponsor	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404

Confidentiality Statement

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

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonisation (ICH) E6(R2), and all applicable country and regional (local) regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Re-consent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	ENHANCE: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome
Protocol Number	5F9009
Version Date	Amendment 8: 11 October 2022

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Name:	Title:	Signature:	Date:
PPD	Medical Monitor, Senior Director, Clinical Development, Oncology	*[See appended electronic signature]*	*[See appended electronic signature]*

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 5F9009 and agree to the following:

To conduct this study as described by the protocol and any accessory materials

To protect the rights, safety, and welfare of the participants under my care

To provide oversight to all personnel to whom study activities have been delegated

To control all investigational products provided by the Sponsor and maintain records of the disposition of those products

To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and GCP as outlined by ICH E6(R2)

To obtain institutional review board (IRB)/independent ethics committee (IEC) and other committee approval as required for the protocol and all written materials provided to participants prior to initiating the study at my site

To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants

To maintain records of each participant's participation and all data required by the protocol

Name	**Title**	**Site Number**
Signature		**Date**

SUMMARY OF CHANGES, PROTOCOL 5F9009 AMENDMENT 8

In **Amendment 8**, Protocol 5F9009 has been updated to clarify current language that does not specifically include the use of publicly available records as part of survival data in the case of withdrawal of consent.

The major updates to the protocol and related rationale are as follows:

- Sections 4 and 5.7: Text is clarified to explicitly include withdrawal of consent as a circumstance in which sites may use public records in order to obtain information about survival status.
- Section 5.7.2: Text is removed that limits data analysis to data collected up until withdrawal of consent, in order to allow analysis of survival data collected from the search of public records.

Additional changes to the protocol include the correction of typographical and formatting errors, where appropriate.

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ABO	any of the 4 blood groups A, B, AB, and O comprising the ABO system
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	antibody against hepatitis B core antigen
AST	aspartate aminotransferase
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DAT	direct antiglobulin test
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EQ-5D-5L	5-level EuroQol 5 dimensions
EQ VAS	EuroQol visual analogue scale
EOT	end of treatment
EU	European Union
FACT-Anemia	Functional Assessment of Cancer Therapy – Anemia
FACT-G	Functional Assessment of Cancer Therapy-General
FACT TOI-An	Functional Assessment of Cancer Therapy Trial Outcome Index-Anemia scale
FACT TOI-F	Functional Assessment of Cancer Therapy Trial Outcome Index-Fatigue scale
FDA	Food and Drug Administration

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HI	hematologic improvement
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
Hu5F9-G4 (GS-4721)	humanized monoclonal antibody that blocks the antiphagocytic signal CD47 (5F9; magrolimab)
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDCC	independent data coordinating center
IEC	independent ethics committee
IgG	immunoglobulin
IHC	immunohistochemistry
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
IXRS	interactive voice/web/mobile response system
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MNS	a human blood group system based upon 2 genes (glycophorin A and glycophorin B) on chromosome 4
MOA	mechanism of action
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial remission
PR/CR	partial/complete remission
PRO	patient-reported outcome
Q2W	every 2 weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RFS	relapse-free survival
Rh	Rhesus factor
RNA	ribonucleic acid
RO	receptor occupancy
R/R	relapsed/refractory
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCT	stem cell transplant
SIRPα	signal regulatory protein alpha
SOC	standard of care
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. SYNOPSIS

Title	A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome
Short Title	Magrolimab + Azacitidine versus Azacitidine + Placebo in Untreated MDS
Acronym	ENHANCE: Efficacy of a Novel Hu5F9-G4 + Azacitidine Therapy in Treatment-Naïve Patients with MyelodysplastiC SyndromE
Phase	3
Study Design	This is a randomized, double-blind, placebo-controlled, multicenter study investigating magrolimab + azacitidine compared with azacitidine + placebo in previously untreated participants with intermediate/high/very high risk myelodysplastic syndrome (MDS) by Revised International Prognostic Scoring System (IPSS-R).
Rationale	Novel therapies that can be combined with hypomethylating agents while maintaining an acceptable safety profile and improving durable complete remissions or survival probability are needed for individuals with higher risk MDS. No new therapies have been approved in MDS for over a decade, which underscores a high unmet medical need in this population. Patients with MDS experience frequent comorbidities and mortalities as a result of cytopenias due to the disease and to hypomethylating agents. The need for combination therapies that can induce hematologic improvement and disease remission leading to a clear clinical benefit is quite evident. Magrolimab in combination with azacitidine is being developed in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R to improve clinical activity and maintain an acceptable safety profile.
Target Population	Previously untreated participants ≥ 18 years of age with MDS defined according to World Health Organization classification with an IPSS-R risk category of intermediate, high, or very high risk.
Number of Participants	Total: Approximately 520 participants globally

Length of Participation	On treatment: Until disease progression, loss of clinical benefit, or unacceptable toxicities occur On study (including screening and follow-up): Up to 4 years after the last participant is randomized
Intervention	Magrolimab + azacitidine, or azacitidine + placebo as follows: Magrolimab • Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11 and 15; and then 30 mg/kg weekly for a total of 5 doses (on Days 22, 29, 36, 43, and 50). • Maintenance doses of magrolimab: 30 mg/kg on Day 57, and 30 mg/kg every 2 weeks thereafter. Placebo • Saline placebo to mirror the magrolimab dosing schedule above. Azacitidine • 75 mg/m^2 on Days 1 to 7 of a 28-day cycle • Alternative schedule: 75 mg/m^2 on Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience
Primary Objectives and Primary Endpoints	**Synopsis Table 1. Primary Objectives and Endpoints** **Objective** / **Endpoint** To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R as measured by CR rate — CR rate as assessed by Investigators To evaluate the survival benefit of magrolimab + azacitidine compared with that of azacitidine + placebo — OS Abbreviations: CR = complete remission; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; OS = overall survival.
Number of Sites	Approximately 200 sites in the United States, Australia, Europe, and other countries as required, based on enrollment and study timelines

Study Duration	Estimated study duration: up to 4 years after the last participant is randomized
Data Monitoring Committee	The data monitoring committee (DMC) will review the unblinded data generated during the clinical study. The mandate of the DMC is to serve as an independent committee with pertinent clinical and trial conduct expertise to monitor and ensure the safety of the therapies for participants on trial. Prior to the final overall survival (OS) analysis, 2 planned interim efficacy analyses will be conducted by the DMC. The composition, structure, and function of the DMC and the scope of data for review are defined in the DMC Charter. The timing of such data review will be predefined in the DMC Charter.

2. INTRODUCTION

2.1. Background

Myelodysplastic syndrome (MDS) is a premalignant clonal hematopoietic disorder characterized by bone marrow failure due to production of dysfunctional, dysplastic bone marrow cells. Low and very low risk patients, as defined by the Revised International Prognostic Scoring System (IPSS-R;{Greenberg 2012}), are often treated with erythroid and myeloid growth factor support and carry a low risk of leukemic progression. In contrast, intermediate, high, and very high risk patients with MDS are generally treated with hypomethylating agents and carry an elevated risk of leukemic progression. Azacitidine (Vidaza®) is standard of care (SOC) for newly diagnosed MDS patients with specific high risk subtypes. However, complete remission (CR) rates are low, and overall survival (OS) is only around 18 months {Silverman 2002}. Thus, novel therapies that replace or augment the efficacy of azacitidine are needed to extend survival for patients with MDS.

CD47 is a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system. CD47 appears to be an indispensable means by which cancer cells, including cancer stem cells, overcome intrinsic expression of their 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 acute myeloid leukemia (AML; {Majeti 2009}), and since then, it has been found that CD47 expression is increased on the surface of cancer cells from a large number of diverse 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 on cancer cells to its ligand signal regulatory protein alpha (SIRPα) expressed on phagocytes leads to inhibition of tumor 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 induces an anticancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis {Liu 2015b, Tseng 2013}. Furthermore, CD47-blocking mAbs have shown synergistic efficacious activity with cancer-specific targeting antibodies, including anti-CD20 antibody rituximab in a nonclinical model of non-Hodgkin lymphoma (NHL; {Chao 2010a}).

Magrolimab (also known as Hu5F9-G4 or 5F9 [GS-4721]), a humanized anti-CD47 mAb, has been investigated in a Phase 1 AML study (Study SCI-CD47-002; EudraCT No. 2015-000720-29) conducted in the United Kingdom (UK) and has been further investigated in an ongoing Phase 1b study (Study 5F9005; EudraCT No. 2017-000678-12) in multiple subtypes of AML and intermediate/high/very high risk MDS, both as monotherapy and in combination with azacitidine.

2.1.1. Target Indication and Population

Myelodysplastic syndrome is a premalignant clonal hematopoietic disorder characterized by peripheral blood cytopenias, dyspoiesis, and increased risk of AML development. The disorder affects primarily individuals in their seventh decade of life ({Ma 2012}), and treatment strategies are based on standard prognostic scoring. Patients classified as low or very low risk categories, as defined by the IPSS-R {Greenberg 2012}, are normally treated with erythroid and myeloid growth factor support. These individuals also have a low risk of progression to acute leukemia. In contrast, patients with intermediate, high, or very high risk MDS have a 25% chance of leukemic transformation and are generally treated with hypomethylating agents {(NCCN) 2018}. Specifically, azacitidine is the standard of care for newly diagnosed MDS categorized as intermediate, high, or very high risk. However, the overall response rate (CR + partial remission [PR]) was only about 16% (azacitidine prescribing information), and median OS is approximately 18 months {Silverman 2002}. Thus, new therapies that may replace or augment the efficacy of azacitidine are needed to improve outcomes for these patients.
Magrolimab + azacitidine (compared with azacitidine + placebo) is being investigated for the treatment of previously untreated patients with intermediate/high/very high risk MDS by IPSS-R.

2.1.2. Description of Magrolimab

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 Fc-dependent effector functions, although the presence of the immunoglobulin 4 (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, NHL, myeloma, MDS, and others).

2.1.2.1. Justification for Dosing Strategy

The following magrolimab dosing regimen is proposed for this study:

- Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11 and 15; and then 30 mg/kg weekly for a total of 5 doses (Days 22, 29, 36, 43, and 50).

- Maintenance doses of magrolimab: 30 mg/kg on Day 57 and 30 mg/kg every 2 weeks thereafter.

Rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and pharmacokinetic (PK)/pharmacodynamic data and modeling and simulation analyses based on data obtained from all ongoing and completed clinical trials with magrolimab in participants with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab (SCI-CD47-001) in participants 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 to the dosing regimen based on mitigation of the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged red blood cells (RBCs) that are sensitive to CD47 blockade and triggers a 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 top dose of 45 mg/kg has an acceptable safety profile, and no maximum tolerated dose (MTD) was identified in this study. In Studies SCI-CD47-002 and 5F9005, in participants 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 weekly. In these studies, no significant dose-limiting toxicity was observed, and magrolimab has an acceptable safety profile over the tested dose range up to a maximum of 30 mg/kg twice a week. Furthermore, in these 2 studies, an intrapatient dose escalation approach was followed; after the priming dose, the participants 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 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 other week. 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, the proposed dosing regimen of magrolimab is expected to have an acceptable safety profile.

Currently, there are limited data on dose/exposure-response in the treatment-naïve MDS population, but available dose-ranging data in patients with NHL also support the proposed dosing regimen. After a priming dose of 1 mg/kg in the first week, maintenance doses in the range of 10 to 45 mg/kg every week and 30 to 45 mg/kg every 2 weeks (Q2W) are being tested in an ongoing Phase 1b/2 study of magrolimab in combination with rituximab in participants

with relapsed/refractory (R/R) NHL (Study 5F9003). Based on data obtained from this study so far, there was no significant difference in efficacy across the dose range tested. For instance, in R/R diffuse large B-cell lymphoma (DLBCL), the objective response rate (ORR) of participants in the combined 30 mg/kg dose arm (N = 35) and at 45 mg/kg (n = 17) was 34% and 38%, respectively {Advani 2019}. Preliminary PK/pharmacodynamic modeling indicated lack of relationship between exposure and ORR across the dose/concentration range. Also, no relationship was observed between concentrations and duration of response (DOR) in responders across the tested dose range. Together, these results indicated maximal efficacy at 30 mg/kg with no further efficacy benefit at higher doses.

In addition, in Study SCI-CD47-002 and Study 5F9005, CD47 receptor occupancy (RO) was tested at baseline and at multiple time points on treatment for both peripheral blood and bone marrow cells, including leukemic blasts. A PK/pharmacodynamic model linking dose exposure and blood and bone marrow RO was developed and described this relationship well. Simulations with the model predicted that > 90% RO would be achieved in the bone marrow cells at the magrolimab dosing regimen proposed in this study. This level of RO is typically associated with maximal efficacy for many immune-oncology antibodies. Therefore, the proposed dose regimen is expected to maximize efficacy in the MDS patient population. 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 in combination with azacitidine in treatment-naïve patients with MDS to mitigate on-target toxicities such as anemia and other toxicities observed in nonclinical AML models. The intrapatient dose escalation regimen uses initial twice-weekly dosing at a starting magrolimab dose of 1 mg/kg for Week 1 (Days 1 and 4), with escalation to 15 mg/kg on Day 8 and 30 mg/kg on Days 11 and 15, followed by 30 mg/kg weekly for 5 doses (Days 22, 29, 36, 43, 50). The maintenance dose of magrolimab is 30 mg/kg on Day 57 and every 2 weeks, thereafter. Treatment should be continued until disease progression, loss of clinical benefit, or unacceptable toxicities occur. The strategy of intrapatient dose escalation was found to result in both mitigation of acute toxicities seen in nonclinical models and in expected RBC toxicities that were manageable for this patient population.

In summary, the proposed dose regimen has been shown to have an acceptable safety profile in multiple oncology patient populations, including MDS patients. Based on PK/pharmacodynamic modeling, the proposed dose is predicted to result in optimal efficacy in this population. Further increases in dose beyond 30 mg/kg are not predicted to result in increased efficacy.

2.1.3. Description of Azacitidine

Azacitidine is a nucleoside analog, specifically a chemical analog of cytidine. Azacitidine has 2 known primary antineoplastic MOA: 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 United States (US) for treatment of subtypes of MDS including, but not limited to, MDS with refractory with anemia excess blasts, a subtype that is mostly composed of patients with intermediate to very high risk MDS by IPSS-R criteria. Azacitidine is also an SOC therapy for newly diagnosed patients with AML who are ineligible for induction chemotherapy or stem cell transplant (SCT) based on age, comorbidities, or other factors. In Europe, azacitidine is approved for patients with intermediate-2 and high risk MDS according to the International Prognostic Scoring System (IPSS) criteria and for patients with AML who are ineligible for SCT.

The adverse event (AE) profile of azacitidine primarily includes myelosuppression (anemia, leukopenia, and thrombocytopenia) and clinical sequelae of myelosuppression (neutropenic fever, infections, bleeding, and fatigue). Common nonhematologic AEs include gastrointestinal events (diarrhea, nausea, constipation, and decreased appetite), skin disorders (rash, pruritus, petechiae, and ecchymosis), injection site/infusion-related reactions (injection site erythema and/or pain for subcutaneous [SC] administration), and fever. Generally, these toxicities can be managed with supportive care interventions, pharmacologic treatment, or dose delays and/or adjustments. Further information on the safety profile of azacitidine is outlined in the summary of product characteristics for SC and the prescribing information for SC or intravenous (IV) use.

2.1.3.1. Justification for Dosing Strategy

Azacitidine will be dosed according to region-specific drug labeling, either SC or IV, at the standard clinical dose of 75 mg/m^2 on Days 1 to 7 of a 28-day cycle in combination with magrolimab/placebo. Azacitidine may be administered on an alternative schedule of Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience. In accordance with the azacitidine drug label, it is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued until disease progression, loss of clinical benefit, or unacceptable toxicities occur, as described in the azacitidine prescribing information references. Participants with MDS enrolled on this study will consist of participants in both the US, Australia, and other relevant country-specific-based azacitidine approval indications.

2.1.4. Supportive Nonclinical Data

The nonclinical studies referred to in the publications referenced in this section have been conducted with a commercially available CD47-blocking mAb (clone B6H12, mouse IgG1), and additional nonclinical studies have been conducted with the humanized CD47-blocking mAb magrolimab.

An anti-CD47 antibody has demonstrated therapeutic efficacy in MDS in nonclinical models. Blockade of CD47 may be therapeutic in patients with higher risk MDS as CD47 expression increases with progression from low risk to high risk MDS to AML. In nonclinical models, dysplastic cells from high risk MDS patients were eliminated by phagocytosis with an anti-CD47 antibody {Pang 2013}.

Since MDS is pathophysiologically considered a spectrum of disease sharing many characteristics to AML, nonclinical studies evaluating magrolimab in AML have relevance to MDS and are reported here. Magrolimab treatment eliminated both circulating leukemic and bone marrow disease in nonclinical mouse models engrafted with human patient AML cells as monotherapy {Liu 2015a}.

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 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 monotherapy. These data serve as the mechanistic and nonclinical rationale for combining magrolimab with azacitidine in MDS. Further nonclinical data including efficacy, toxicology, and pharmacology can be found in the investigator's brochure (IB).

2.1.5. Supportive Clinical Data

2.1.5.1. Clinical Pharmacology and Pharmacokinetics

Clinical PK data have been collected in all ongoing trials of magrolimab conducted to date. PK data have been analyzed for participants in the solid tumor Phase 1 study (SCI-CD47-001). In this study, participants have been 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 has been 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 have been achieved. Evidence of sustained target trough levels has been observed at doses of 10 mg/kg weekly and higher. Nine of 88 (10%) evaluable participants 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 participants.

For the Phase 1 AML study (SCI-CD47-002), PK data have been analyzed for all cohorts (dose range from 0.1 to 30 mg/kg twice weekly). Similar to the solid tumor Phase 1 study, nonlinear PK consistent with target-mediated clearance has been observed. Pharmacokinetics sampling is continuing in other ongoing magrolimab trials. Three of 20 (15%) evaluable participants tested positive for ADA against magrolimab at any time point including baseline; ADA positivity had no impact on PK. ADA positivity in either study was not associated with increased AEs.

Preliminary PK data of magrolimab from other ongoing studies (5F9003, 5F9004, and 5F9005) of magrolimab indicate similar PK properties across all tumor populations and in the presence of coadministered drugs. Across all studies, 21 out of 264 (8%) participants tested positive for ADA against magrolimab at any time point including baseline. ADA positivity was not associated with changes in PK or AE profile.

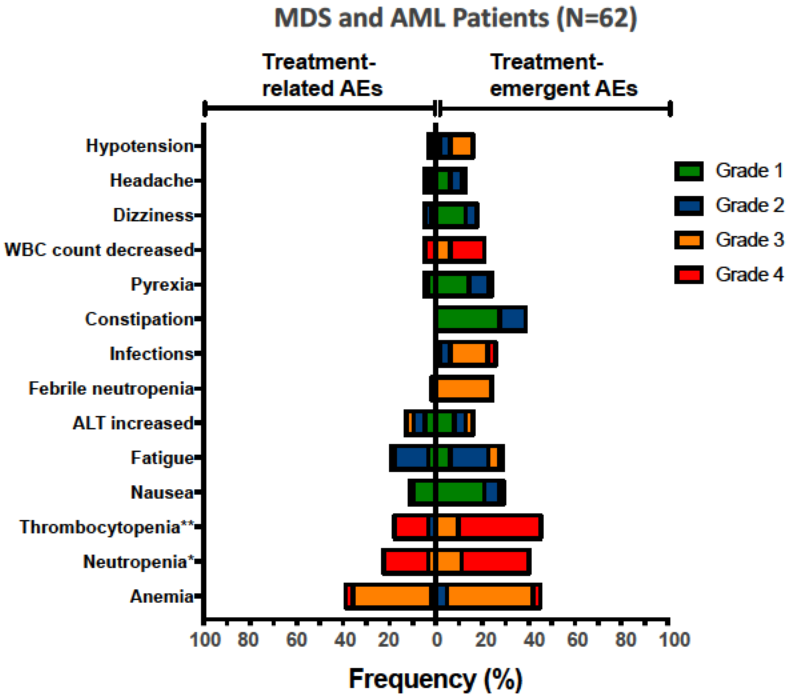
A preliminary population PK analysis of combined magrolimab PK data indicated that results for magrolimab population PK were typical of other nonlinear antibodies {Dirks 2010}. No clinically significant covariates of PK variability were identified.

2.1.5.2. Clinical Safety

Magrolimab is administered as an IV infusion, and it is currently being studied in 6 clinical trials. Two single-agent Phase 1 studies include Study SCI-CD47-001 in participants with advanced solid tumors and lymphomas and Study SCI-CD47-002 in participants with R/R AML. Four combination trials include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in participants with R/R NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in solid tumor and colorectal cancer participants; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in AML and MDS participants; and Study 5F9006, a Phase 1b study of magrolimab with avelumab in solid tumor and ovarian cancer participants. As of July 2019, approximately 400 participants have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no MTD reached in any study with dosing up to 45 mg/kg.

As of November 2019, 62 participants (35 untreated higher risk MDS participants and 27 untreated induction chemotherapy-ineligible AML participants) have been enrolled in Study 5F9005 with the combination of magrolimab + azacitidine {Sallman 2019}. 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 (39%), neutropenia/neutrophil count decreased (23%), and thrombocytopenia/platelet count decreased (18%) (Figure 1). Treatment discontinuation due to any AE occurred in only 1 of 62 (1.6%) participants, with no MDS participants discontinuing treatment due to any AE.

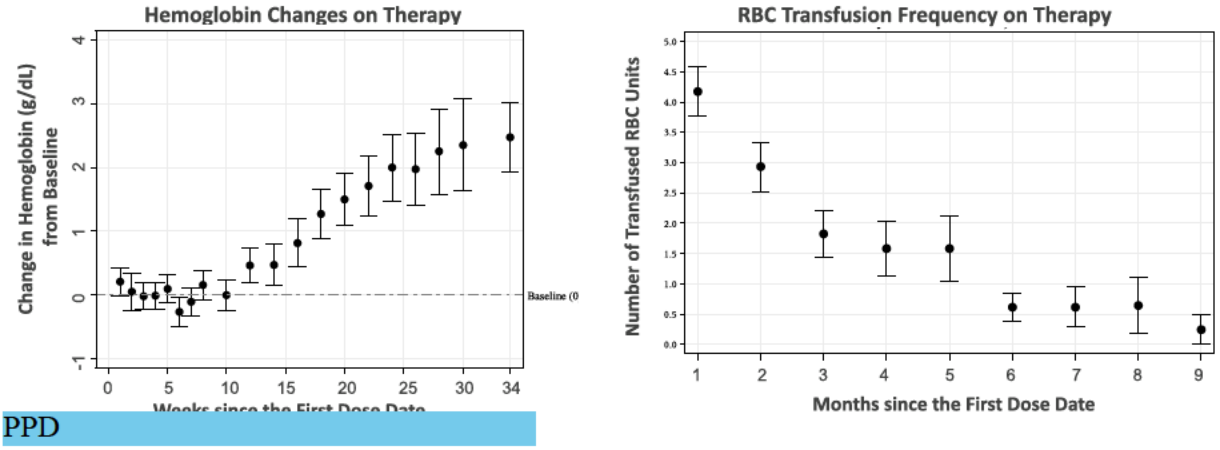
Figure 1. **Treatment-related and Treatment-emergent Adverse Events in AML/MDS Patients Treated with Magrolimab in Combination with Azacitidine in Study 5F9005**



Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; WBC = white blood cell.
There were 62 patients treated with magrolimab in combination with azacitidine. AEs greater than or equal to 15% or AEs of interest are shown. Treatment-related AEs are presented for magrolimab.

On-target anemia due to CD47 blockade-mediated RBC clearance was mitigated with a priming/maintenance dose strategy (Figure 2). The average hemoglobin decline with the first (priming) dose was 0.4 g/dL, with many participants improving their hemoglobin on therapy with a decrease in RBC transfusion requirements.

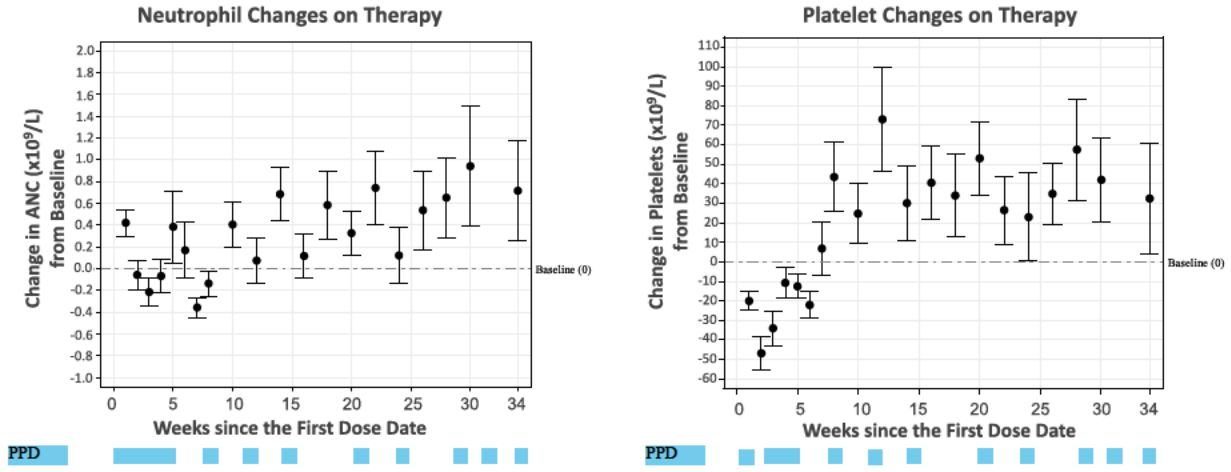
Figure 2. **Magrolimab Priming/Maintenance Dose Regimen Alleviates Anemia in AML/MDS Patients Treated with Magrolimab in Combination with Azacitidine in Study 5F9005**



Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; RBC = red blood cell.

Neutrophil and platelet counts were also minimally affected on therapy, with most participants improving their neutrophil and platelet counts on treatment (Figure 3).

Figure 3. **Neutrophil and Platelet Counts in MDS/AML Patients Treated with Magrolimab in Combination with Azacitidine in Study 5F9005**



Abbreviations: AML = acute myeloid leukemia; ANC = absolute neutrophil count; MDS = myelodysplastic syndrome.

In summary, the safety profile of magrolimab + azacitidine is acceptable in MDS and AML participants, with no significant exacerbation of azacitidine toxicities, no significant myelosuppression, and a minimal treatment discontinuation rate.

For further safety information, please refer to the IB.

2.1.5.3. Clinical Efficacy

As of November 2019 in Study 5F9005, clinical activity was assessed for magrolimab + azacitidine in participants with treatment-naïve/unfit AML and treatment-naïve intermediate to higher risk (by IPSS-R) MDS {Sallman 2019}. Forty-six (24 MDS and 22 AML) participants were evaluable for efficacy. In MDS, the ORR was 92%, with 50% achieving a CR. In AML, the ORR was 64%, with 41% achieving a CR and 14% achieving complete remission with incomplete hematologic recovery (Cri). Time to response was rapid at 1.9 months. Complete cytogenetic responses were observed in 26% of MDS participants and 60% of AML participants of whom had abnormal cytogenetics at baseline. Twenty-three percent of MDS and 57% of responding AML participants achieved minimal residual disease (MRD) negativity, as assessed by flow cytometry. With a median follow-up of 6.4 months and 8.8 months for MDS and AML, respectively, no median DOR had been reached, with several participants in response over 14 months on therapy. In addition, putative CD34+CD48− leukemia stem cell progenitors were substantially reduced or eradicated by magrolimab in combination with azacitidine in responding participants who were evaluated. In summary, magrolimab in combination with azacitidine has meaningful clinical activity that appears to be enhanced compared with azacitidine monotherapy in both MDS and AML participants.

For further clinical efficacy information, please refer to the magrolimab IB.

2.1.6. Benefit-risk Assessment

Overall, nonclinical and clinical data to date on magrolimab in combination with azacitidine show the therapy to have evidence of efficacy in untreated higher risk MDS and show the therapy to have an acceptable safety profile in this patient population. This encouraging activity is based on a 92% ORR and 50% CR rate observed with no median DOR reached throughout a median follow-up of 6.4 months. The safety profile of the combination is acceptable, with no MTD reached and a treatment discontinuation rate due to AEs of 1.6%. No significant exacerbation of azacitidine AEs by magrolimab has been observed, as evidenced by the minimally observed myelosuppression from the combination. The efficacy of magrolimab + azacitidine compares favorably to azacitidine monotherapy in higher risk MDS. To this point, based on large historical studies, the ORR for azacitidine monotherapy ranges from 40% to 50%, and the CR rate ranges from 6% to 17% (azacitidine US package insert,{Fenaux 2009, Silverman 2006}. One additional study evaluating azacitidine demonstrated a CR rate of 24%; however, this study also included lower risk MDS by IPSS-R and chronic myelomonocytic leukemia participants with the CR rate specifically in higher risk MDS participants not reported {Sekeres 2017}.

The potential risks and mitigations associated with participants being unable to attend study visits as a result of a pandemic have been identified for this study and are described in Appendix H. Given the risk-mitigation measures that are being implemented, the expected benefit-risk assessment to the participant remains unchanged.

Overall, based on the scientific rationale, nonclinical data, and acceptable safety profile and encouraging clinical activity data obtained for magrolimab in combination with azacitidine, the risk-benefit ratio is acceptable for proceeding forward with this study in untreated higher risk MDS.

2.2. Study Rationale

Azacitidine upregulates prophagocytic signals in leukemia cells and results in increased phagocytosis when combined with magrolimab's blockade of CD47, a major antiphagocytic signal. Nonclinical data have demonstrated enhanced phagocytosis of leukemia cells in vitro and long-term remissions in AML-engrafted mice with magrolimab in combination with azacitidine compared with either single agent alone. Magrolimab in combination with azacitidine is being developed in multiple indications within MDS and AML, specifically in a potential pivotal single-arm study in untreated intermediate to very high risk MDS participants as assessed by IPSS-R criteria. Data reported from December 2019 demonstrated an ORR of 92% and a CR rate of 50% in 24 MDS participants, an acceptable safety profile, and a treatment discontinuation rate due to AEs of only 1.6% {Sallman 2019}. The SOC therapy for this population is hypomethylating agents (azacitidine and decitabine); however, efficacy is limited, with CR rates of approximately 6% to 17% and a median OS of approximately 18 months (azacitidine US package insert,{Fenaux 2009, Silverman 2006}). For higher risk MDS, azacitidine is in general more widely used than decitabine, given azacitidine's approval for MDS in the US, Europe, and other regions. Novel effective therapies that can be combined with hypomethylating agents while maintaining an acceptable safety profile are needed for individuals with higher risk MDS. As of December 2019, no new therapies have been approved in MDS for over a decade, which underscores a high unmet medical need in this population. Participants with MDS experience frequent comorbidities and mortalities as a result of cytopenias due to both the disease and to hypomethylating agents. The need for combination therapies that can induce hematologic improvement and disease remission leading to a clear clinical benefit is quite evident. Magrolimab in combination with azacitidine is being developed in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R to improve clinical activity and maintain an acceptable safety profile. This study will compare the efficacy and safety of magrolimab + azacitidine with that of azacitidine + placebo.

3. OBJECTIVES AND ENDPOINTS

The aim of this study is to evaluate the efficacy and safety of magrolimab + azacitidine compared with azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R prognostic risk categories.

Tier	Objectives	Endpoints
Primary: Efficacy	To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R as measured by CR rate	CR rate as assessed by Investigators
Primary: Efficacy	To evaluate the survival benefit of magrolimab + azacitidine compared with that of azacitidine + placebo	OS
Secondary: Efficacy	To evaluate the duration of CR of magrolimab + azacitidine compared with that of azacitidine + placebo	Duration of CR
Secondary: Efficacy	To evaluate ORR and DOR of magrolimab + azacitidine compared with that of azacitidine + placebo	ORR and DOR
Secondary: Efficacy	To evaluate RBC transfusion independence rate of magrolimab + azacitidine compared with that of azacitidine + placebo among all participants who are RBC transfusion-dependent at baseline	RBC transfusion independence rate
Secondary: Efficacy	To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo as measured by EFS	EFS
Secondary: Efficacy	To evaluate CR of magrolimab + azacitidine compared with that of azacitidine + placebo in TP53 mutant population	CR rate in TP53 mutant population
Secondary: Efficacy	To assess the level of MRD negativity of magrolimab + azacitidine compared with that of azacitidine + placebo	MRD-negative response rate
Secondary: Efficacy	To assess time to transformation to AML of magrolimab + azacitidine compared with that of azacitidine + placebo	Time to transformation to AML

Tier	Objectives	Endpoints
Secondary: Efficacy	To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo, as measured by PFS	PFS
Secondary: Safety	To assess the safety and tolerability of magrolimab + azacitidine compared with that of azacitidine + placebo	Measurement of AEs according to NCI CTCAE, Version 5.0 (Appendix A)
Secondary: Pharmacokinetics	To evaluate PK of magrolimab	Magrolimab concentration versus time
Secondary: Immunogenicity	To evaluate the immunogenicity of magrolimab	ADA to magrolimab
Secondary: PRO	To evaluate the HRQoL of magrolimab + azacitidine compared with that of azacitidine + placebo, as measured by FACT-Anemia response rate	FACT-Anemia response rate
[redacted]	CCI [redacted]	[redacted]
[redacted]	CCI [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Tier	Objectives	Endpoints
		CCI [redacted]

Abbreviations: ADA = antidrug antibody; AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CyToF = mass cytometry; DOR = duration of response; EFS = event-free survival; EQ-5D-5L = 5-level EuroQol 5 dimensions; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; HRQoL = health -related quality of life; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; MRD = minimal residual disease; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient-reported outcome; RBC = red blood cell.

4. STUDY PLAN

4.1. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled multicenter study investigating magrolimab + azacitidine compared with azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R. The primary endpoints are CR rate and OS. Participants will be randomized in 1:1 ratio to receive either magrolimab + azacitidine (experimental arm) or azacitidine + placebo (control arm). Randomization will be stratified by 3 factors: 1) geographic region (US versus ex-US sites); 2) cytogenetic risk status (very good/good/intermediate versus poor/very poor versus unknown) according to IPSS-R {Greenberg 2012}); and 3) percentage of bone marrow blasts (≥ 10% versus < 10% blasts). The primary analysis of CR rate will be conducted 8 months after 348 participants are randomized.

Participant participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment, during which time the participant's eligibility and baseline characteristics will be determined. Participants will receive study treatment per the dose schedule in Table 1. No cross-over between arms is allowed. Study treatment may be continued until disease progression (including treatment failure by International Working Group [IWG] 2006 criteria or relapse after partial/complete remission [PR/CR]), loss of clinical benefit, or unacceptable toxicities occur. In case participants discontinue the study treatment due to reasons other than disease progression, participants will be followed up for response assessments until documented disease progression occurs. For participants who come off the study treatment to receive an SCT, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs or start of new anticancer therapy, whichever occurs first. The participants will be followed for survival, unless the participant explicitly indicates a desire to forego survival follow-up in writing to their study investigator, until death, withdrawal of consent, loss to follow-up, or study termination, whichever occurs first. For any participant who dies during this follow-up period, the immediate cause of death must be reported to the Sponsor. For participants who are lost to follow-up or withdraw consent, study staff may use public records (eg, public health records) to obtain information about survival status where allowable by local regulation.

Table 1. Dose Level and Schedule

Treatment Arms	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	**Cycle 2**	**Cycle 3+**
Experimental arm (Magrolimab+ azacitidine) **And Control arm** (azacitidine + placebo)	Azacitidine 75 mg/m^2 SC or IV[a]	Days 1–7 or Days 1–5 and 8-9	Days 1–7 or Days 1–5 and 8–9	Days 1–7 or Days 1–5 and 8-9
Treatment Arms	**Drug/Dose/Route**	**Dose Schedule**		
		Priming Dose		**Maintenance Dose**
Experimental arm (Magrolimab+ azacitidine)	Magrolimab 1 mg/kg IV	Days 1, 4		
	Magrolimab 15 mg/kg IV	Day 8		
	Magrolimab 30 mg/kg IV	Days 11, 15, followed by weekly administration for 5 doses (Days 22, 29, 36, 43, 50)		Day 57 and every 2 weeks thereafter
Control arm (azacitidine + placebo)	Placebo	to mirror the magrolimab dosing schedule above		to mirror the magrolimab dosing schedule above

Abbreviations: IV = intravenous; SC = subcutaneous.
a Azacitidine administered per region-specific labeling.

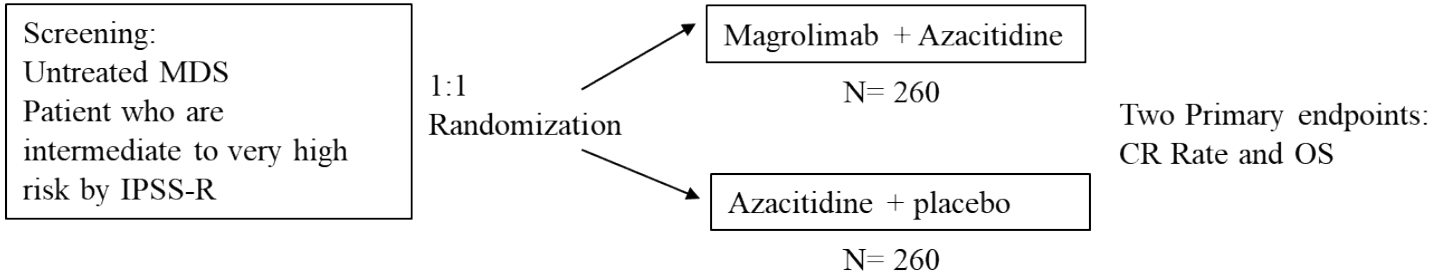
Treatment with azacitidine as standard of care is recommended for a minimum of 6 cycles. Therefore, in this study, participants without evidence of disease progression (including treatment failure by IWG 2006 criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicity should continue azacitidine for at least 6 cycles. Participants may be discontinued from the treatment per Investigator's discretion prior to reaching the recommended minimum cycles for any of these reasons detailed in Section 5.7.

The schedules of assessments are provided in Section 4.3.

4.2. Study Schematic

The study schematic is presented in Figure 4.

Figure 4. Study 5F9009 Schematic



Magrolimab (or saline placebo) dosing:

Priming Dose:
1 mg/kg on Days 1 and 4
15 mg/kg on Day 8
30 mg/kg Days 11, 15
30 mg/kg weekly for 5 doses (Days 22, 29, 36, 43, 50)

Maintenance Dose:
30 mg/kg on Day 57 and 30 mg/kg every 2 weeks thereafter

Azacitidine dosing:
75 mg/m^2 IV or SC Days 1-7 (or Days 1-5 and 8-9) every 28-day cycle

Abbreviations: CR= complete remission; IPSS-R = Revised International Prognostic Scoring System; IV= intravenous; MDS=myelodysplastic syndrome; OS = overall survival; SC=subcutaneous

4.3. Schedule of Assessments

The schedule of assessments is presented in a separate table for each study period: screening (Table 2), treatment period- azacitidine dosing and study assessments (Table 3), treatment period-magrolimab or placebo dosing and study assessments (Table 4), posttreatment (Table 5), and repriming (Table 6). A cycle is 28 days long.

Table 2. Schedule of Assessments - Screening

Assessment	Study 5F9009 Day -30 to –1
Informed consent	X[a]
Demographics	X
Medical and cancer history	X
Pregnancy test	X[b]
Serum or plasma chemistry	X
Serum uric acid, phosphorus	X
Hematology[d]	X
Blood phenotyping or genotyping, type, screen (ABO/Rh), DAT[e]	X
Urinalysis	X
Bone marrow biopsy and aspirate for blast evaluation, biomarker studies, cytogenetics, and MRD assessment[c]	X
ECOG	X
Vital signs, height, and weight	X
Complete physical examination	X
ECG (single)	X
Hepatitis B, hepatitis C, and HIV[f]	X
Adverse events related to protocol-mandated procedures	X
Concomitant medications	X
Entry criteria	X
Randomization	X[a]

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; MRD = minimal residual disease; RBC = red blood cell; Rh = Rhesus factor; SOC = standard of care.

a Screening must be completed before randomization. Randomization must occur within 30 days of signing informed consent. The first dose of study treatment (Table 3 and Table 4) must be given within 72 hours after randomization.

b Screening pregnancy test may be used as the Day 1 test if performed within 72 hours of first dose; additional guidance is provided in Section 5.1.1. FSH test is required for female participants 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. A bone marrow biopsy collected per SOC within 30 days of randomization can be considered the screening sample, and shipped to central laboratory. This procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample must be collected at the screening visit for blast evaluation, MRD assessment, biomarker studies, baseline for response assessment and biobanking. It is preferred that bone marrow aspirate samples are obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics to be tested per institutional standards.

d Hematology analytes to be assessed at screening are provided in Table 7.

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

f Refer to Exclusion Criteria 13 and Other Laboratory Measurements in Table 7.

Table 3. Schedule of Assessments - Treatment Period-Azacitidine Dosing and Study Assessments

	Cycle (28-day Cycles)																			
	1							2							3+					
Visit Window (Days)	None	± 3						± 3							± 3					
Cycle Day	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
PRO assessment[a]	X							X							X						
CBC with differential, platelets, reticulocytes[b]	X							X							X						
Serum or plasma chemistry[b]	X							X							X						
Bone marrow biopsy and aspirate for biomarker studies[c]															X[d,e]						
Bone marrow aspirate biopsy for MRD monitoring, cytogenetics, and response assessment[d,f]															X Q2C, Q3C[e]						
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical examination[b]	X							X							X						
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood transfusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Azacitidine[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CBC = complete blood count; EQ-5D-5L = 5-level EuroQol 5 dimensions; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; MRD = minimal residual disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; Q2C = every 2 cycles; Q3C = every 3 cycles.

a Four PRO questionnaires will be administered in this study: the FACT-Anemia questionnaire, the EQ-5D-5L, the PGIS, and the PGIC. The participant should complete these questionnaires before other study procedures at required visits. No PGIC assessment at Cycle 1 Day 1. FACT-Anemia and EQ-5D-5L should be implemented prior to PGIS/PGIC.

b If magrolimab and azacitidine are administered on the same day, only one such study assessment is needed. Assessments should be performed prior to study treatment administration. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to study treatment administration.

c Bone marrow biopsy samples will be collected at Day 1 of Cycles 3 and 10.

d An aspirate sample will be collected for response assessment, biomarker studies, and MRD assessment. Conventional cytogenetics to be tested per institutional standards. Response assessments may be adjusted by ± 1 week for Cycle 3 Day 1. After Cycle 3 Day 1, the window is ± 14 days.

e An aspirate sample will be collected for biomarker studies at Day 1 of Cycles 3, 5, 7, 10, and 13.

f Samples will be collected at Day 1 of Cycles 3, 5, and 7 and then every 3 cycles thereafter during study treatment. Bone marrow aspirate biopsies for response assessments may be adjusted by ± 1 week for Cycle 3 Day 1. After Cycle 3 Day 1, the window is ± 14 days.

g Vital signs will be assessed prior to infusion/injection of each study treatment. Weight will be assessed on Day 1 of each cycle. Details are provided in Section 5.1.5.

h If azacitidine and magrolimab/placebo are administered on the same day, azacitidine administration should be completed at least 1 hour before magrolimab/placebo administration. Azacitidine may be administered on an alternative schedule of Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience.

Table 4. Schedule of Assessments - Treatment Period-Magrolimab or Placebo Dosing and Study Assessments

Dose Schedule	**Priming Dosing**											**Maintenance Dosing**	
Visit Window (Days)	**None**		**± 3**									**± 3**	
Day	**1**	**2**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**every 2 Weeks thereafter**
Pregnancy test[a]	X							X				X Q4W	
CBC with differential, platelets, reticulocytes[b,c,d]	X[e]	X	X[e]	X	X	X	X	X	X	X	X	X	X
Haptoglobin and LDH[c]	X			X				X					
Serum or plasma chemistry[b,c]	X			X		X	X	X		X		X	X
Peripheral smear[c,f]	X	X			X								
Peripheral blood sample for biomarker studies[g]	X			X				X				X[h]	
PK[g]	X			X				X				X[i]	
Antidrug antibodies[c,j]	X							X				X[i]	
Vital signs[k]	X		X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical examination[b,c]	X			X		X		X				X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood transfusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Premedication[l]	X		X	X	X								
Magrolimab or placebo[m]	X[n]		X[n]	X	X	X	X	X	X	X	X	X	X

Abbreviations: CBC = complete blood count; D = day; EOT = end of treatment; LDH = lactate dehydrogenase; MRD = minimal residual disease; PK = pharmacokinetic(s); PRO = patient-reported outcome; Q4W = every 4 weeks; WBC = white blood cell.

a Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted once every month; additional guidance is provided in Section 5.1.1.

b If magrolimab and azacitidine are administered on the same day, only one such study assessment is needed. Assessments should be performed prior to study treatment administration. For monitoring of infusion-related reactions, please refer to Section 6.5

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

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/placebo dose during the first 28 days of magrolimab priming dose. Peripheral blasts should be included in the CBC assessments.

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

f Peripheral smears will be collected predose and assessed locally.

g Samples for PK and biomarker studies will be collected predose within 12 hours prior to study treatment administration.

h Samples will be collected prior to first maintenance dose (Day 57), ninth (Day 169) maintenance dose, and EOT.

i Samples will be collected predose on Day 57, Day 113, Day 169, Day 253, Day 337, and EOT.

j 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.

k Vital signs will be assessed prior to infusion/injection of each study treatment. Weight will be assessed every 4 weeks. Details are provided in Section 5.1.5.

l Premedication is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication for subsequent treatment periods may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent treatment periods is required (Section 6.5).

m Magrolimab or saline placebo should not be given on consecutive days. The duration of each magrolimab/placebo infusion including flush will be 3 hours (± 30 minutes) for the first 3 doses of treatment, and then 2 hours (± 30 minutes) for infusions beyond the first 3 doses. All participants should be monitored for 1 hour after infusion for doses during the first 28 days and the repriming doses.

n Within 24 hours prior to each of the first 2 doses of magrolimab/placebo infusion, all participants must have a documented hemoglobin ≥ 9 g/dL. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of magrolimab/placebo.

Table 5. Schedule of Assessments - Posttreatment

	End-of-treatment Visit	Safety Follow-up Visit/Call (Telephone)[a]		Long-term Follow-up	Survival Follow-up
	Within 7 Days after Last Dose or EOT Decision	30 Days after Last Dose	70 Days after Last Dose[k]	Until Start of New Anticancer Therapy or Transformation to AML[b]	Every 2 Months Until Death or End of Study
Visit Window	± 7 Days	± 7 Days	± 7 Days	+4 Weeks	
Serum or urine pregnancy test	X			Q4W[c]	Q4W[c]
CBC with differential, platelet count, reticulocytes	X			Q8W[d]	
Serum or plasma chemistry	X				
Peripheral blood for biomarker studies	X				
Pharmacokinetics	X				
Antidrug antibodies	X				
Bone marrow biopsy and aspirate for MRD monitoring and cytogenetics[d,e]	X			Q8W[d]	
Response assessment[e,f]	X			Q8W[d]	
ECOG	X				
Vital signs	X				
Symptom-directed physical examination	X				
PRO assessment[g]	X			X	
Adverse events[h]	X	X	X		
Concomitant medications	X	X	X		
Blood transfusion[i]				X	X
New anticancer therapy[j]				X	X
Survival follow-up					Q2M

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood count; CR = complete remission; eCRF = electronic case report form; EOT = end of treatment; EQ-5D-5L = 5-level EuroQol 5 dimensions; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; IWG = International Working Group;

MDS = myelodysplastic syndrome; MRD = minimal residual disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PR = partial remission; PRO = patient-reported outcome; QxM = every x months; QxW = every x weeks; SAE = serious adverse event.

a If the participant experiences a treatment-related AE or an SAE (regardless of attribution), the participant must be asked to come to the site.
b Until start of new anticancer therapy or transformation to AML, whichever comes first.
c Collect until the end of the contraception requirement.
d Bone marrow assessment, MRD, CBC, and response assessment should be performed until start of new anticancer therapy or transformation to AML, whichever comes first. Conventional cytogenetic testing (per institutional standards) is required for all participants.
e For participants who come off the study treatment to undergo a stem cell transplant, response assessments for relapse/remission status and bone marrow aspirate results are required to be obtained locally and entered into the eCRF.
f Response assessment at EOT visit not required if performed within the last 30 days or progressive disease has been documented. After disease progression (including treatment failure by IWG criteria and relapse after CR or PR), response assessment will focus on evaluation of transformation to AML.
g Paper PROs will be administered in this study: The FACT-Anemia questionnaire, the EQ-5D-5L, the PGIS, and the PGIC will be administered. The participant should complete these questionnaires before other study procedures at required visits. FACT-Anemia and EQ-5D-5L should be implemented prior to PGIS/PGIC.-FACT-Anemia, EQ-5D-5L, the PGIS, and the PGIC should also be collected during long-term follow-up prior to initiation disease progression or initiation of a new anticancer therapy.
h Report all AEs through the Safety Follow-up Visit/Call and any treatment-related SAEs thereafter.
i Collect blood transfusions until start of new anticancer therapy.
j Collect new anticancer therapy data following the last dose of study treatment.
k For participants who do not initiate new anticancer therapy after the last dose. See Section 5.1.10 for adverse event reporting details.

Table 6. Schedule of Assessments - Repriming (Required After > 4 Weeks Have Lapsed Since the Last Dose of Magrolimab/Placebo Delays)

	Day										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**
Visit Window (Days)	**-**	**-**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Pregnancy test	X										
CBC with differential, platelets, and reticulocytes[a,b]	X	X		X				X	X	X	X
Haptoglobin and LDH	X							X			
Serum or plasma chemistry[a]	X							X		X	X
Peripheral smear[a,c]	X	X							X		
Peripheral blood for biomarker studies[d]	X							X			
PK[d]	X							X			
Antidrug antibodies[a]	X										
Vital signs[e]	X	X						X		X	X
Symptom-directed physical examination[a]	X							X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Blood transfusions	X	X	X	X	X	X	X	X	X	X	X
Premedication[f]	X			X				X	X		
Magrolimab/placebo: repriming[g]	X			X				X	X	X	X

Abbreviations: CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PK = pharmacokinetic(s); PRO = patient-reported outcome; WBC = white blood cell.

a Pretreatment assessments are to be collected within 24 hours prior to study treatment administration.

b Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ $20 \times 10^3/\mu L$ for the repriming cycle.

c Peripheral smears will be collected and assessed locally.

d Samples for PK and biomarker studies will be collected predose within 12 hours prior to study treatment administration.

e Vital signs prior to infusion/injection of study treatment. Weight at Day 1. Details are provided in Section 5.1.5.

f Premedication is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication for subsequent cycles may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent cycles is required (Section 6.5).

g Magrolimab or saline placebo should not be given on consecutive days. During repriming, the duration of each magrolimab/placebo infusion including flush will be 3 hours (± 30 minutes) for the first 3 doses of treatment and 2 hours (± 30 minutes) for infusions beyond the first 3 doses. All participants should be monitored for 1 hour after infusion for doses during the first 28 days and the repriming doses. After Day 22, participants should return to their original dose schedule.

4.4. Design Rationale

This study is a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R. The primary efficacy endpoints of this study are CR rate and OS. This trial is designed to adequately determine the efficacy of magrolimab + azacitidine compared with azacitidine + placebo based on CR rate and OS, which are both standard approvable endpoints for this participant population. The CR rate of azacitidine monotherapy is well benchmarked in several prospective studies in higher risk MDS. Based on large historical studies, the CR rate of azacitidine monotherapy ranges from 6% to 17%, accounting for analysis under the IWG criteria (azacitidine US package insert,{Fenaux 2009, Silverman 2006}. One additional study evaluating azacitidine demonstrated a CR rate of 24%; however, this study also included lower risk MDS by IPSS-R and chronic myelomonocytic leukemia participants; the CR rate specifically in higher risk MDS participants was not reported {Sekeres 2017}. Given the range of CR rates and median OS data for azacitidine reported in large historical studies, with approximately 520 participants randomized in a 1:1 ratio, this study is adequately powered to show a superior CR rate or OS for the experimental arm compared with the control arm, assuming a CR rate of 20% in the control arm and a CR rate of 39% in the experimental arm, and an OS of 18 months in the control arm and 25.4 months in the experimental arm. Randomization will be stratified by 3 factors: 1) geographic region (US versus ex-US sites), 2) cytogenetic risk status, and 3) bone marrow blast percentage. The second and third stratification factors are reported as determinants of response and duration for azacitidine monotherapy based on a large retrospective analysis in higher risk MDS {Itzykson 2011}.

4.5. Recruitment

Approximately 200 sites in the US, Australia, Europe, and other countries as required, based on enrollment and study timelines, will be included in this study. A total of approximately 520 participants will be enrolled for the 2 primary analyses of CR rate and OS.

All participants must be provided an informed consent form (ICF) describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the institutional review board (IRB)/independent ethics committee (IEC) approved ICF prior to participation in any study-specific procedure. Data from assessments performed as part of SOC prior to ICF signature may be used if they are within the required Screening period. The participant must receive a copy of the signed and dated consent documents. A signed copy of the consent documents must be retained in the site file.

Once participants sign the ICF, they enter the Screening Period for the study and receive a unique patient identification number before any study procedures are performed. This number is used to identify the participant throughout the clinical study and must be used on all study documentation related to that participant, including if a participant is rescreened.

Participant screening laboratory assessments may be repeated beyond the initial screening assessments within the 30-day Screening Period. Participants who fail screening may undergo repeated screening if the participant's medical condition has changed. However, once a participant has been randomized, that participant cannot be rerandomized.

All participants who provide informed consent must be registered in the electronic data capture (EDC) and interactive voice/web/mobile response system (IXRS) systems, including any screen failures.

4.6. Definitions of Enrollment and Screen Failure

Participants officially enter the Screening Period following provision of informed consent. After signing the ICF, eligible participants must be randomized within 30 days. Treatment will start within 72 hours after randomization.

A participant is defined as enrolled in the study when that participant has been randomized.

A screen failure is a consented participant who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to randomization. Screen failures may be rescreened if the participant's medical condition has changed.

4.7. Inclusion Criteria

To be included in this study, each individual must satisfy all the following criteria:

1) Participants with MDS defined according to World Health Organization classification, with an IPSS-R {Greenberg 2012} prognostic risk category of intermediate, high, or very high risk. Note: participants who require AML-like therapy are not eligible.

2) White blood cell (WBC) count $\leq 20 \times 10^3/\mu L$ prior to randomization. If the participant's WBC is $> 20 \times 10^3/\mu L$ prior to randomization, the participant can be randomized, assuming all other eligibility criteria are met. Of note, while this does not impact eligibility, please ensure that the WBC is $\leq 20 \times 10^3/\mu L$ prior to the first dose of study treatment and prior to each magrolimab/placebo dose for priming doses of magrolimab.

    a) Participants can be treated with hydroxyurea (up to 4 g/day) throughout the study or prior to randomization to reduce the WBC to $\leq 20 \times 10^3/\mu L$ to enable eligibility and magrolimab dosing. Oral etoposide (up to 200 mg orally per day) may be given as an alternative to hydroxyurea for participants who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.

3) Participant has provided informed consent.

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

5) Male or female, age ≥ 18 years.

6) Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2.

7) Willing to undergo blood transfusions as deemed clinically necessary.

8) Pretreatment blood cross-match including ABO (any of the 4 blood groups A, B, AB, and O comprising the ABO system)/Rh (Rhesus factor), DAT (direct antiglobulin test), and phenotyping or genotyping completed (as detailed in Section 5.1.4).

9) Biochemical indices within the ranges shown below:

   b) Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 3.0 × upper limit of normal (ULN)

   c) Total bilirubin ≤ 1.5 × ULN or 3.0 × ULN and primarily unconjugated if participant has a documented history of Gilbert's syndrome or genetic equivalent

   d) Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2

10) All participants must have a documented hemoglobin ≥ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab/placebo infusion. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of magrolimab/placebo. Transfusions are allowed in order to meet hemoglobin eligibility (see Section 7.10.1.1).

11) Female participants of childbearing potential must not be nursing or planning to be pregnant and must have a negative urine or serum pregnancy test within 30 days before randomization and within 72 hours before the first administration of study treatment.

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

13) 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.

4.8. Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

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

2) Prior therapy for the treatment of MDS with an IPSS-R prognostic risk category of intermediate, high or very high risk (excluding hydroxyurea or oral etoposide), prior treatment with hypomethylating agents and/or low dose cytarabine. NOTE: Localized noncentral nervous system (CNS) radiotherapy, erythroid and/or myeloid growth factors, 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. Prior lenalidomide is also not exclusionary.

3) Immediately eligible for an allogeneic SCT, as determined by the Investigator, with an available donor.

4) Contraindications to azacitidine, including advanced malignant hepatic tumors or known hypersensitivity to azacitidine or mannitol.

5) Known inherited or acquired bleeding disorders.

6) Previous SCT within 6 months prior to randomization, active graft-versus-host disease, or requiring transplant-related immunosuppression.

7) Clinical suspicion of active CNS involvement by MDS.

8) Significant medical diseases or conditions, as assessed by the Investigators 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.

9) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which participants are not on active anticancer therapies and have had no evidence of active malignancy for at least ≥ 1 year.

10) History of psychiatric illness or substance abuse likely to interfere with the ability to comply with protocol requirements or give informed consent.

11) Pregnancy or active breastfeeding.

12) Known active or chronic hepatitis B or C infection or HIV infection in medical history.

13) Active hepatitis B virus (HBV) and/or active hepatitis C virus (HCV), and/or HIV following testing at Screening:

    a) Participants who test positive for hepatitis B surface antigen (HBsAg). Participants who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

    b) Participants who test positive for HCV antibody. These participants will require HCV RNA by quantitative PCR for confirmation of active disease.

    c) Participants who test positive for HIV antibody.

    d) Participants not currently on antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study.

4.9. Lifestyle Restrictions

4.9.1. Female Participants

Female participants of childbearing potential who have a negative serum or urine pregnancy test before enrollment must agree to use one of the highly effective forms of contraception described in Appendix G.

4.9.2. Male Participants

A male participant who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use contraception described in Appendix G during the study treatment period.

5. STUDY CONDUCT

It is anticipated that this study will take up to 6 years to complete, assuming 22 months for enrollment, plus 1 month screening, 6 or more cycles of study treatment, 30 day and 70 day (or until administration of novel anticancer therapy, whichever is earlier) safety follow-ups for each participant, and up to 4 years of follow-up after the last participant is randomized.

During the study, study assessments will be performed as listed by study visit in Section 4.3 and described in the current section.

5.1. Study Procedures

5.1.1. Pregnancy Test

Pregnancy tests are required only for female participants of childbearing potential. Note that a woman is considered to be of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal (defined as no menses for 12 months without an alternative medical cause) unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient. A urine or serum pregnancy test is required at Screening and within 72 hours before study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the Screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will also be required monthly and posttreatment until the end of the contraception requirement.

5.1.2. Complete Blood Counts

Samples for complete blood counts (CBCs) should be collected per the schedules of assessments in Section 4.3. WBC count needs to be $\leq 20 \times 10^3/\mu L$ prior to randomization and prior to each magrolimab/placebo dose for the first 28 days of magrolimab/placebo dosing and Repriming Cycle (see Section 4.7, Inclusion Criterion 2), for details). Additional samples for CBC may be collected outside of the protocol-specified time points to ensure WBC level $\leq 20 \times 10^3/\mu L$ for the first cycle and Repriming Cycle.

All participants must have a documented hemoglobin ≥ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab/placebo infusion. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to administering each of the first 2 doses of magrolimab/placebo.

5.1.3. Peripheral Blood Smear Assessment

Peripheral smears should be collected per the schedules of assessments and assessed for standard cell morphology. These samples should be collected from the arm contralateral to the arm being used for drug infusion/injection, if possible. All other observed findings should be reported according to local laboratory hematopathology standard procedures. Peripheral smears will be assessed locally (see also Section 7.10.1.3).

5.1.4. 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, blood phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab, as described in Section 7.10.1.1.

Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a participant received any RBC or whole blood transfusion within the previous 3 months (unless the laboratory has availability for special techniques for performing phenotyping for participants with a recent transfusion). RBC genotyping instead of extended RBC phenotyping is acceptable for any participant. Red blood cell phenotyping/genotyping, ABO type, and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available, unless the participant was transfused since that time. Results must be available before the first dose of magrolimab.

5.1.5. Vital Signs

Vital signs should include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height should be recorded during Screening only. Weight should be recorded during Screening and on Day 1 of each cycle. Vital signs are to be recorded prior to infusion/injection of each study treatment at the visits specified in the schedules of assessments in Section 4.3.

5.1.6. Physical Examination

Complete physical examination should be performed at Screening. Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and neurologic system. Symptom-related physical examination should be completed on Day 1 of each cycle or as clinically indicated.

5.1.7. Electrocardiogram

A single electrocardiogram (ECG) will be performed at Screening.

5.1.8. Bone Marrow Assessments

Bone marrow assessments (including aspirate and core/trephine biopsy) are required for response assessments (refer to Section 5.3 and Appendix B), including conventional cytogenetic analysis per institutional standards. In addition, bone marrow specimens may be used for biomarker studies, MRD monitoring, CCI [redacted], and biobanking. Minimal residual disease testing will be performed by a central laboratory. Bone marrow aspirate slides for response assessment will also be sent to a central laboratory. 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.

Bone marrow assessments include collection of both aspirate and core biopsy (trephine) specimens at each time point according to the schedules of assessments in Section 4.3.

Bone marrow biopsies for response assessments may be adjusted by ± 1 week for Cycle 3 Day 1. After Cycle 3 Day 1, the window is ± 14 days.

Response assessment at End-of-Treatment (EOT) Visit is not required if performed within the last 30 days or progressive disease has been documented. Bone marrow response assessments should continue during long-term follow-up approximately every 8 weeks until transformation to AML is documented or start of new anticancer therapy, whichever comes first. For participants who come off the study treatment to receive an SCT, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until documented relapse or progressive disease occurs. After documented relapse or progressive disease, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until transformation to AML occurs or start of new anticancer therapy, whichever comes first.

5.1.9. Patient-reported Outcomes

Four patient-reported outcome (PRO) instruments will be administered in this study: the Functional Assessment of Cancer Therapy-Anemia (FACT-Anemia), the 5-level EuroQol 5 dimensions (EQ-5D-5L), the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC). The participant should complete these questionnaires before any other study procedures at required visits.

5.1.9.1. FACT-Anemia

The FACT-Anemia questionnaire is a 47-item instrument used to assess anemia- and fatigue-related quality of life for patients with cancer and chronic disease. A sample is provided in Appendix C. This instrument consists of 5 subscales, including physical well-being, emotional well-being, functional well-being, social well-being, and anemia symptoms. Each subscale measures items on a 5-point Likert scale from 0 to 4, where 0 = not at all and 4 = very much. The FACT-Anemia instrument has demonstrated good validity and reliability in the general population as well as in patients with cancer {Cella 2012, Revicki 2013}.

5.1.9.2. EQ-5D-5L

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

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

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

5.1.9.3. PGIS/PGIC

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

5.1.10. Adverse Events

At each visit, the following AEs are to be reported using the applicable electronic case report form (eCRF; Section 10.2.3.1):

- After informed consent, but prior to initiation of study treatment, all AEs related to protocol-mandated procedures.
- After the first dose of study treatment, all AEs observed by the Investigator or reported by the participant that occur through 30 days after last dose of study treatment. Adverse events occurring after 30 days of last dose of study treatment will be reported until either 70 days after the last dose or until the initiation of new anticancer therapy (including SCT), whichever is earlier.

Details of adverse event reporting can be found in Section 7.2.

5.1.11. Concomitant Medications

All concomitant medications, including all prescription medications, over-the-counter medications, herbal supplements, and IV medications and fluids, taken by a participant within 30 days before the first dose of study treatment and while on study are to be documented. Changes in baseline concomitant medication information is to be collected after informed consent through the end of 70-day Safety Follow-up Period or until the initiation of new anticancer therapy (including SCT), whichever is earlier. 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.

5.1.11.1 COVID-19 Vaccine

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and magrolimab. There is no contraindication to the COVID-19 vaccine with magrolimab. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. 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 participants (receiving magrolimab/placebo + azacitidine therapy) 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. If participants are neutropenic, Investigators may use clinical judgment in determining the timing of the COVID-19 vaccine. Investigators should document vaccinations. Investigators should notify participants of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection in the source. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug(s).

5.2. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories at Screening are presented in Table 7. See Appendix F for ECOG assessment information.

Table 7. Laboratory Analyte Listing (To Be Performed at Screening)

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine Uric acid Total bilirubin Direct bilirubin Indirect bilirubin LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Neutrophils Eosinophils Basophils Lymphocytes Monocytes Reticulocytes Haptoglobin PT INR aPTT or PTT Peripheral blood smear	RBC Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity	Pregnancy Biomarker studies[a] Blood phenotyping or genotyping Type and screen (ABO/Rh), DAT Cytogenetics MRD[a] Hepatitis B and hepatitis C assessments: HBsAg, anti-HBc, HCV antibody; HBV DNA and HCV RNA as required HIV antibody

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; anti-HBc = antibody against hepatitis B core antigen; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; HBV = hepatitis B virus; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; 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 cells.
Note: Refer to Section 4.3 for collection time points.
a These assays will be performed at a central laboratory.

Analytes to be assessed by the local laboratory or specialty laboratories during the study are presented in Table 8.

Table 8. Laboratory Analyte Listing (To Be Performed During the Study)

Chemistry (Serum or Plasma)	Hematology	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Albumin Glucose BUN or urea Creatinine Total bilirubin Direct bilirubin Indirect bilirubin LDH[b] AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Platelets WBC Neutrophils Lymphocytes Reticulocytes Haptoglobin[b] Peripheral blood smear Peripheral blasts	Pregnancy Biomarker studies[a] Pharmacokinetics[a] Antidrug antibodies[a] Cytogenetics MRD[a]

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C2D1 = Cycle 2 Day 1; DAT = direct antiglobulin test; LDH = lactate dehydrogenase; MRD = minimal residual disease; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell.
Note: Refer to Section 4.3 for collection time points.
a These assays will be performed at a central laboratory.
b Please refer to Table 3 for LDH and Haptoglobin collection time points during treatment. Collection is not required after C2D1 unless participant is repriming.

5.3. Efficacy Assessments

Clinical response will be assessed using the guidelines in Appendix B, which are based primarily on IWG criteria {Cheson 2003, Cheson 2006}, as described in Appendix B.

Response assessments will be done in conjunction with bone marrow assessments, according to the Schedule of Assessments (Section 4.3). Accompanying laboratory results ± 2 weeks from the protocol-specified bone marrow efficacy assessment can be used to support an efficacy assessment of CR. Response assessments are scheduled on Day 1 of Cycles 3, 5, and 7 and then every 3 cycles thereafter during study treatment. These supporting laboratory results will be entered into the clinical database. Absolute neutrophil count, platelets, and hemoglobin, that reflect CR or PR per IWG 2006 criteria (hemoglobin ≥ 11 g/dL, platelets ≥ 100×10^9/L, neutrophil ≥ 1.0×10^9/L, peripheral blast = 0%; Appendix B) must be from CBCs collected on the same day. If a participant achieves a CR, subsequent bone marrow biopsies and response assessments are still required to be performed as per the Schedule of Assessments (Section 4.3).

Per Schedule of Assessments during the treatment period (Table 3, and Table 4), treatment cycles are associated with azacitidine dosing. Therefore if azacitidine is delayed, all assessments per Table 3 (e.g., bone marrow aspirate biopsy and MDS disease assessment) will also be delayed until resumption of azacitidine dosing.

Slides used for MDS disease response assessments may be collected by the Sponsor for CCI independent pathology 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. Response assessments should continue during long-term follow-up approximately every 8 weeks until transformation to AML is documented or start of new anticancer therapy, whichever comes first. For participants who come off the study treatment to receive an SCT, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate and CBC results will continue until documented relapse or progressive disease occurs. After documented relapse or progressive disease, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until transformation to AML occurs or start of new anticancer therapy, whichever comes first.

5.4. Pharmacokinetics

PK samples will be collected as described in Section 4.3, and evaluated for magrolimab concentrations. Serum magrolimab assessment will be done using a validated assay.

Azacitidine PK assessment may be conducted using residual samples used for magrolimab PK and ADA analysis. These samples may also be used for pharmacodynamics analyses related to magrolimab in combination with azacitidine. This could include using leftover serum for CCI alternative PK assay development and analysis.

5.5. Immunogenicity (Antidrug Antibodies)

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described in Section 4.3. When collected on the day of magrolimab/placebo dosing, the blood sample must be collected at the same time as the predose PK specimen. Neutralizing antibodies to magrolimab will also be assessed for samples that test positive for ADA.

5.6. Pharmacodynamics and Biomarker Assessments

5.6.1. Biomarker Blood Samples

Biomarker studies will be performed on peripheral blood samples to study the biological activity of magrolimab in combination with azacitidine. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating immune cells, quantification of circulating normal and tumor DNA levels, and other studies. Samples for biomarker studies in the peripheral blood will be collected per Section 4.3.

5.6.1.1. Measurement of Plasma Cytokines

Cytokine release by immune cells is one surrogate measure of immune cell activation (including T cells and macrophages). Since magrolimab activates both macrophages and T cells, it is hypothesized that a specific cytokine profile relating to immune cell activation will correlate with clinical response to therapy. Fluorescence-based platforms allow for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity {Swartzman 1999}. A predefined multiplex panel of human cytokines will be measured from a small thawed vial of plasma, detecting and quantifying the soluble proteins and peptides that help control cellular function. The observed systemic biochemical changes in the blood may provide a further correlate with tumor progression and therapeutic response and help provide a much broader understanding of disease. Cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be specifically interrogated.

5.6.1.2. Characterization of Circulating Immune Cells

In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation {Tseng 2013}. It is therefore predicted that magrolimab administration may lead to T-cell activation in participants. Peripheral blood samples will be collected, and T-cell activation/repression markers/studies may be performed by flow cytometry, mass cytometry, in vitro T-cell activation assays, and/or T-cell receptor sequencing. Additional peripheral blood mononuclear cells, serum, and plasma at the specified time points will also be cryopreserved and biobanked for CCI analyses.

5.6.2. Minimal Residual Disease Monitoring

Minimum residual disease monitoring has become a powerful prognostic factor that is beginning to play a central role in the treatment of participants with MDS and AML both in the pretransplant and posttransplant settings. In multiple large studies of newly diagnosed participants with MDS and AML, as well as in advanced MDS participants who achieved CR, MRD positivity posttherapy was an independent poor prognostic factor and a predictor of relapse {Buccisano 2012, Freeman 2013, Platzbecker 2018, Sievers 2003}. In a large prospective study of MRD monitoring in both MDS and AML who achieved CR and received postremission azacitidine, the 12-month relapse-free survival (RFS) for those who were MRD positive was 46% compared with 88% in participants who were MRD-negative. In another study of MDS participants who received hematopoietic SCT, participants who were MRD positive had a 1-year relapse rate of 35% compared with just 5% in the MRD-negative group {Pavlu 2019}. Several methods for MRD monitoring have been utilized in MDS, including 1) multiparameter flow cytometry for detection of aberrant hematopoietic surface antigens, 2) molecular monitoring of leukemia-specific mutational burden, and 3) cytogenetic monitoring of leukemia-associated chromosomal abnormalities.

Multiparameter flow cytometry will be utilized as the main method of MRD analysis and, when available, may be compared to molecular or cytogenetic approaches to MRD monitoring. Minimal residual disease testing by flow cytometry will be performed by a central laboratory, Hematologics, Inc., and incorporated for response assessments, where appropriate. This MRD assay is based on a "difference from normal" technique, which is based on correlating the quantitative expression of multiple cell surface antigens (gene products) in the specimens using standardized antibody panels. This approach identifies all the normal regenerating cells within the specimen first, subtracts them away, and then detects clusters of abnormal cells within the remaining data set. With the use of this technique, it is possible to define the precise composition of the specimen, identifying cells of all lineages and maturational stages as well as assessing specimen quality in addition to detecting and quantifying any abnormal cell population. The lower limit of detection is 0.02% and is performed in a College of American Pathologists/Clinical Laboratory Improvement Amendments licensed clinical laboratory.

MRD assessments in the bone marrow will be collected at the same time as the bone marrow efficacy response assessments, as outlined in Table 3.

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5.7. Discontinuation or Withdrawal

5.7.1. Permanent Discontinuation of Treatment

The participant's health and welfare are the primary consideration in any determination to discontinue study treatment. In general, participants are expected to remain on study treatment until at least completion of Cycle 6, but participants may decline to continue receiving study treatment at any time during the study, although they will continue follow-up study visits unless they withdraw completely from the study (Section 5.7.2).

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

- Disease progression (including treatment failure by IWG criteria or relapse after PR/CR), with confirmation in subsequent assessment at least 4 weeks apart (i.e., disease worsening compared with the previous assessment)
- Unacceptable toxicity
- Loss of clinical benefit
- Clinically significant change in the participant's status that precludes further treatment (e.g., pregnancy or other AEs)
- Participant request, with or without a stated reason
- SCT
- Investigator or treating physician decision in the absence of any of the above

This decision to discontinue study treatment would not require approval from the Sponsor/Medical Monitor. Participants who discontinue both magrolimab/placebo and azacitidine but continue in a response or are achieving clinical benefit will continue to be followed on study for response assessments to ascertain relapse and for long-term survival. If magrolimab/placebo is discontinued for reasons other than disease progression, treatment with azacitidine may continue with corresponding assessments until progression, toxicity, or death.

Although disease progression (including treatment failure by IWG criteria or relapse after PR/CR) is considered a sufficient reason for discontinuing a participant from study treatment, given the delayed treatment benefit commonly seen in immune therapies, the Investigator is advised to continue to treat the participant until the confirmation of disease progression through a subsequent response assessment at least 4 weeks apart (i.e., disease worsening compared with the previous assessment), or until the Investigator considers the study treatment to be no longer clinically beneficial to the participant or the change of disease state renders the participant unacceptable for further treatment in the judgment of the Investigator. All participants must be followed through completion of all study treatment.

Participants who discontinue study treatment are to return for an EOT Visit for evaluation of safety within 7 days of their last dose or the decision to end study treatment. In addition, participants are to have Safety Follow-up telephone calls 30 days (± 7 days) after their last dose of study treatment. Participants are also to have Safety Follow-up telephone calls 70 days (± 7 days) after their last dose of study treatment or initiation of new anticancer therapy, whichever is earlier. When a serious AE (SAE) or treatment-related AE is reported during the telephone call, the participant 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 participant begins another anticancer therapy.

All participants who discontinue study treatment will participate in long-term follow-up for disease response until documented transformation to AML or start of new anticancer therapy, whichever occurs first, unless the participant withdraws consent for such follow-up or withdraws completely from the study (Section 5.7.2).

For participants who come off the study treatment to receive an SCT, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate and CBC results will continue until documented relapse or progressive disease occurs. After documented relapse or progressive disease, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until transformation to AML occurs or start of new anticancer therapy, whichever occurs first. When considering SCT, note that no significant magrolimab-related transplant complications have been observed in participants who have achieved a response and undergone SCT in an ongoing magrolimab study in AML and MDS (Study 5F9005). However, a 4-week washout period for magrolimab is recommended prior to start of conditioning treatment for SCT.

All participants will be followed for survival, unless the participant explicitly indicates a desire to forego survival follow-up in writing to their study investigator, until death, withdrawal of consent, loss to follow-up, or study termination, whichever occurs first. For any participant who dies during this follow-up period, the immediate cause of death must be reported to the Sponsor. For participants who are lost to follow-up or withdraw consent, study staff may use public records (eg, public health records) to obtain information about survival status where allowable by local regulation.

The assessments to be performed at each of the posttreatment visits are listed in Table 5 and Table 6.

5.7.2. Withdrawal from Study

Participants have the right to withdraw completely from the study and end study data collection at any time and for any reason without prejudice to their future medical care. Participants may decline to continue receiving study treatment and/or other protocol-required therapies or procedures at any time during the study but are encouraged to continue follow-up study visits and study data collection per Section 4.3, if possible. The Investigator is to discuss with the participant the appropriate procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any participant from study participation.

Reasons for participant withdrawal from study participation may include, but are not limited to, the following:

- Death
- Withdrawal of consent
- Lost to follow-up
- Study termination

For participants who are lost to follow-up or withdraw consent, study staff may use public records (eg, public health records) to obtain information about survival status where allowable by local regulation.

5.7.3. Replacement of Participants

Given that the primary analysis will be conducted in an intent-to-treat (ITT) population, participants who are randomized will not be replaced.

5.7.4. Participants Lost to Follow-up

If the participant is lost to follow-up, efforts to obtain follow-up should be appropriately documented as such in the participant's source documentation. If repeated attempts (at least 3) to obtain follow-up for the participant by telephone are unsuccessful, then a certified letter should be mailed to the permanent home address informing the participant of the need for follow-up. If the participant does not respond after delivery of the certified letter, no further attempts to obtain follow-up will occur. For participants who discontinue from the study prior to completion of all protocol-required visits for study assessment or survival follow-up as described in Section 4.3, the Investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status.

5.8. Poststudy Care

Upon withdrawal from study treatment, participants will receive the care upon which they and their physicians agree. Participants will be followed for survival and AEs as specified in Table 5 and Table 6.

5.9. End of Study

All Participants: The end of the entire study for all participants is defined as the date on which the last participant remaining on study completes the last study visit/call or when the Sponsor decides to end the study. Gilead Sciences, Inc. reserves the right to terminate the study at any time for any reason (including safety).

Individual Participants: Participants are considered to have completed study participation altogether when they are no longer followed for disease progression (including treatment failure by IWG criteria or relapse after PR/CR), transformation to AML, or survival.

6. STUDY TREATMENT

6.1. Description of Products

The active pharmaceutical ingredient of magrolimab is Hu5F9-G4 (GS-4721), a humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser Pro substitution in the hinge region (position 228) of the heavy chain to reduce Fab-arm exchange. It comprises a disulfide linked glycosylated tetramer consisting of 2 identical 444 amino acid heavy gamma chains and 2 identical 219 amino acid kappa light chains. Magrolimab targets the human CD47 antigen. Magrolimab drug product is a sterile, clear, colorless, preservative-free liquid intended for IV infusion.

Azacitidine is a nucleoside metabolic inhibitor. Azacitidine is a white to off-white solid supplied in a sterile form for reconstitution as a suspension for SC injection or (in the US only) reconstitution as a solution with further dilution for IV infusion.

Table 9 provides a summary of the study treatment in this study.

Table 9. Investigational Interventions Used in This Study

Product	Section	Dose and Frequency	Route	Duration	Manufacturer
Magrolimab (Hu5F9-G4) (GS-4721)	6.2	**Priming Dose**: • 1 mg/kg on Days 1 and 4 • 15 mg/kg on Day 8 • 30 mg/kg on Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50) **Maintenance Dose**: • 30 mg/kg on Day 57 and 30 mg/kg every 2 weeks thereafter	IV	Until progression, relapse, loss of clinical benefit, or unacceptable toxicities	Gilead Sciences, Inc.
Placebo (saline)	NA	Mirrors magrolimab dosing schedule	IV	Until progression, relapse, loss of clinical benefit, or unacceptable toxicities	Provided by site
Azacitidine	6.3	28-day cycles: 75 mg/m^2 IV or SC[a] on Days 1–7 (or Days 1–5, 8, and 9)	SC or IV[a]	At least 6 cycles and until progression, relapse, loss of clinical benefit, or unacceptable toxicities	Marketing Authorization Holder, NDA

Abbreviations: IV = intravenous; NA = not applicable; NDA = new drug application; SC = subcutaneous.
a Azacitidine will be administered according to region-specific drug labeling.

6.2. Magrolimab Formulation, Storage, Preparation, and Handling

Magrolimab is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at a pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.

CCI [redacted]

Additional details about magrolimab are provided in the Pharmacy Manual.

6.3. Azacitidine Formulation, Storage, Preparation, and Handling

Single-use vials of azacitidine contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder.

CCI [redacted]. Additional details about azacitidine are provided in the Pharmacy Manual.

6.4. Dosing and Administration

The following magrolimab dosing regimen is proposed for this study:

- Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11 and 15; and then 30 mg/kg weekly for a total of 5 doses (on Days 22, 29, 36, 43, and 50).
- Maintenance doses of magrolimab will be 30 mg/kg on Day 57 and 30 mg/kg every 2 weeks thereafter.

Placebo will be administered as follows:

- Mirror the magrolimab dosing schedule above.

Azacitidine will be dosed according to region-specific drug labeling, either SC or IV, at the standard clinical dose of 75 mg/m^2 on Days 1 to 7 of a 28-day cycle in combination with magrolimab/placebo. Azacitidine may be administered on an alternative schedule of Days 1 to 5, Day 8, and Day 9 of a 28-day cycle for flexibility and convenience.

Participants should be premedicated in accordance with Section 6.5. Magrolimab, placebo, and azacitidine should be prepared as outlined in the Pharmacy Manual for the study.

The dose of each study treatment 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 weight from baseline. Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines. In the event that a dose is modified due to a > 10% weight change, the weight on which the new dose is based, will become the new baseline weight.

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

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 prescribing information references for detailed instructions for preparation and administration).

The duration of each magrolimab/placebo infusion including flush will be 3 hours (± 30 minutes) for the 3 doses of treatment, 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.

The first dose of magrolimab/placebo should be administered within 72 hours after randomization. Magrolimab/placebo doses will be given twice weekly during priming and escalation (2 weeks), with a window of ± 3 days for each dose; however, magrolimab/placebo doses are not to be given on consecutive days. If additional delay is needed to ensure a WBC of $\leq 20 \times 10^3/\mu L$, please contact the Sponsor's Medical Monitor.

During the first 28 days of treatment (Day 1, Day 4, Day 8, Day 11, Day 15, and Day 22), WBC count must be $\leq 20 \times 10^3/\mu L$ prior to each magrolimab dose. Participants with WBC $> 20 \times 10^3/\mu L$ can be treated with hydroxyurea (up to 4 g/day) throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$. Oral etoposide (up to 200 mg orally per day) may be given as an alternative to hydroxyurea for participants who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.

Within 24 hours prior to each of the first 2 doses of magrolimab/placebo infusion, all participants must have a documented hemoglobin ≥ 9 g/dL. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to each of the first 2 doses of magrolimab/placebo. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab/placebo during initial treatment. The participant should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in participants with symptoms of anemia or increased risk for complications of anemia.

All participants should be monitored hourly during infusion and for 1 hour after infusion for doses during the first 28 days and the repriming doses. Participants should be monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion-related reactions, which have been observed in previous magrolimab studies.

Postinfusion monitoring is not required for doses after Day 22. Participants who experience any treatment-related AEs during the observation period should be further monitored as clinically appropriate. Management of infusion-related reactions is further described in Section 7.10.1.2.

Participants may continue study treatment until they show evidence of disease progression (including treatment failure by IWG criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicity (further details about treatment discontinuation in Section 5.7.1).

Repriming for Magrolimab

Given the large CD47 antigen sink on normal cells, participants who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink.

Repriming differs depending on where the participant is in their treatment period as follows:

1) For participants who have not reached Day 57 of magrolimab/placebo, a 2-week dose delay is permitted.
2) For participants who have received Day 57 (or beyond) of magrolimab/placebo, a 4-week dose delay is permitted.

The repriming cycles are stand-alone cycles. After Day 22 of the repriming cycle, participants should return to their original dose schedule. Table 6 illustrates the repriming magrolimab dosing regimen and schedule of assessments.

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. In the event that a dose is modified due to a > 10%, weight change, the weight on which the new dose is based, will become the new baseline weight.

Please notify the blinded Medical Monitor of any planned dose delays. If either magrolimab or azacitidine is dose delayed for > 8 weeks for any reason, the Investigator must consult with the Sponsor's Medical Monitor prior to reinitiating study treatment.

6.5. Premedication

Premedication is required prior to the administration of the first 4 doses of magrolimab/placebo and in case of repriming. Premedication during subsequent infusions may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent infusions is required (Section 7.10.1).

Recommended premedications are oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 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.

6.6. Neutropenic Fever Prophylaxis

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

6.7. Dose Modification and Delays

6.7.1. Magrolimab/Placebo

6.7.1.1. Dose Modifications

In clinical experience with magrolimab, no significant dose-dependent toxicities have been identified. Therefore, in general, dose modifications to magrolimab/placebo should not be made. In rare circumstances, the dose of magrolimab/placebo may be reduced for ≥ Grade 3 AEs that are deemed clearly related to magrolimab/placebo and not azacitidine and that do not resolve to ≤ Grade 2 or baseline value within 14 days of onset. However, dose delay of magrolimab/placebo should occur first, and if the AE does not resolve, then a magrolimab/placebo dose reduction can be considered. Please notify the blinded Medical Monitor of any planned dose delays. If a magrolimab/placebo dose reduction is considered, an initial 33% dose reduction (from 30 to 20 mg/kg) should be done first. If no improvement is observed within at least 28 days, further magrolimab/placebo dose reductions from 20 to 15 mg/kg may be warranted. For persistent bone marrow hypocellularity or peripheral cytopenias (where both azacitidine and magrolimab/placebo may have a contribution), the dose of azacitidine should be reduced (see Section 6.7.2.2). Participants can re-escalate to higher doses of magrolimab/placebo up to the original 30 mg/kg dose if AEs improve, after discussion with the Sponsor's Medical Monitor.

For dose modification for > 10% change in body weight, see Section 6.4.

6.7.1.2. Treatment Delays

A treatment delay is defined as a non–protocol-specified interruption from treatment.

Treatment with magrolimab/placebo may be withheld if a ≥ Grade 3 magrolimab/placebo-related AE occurs that does not resolve to ≤ Grade 2 or baseline value within 14 days of onset. Magrolimab/placebo dosing may also be delayed for participants who experience hospitalization due to an AE that may preclude safe administration of magrolimab/placebo (e.g., intensive care unit admissions, significant bleeding events, severe infections, or other such events). In general, magrolimab/placebo should be continued/restarted without dose reduction. A dose delay for up to 3 days during the first 28 days may be permissible if the participant's WBC count is $> 20 \times 10^3/\mu L$ (applicable to each dose in the first 28 days: Day 1, Day 4, Day 8, Day 11, Day 15, and Day 22), to allow for oral hydroxyurea or etoposide treatment to reduce the WBC count. Magrolimab/placebo dosing may be delayed for AEs; however, starting at maintenance dose, dose delays of up to 4 weeks for other reasons may be allowed at the discretion of the Investigator and Sponsor. Participants with a treatment delay of longer than 4 weeks must undergo intraparticipant dose escalation (repriming; see Table 6 and Section 6.4) again.

Ongoing data analysis across magrolimab + azacitidine trials show that Q2W dosing of magrolimab without significant dose delays is important to yield optimal efficacy. In the event that dose delay is considered due to azacitidine related-toxicities (e.g., cytopenias) or other scenarios, magrolimab/placebo dosing should proceed as per Schedule of Assessment for treatment period - Magrolimab dosing (Table 4). Magrolimab/placebo dose may be delayed in case of serious adverse events or adverse events clearly related to magrolimab/placebo; in the event of magrolimab/placebo delay, dosing should resume as soon as it is clinically appropriate and logistically possible, without waiting to align with the participants' original Q2W schedule.

Magrolimab dosing is anticipated to coincide with azacitidine dosing. However, in the event that magrolimab dosing is decoupled from azacitidine dosing, please refer to Table 4 for assessments to be performed during the treatment visit with magrolimab dosing. Of note, in addition to assessments such as vital signs and symptom-directed physical examinations, collection of PK, ADA and peripheral blood samples for biomarker studies, in addition to other assessments specified in the Schedule of Assessments should always coincide with magrolimab dosing at time points specified in Table 4.

If either magrolimab or azacitidine is dose delayed for > 8 weeks for any reason, the Investigator must consult with the Sponsor's Medical Monitor prior to reinitiating study treatment.

If nonemergency surgical procedures are needed for participants on study treatment, magrolimab/placebo will be delayed and restarted in accordance with Table 10.

Table 10. Magrolimab/Placebo Dosing Guidance for Surgical Procedures on Study

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

Abbreviations: CNS = central nervous system

Finally, please notify the blinded Medical Monitor of any planned dose delays for magrolimab.

6.7.2. Azacitidine

Treatment delay of azacitidine may not occur for participants in the initial 28-day period (Cycle 1).

6.7.2.1. Treatment Delays

After the initial 28-day period, in the absence of MDS disease (as defined in Section 6.7.2.2.1), if hematologic toxicity is observed following azacitidine treatment, the next cycle of treatment should be delayed until platelets are ≥ 50 × 10^9/L and neutrophils are ≥1.0 × 10^9/L or if blood counts are improving from nadir or baseline. If recovery is achieved within 14 days, no dose adjustment is needed. However, if recovery is not achieved within 14 days, the dose should be reduced according to the azacitidine dose modification guidelines in Section 6.7.2.2.1.2. For nonhematologic AEs ≥ Grade 3 that do not resolve to ≤ Grade 2 or baseline value, dosing will be delayed up to 14 days from onset. If recovery is achieved within 14 days, no dose adjustment is needed. However, if recovery is not achieved within 14 days, the dose should be reduced according to the azacitidine dose modification guidelines in Section 6.7.2.2.3. Following dose modifications, the cycle duration should return to 28 days. Azacitidine dosing may also be delayed for participants who experience hospitalization due to an AE that may preclude safe administration of azacitidine (e.g., intensive care unit admissions, significant bleeding events, severe infections, or other such events).

If ≤ 2 doses of azacitidine are missed during the 7-day dosing period, dosing should continue so that the participant 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.

6.7.2.2. Dose Modifications

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

Dose modifications described below are in accordance with the azacitidine prescribing information references, with 1 notable exception: while the US prescribing information allows for dose escalation to 100 mg/m^2 after the first 2 cycles, an azacitidine dose of 75 mg/m^2 is planned throughout this study for both treatment arms. Azacitidine dose increases above 75 mg/m^2 are not allowed. Dose modification guidance for azacitidine should be followed identically for both the experimental and control arms.

6.7.2.2.1. Dose Modification due to Hematologic Toxicity

6.7.2.2.1.1. Dose Modification in the Presence of MDS Disease

Treatment with azacitidine is associated with anemia, neutropenia, and thrombocytopenia. Thus, CBCs will be performed as described in the schedules of assessments and as needed to monitor toxicity. Importantly, these cytopenias are often a result of underlying hematological disease. It is thus critical to distinguish between cytopenias due to azacitidine compared to underlying disease, so as to not limit potential treatment benefit. Hematologic cytopenias in the presence of MDS disease are not defined as hematologic toxicities.

In accordance with this distinction, the dose of azacitidine will not be reduced if hematologic cytopenias are observed in the presence of MDS disease, defined by any of the criteria below:

- > 5% blasts in the bone marrow
- circulating blasts

Nonhematologic toxicities may require dose modifications independent of the presence of MDS disease, given the clearer distinction of these toxicities relating to azacitidine as opposed to effects of MDS. Dose modifications for hematologic toxicity, decreased bone marrow cellularity, and nonhematologic toxicities are described in the sections below.

6.7.2.2.1.2. Dose Modifications Due to Hematologic Toxicity in the Absence of MDS Disease

Azacitidine should be dose modified or delayed for hematologic toxicities without evidence of MDS disease (defined in Section 6.7.2.2.1).

If hematologic toxicity is observed following azacitidine treatment, the next cycle of therapy should be delayed for up to 14 days until the platelet count and the ANC have improved. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery is not achieved within 14 days (Day 42 of the cycle), the dose should be reduced according to Table 11 and Table 12. Following dose modifications, the cycle duration should return to 28 days. Participants with a dose reduction will be reassessed after 2 additional cycles per protocol. For participants with persistent cytopenia (as defined in Table 11 and Table 12), treatment should be delayed for up to 14 days (Day 42 of the cycle); if counts have recovered, no further dose modification is needed. If counts have not recovered, then a further dose reduction is recommended, in accordance with Table 11. The reduced dose should be maintained during subsequent cycles unless further toxicity develops (defined in Table 11 as further occurrences). Azacitidine may be re-escalated back to a higher dose if toxicities have improved.

Separate dose modifications for hematologic toxicity are provided in Table 11 for participants who do not have reduced blood counts at baseline (ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L) and who have reduced baseline blood counts (ANC $< 1.5 \times 10^9$/L or platelets $< 75 \times 10^9$/L).

Table 11. Azacitidine Dose Modification for Participants With and Without Cytopenia in the Absence of MDS

Nadir Counts			% Dose in the Next Cycle if Recovery[a] Is Not Achieved Within 14 Days
ANC (× 10^9/L)		Platelets (× 10^9/L)	
Dose Modification for Participants Without Reduced Blood Counts (ANC ≥ 1.5 × 10^9/L and Platelets ≥ 75 × 10^9/L)			
First occurrence			
≤ 1.0	or	≤ 50.0	67% (50 mg/m^2)
Second occurrence[b]			
≤ 1.0	or	≤ 50.0	50% (37.5 mg/m^2)
Third occurrence[b]			
≤ 1.0	or	≤ 50.0	33% (25 mg/m^2)
Dose Modification for Participants with Reduced Blood Counts (ANC < 1.5 × 10^9/L or Platelets < 75 × 10^9/L)			
First occurrence			
< 0.5[c]	or	< 25[c]	67% (50 mg/m^2)
Second occurrence[b]			
< 0.5[c]	or	< 25[c]	50% (37.5 mg/m^2)
Third occurrence[b]			
< 0.5[c]	or	< 25[c]	33% (25 mg/m^2)

Abbreviation: ANC = absolute neutrophil count; MDS = myelodysplastic syndrome.
a Recovery is defined as a ≥ 25% recovery in the nadir count.
b After initial dose reduction, participants will be reassessed after 2 additional cycles per protocol, and if persistent cytopenias are observed, a further dose reduction of azacitidine should be considered as outlined.
c No dose adjustment is needed if the baseline blood counts are below an ANC < 0.5 × 10^9/L and/or platelets < 25 × 10^9/L.

Following dose modifications, the cycle duration should return to 28 days.

6.7.2.2.2. Dose Modifications Due to Decreased Bone Marrow Cellularity in the Absence of MDS Disease

Azacitidine alone or in combination with magrolimab may result in a decrease in bone marrow cellularity. No dose modification is required if a decrease in bone marrow cellularity is observed without reduced peripheral blood counts or if MDS disease is still observed (as defined in Section 6.7.2.2.1). If hypocellularity AND reduced peripheral blood counts are observed, then the azacitidine dose should be modified in accordance with the instructions in Table 12.

Table 12. Azacitidine Dose Modification: Participants with Reduced Bone Marrow Cellularity and Reduced Peripheral Blood Counts in the Absence of MDS

Bone Marrow Cellularity	Azacitidine Dose Instruction if Recovery[b] Is Not Achieved Within 14 Days			
	First Occurrence	Second Occurrence	Third Occurrence	Recovery[b]
≥ 50% decrease from baseline with a cellularity < 30% in the presence of reduced peripheral blood counts[a] OR Decrease to < 15% cellularity with a baseline cellularity > 20% in the presence of reduced peripheral blood counts[a]	Dose reduce azacitidine to 50 mg/m^2 administered Days 1–7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity after 2 cycles.	Dose reduce azacitidine to 37.5 mg/m^2 administered Days 1–7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity after 2 cycles.	Dose reduce azacitidine to 25 mg/m^2 administered Days 1–7 per cycle AND Repeat bone marrow biopsy to assess bone marrow cellularity within 2 cycles. Upon reassessment after 2 cycles, if reduced cellularity persists, then decrease azacitidine dose to 25 mg/m^2 on Days 1–5 per cycle and reassess bone marrow cellularity after 2 cycles.	Continue at current azacitidine dose. For subsequent cycles, the azacitidine dose can be escalated up to the next highest dose (i.e., escalate to 75 mg/m^2 if initially dose reduced to 50 mg/m^2; escalate to 50 mg/m^2 if previously dose reduced to 37.5 mg/m^2; or escalate to 37.5 mg/m^2 if previously dose reduced to 25 mg/m^2). AND Repeat bone marrow biopsy to assess bone marrow cellularity at the next protocol-defined bone marrow assessment.

Abbreviation: ANC = absolute neutrophil count; MDS = myelodysplastic syndrome

a Reduced peripheral blood counts are defined as ANC < 0.5 × 10^9/L and platelets < 25 × 10^9/L in the absence of MDS disease (i.e., < 5% bone marrow blasts).

b Recovery in bone marrow cellularity is defined as an increase in bone marrow cellularity ≥ 25% from the nadir, increase in bone marrow cellularity to ≥ 15%, or improvement of peripheral blood counts to ANC > 0.5 × 10^9/L and platelets > 25 × 10^9/L.

Following dose modifications, the cycle duration should return to 28 days.

6.7.2.2.3. Dose Modifications Due to Nonhematologic Toxicity Irrespective of Presence of MDS Disease

Renal abnormalities ranging from elevated serum creatinine to renal failure have been reported with rare frequency in participants 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 other azacitidine-related nonhematologic toxicities 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 13.

Table 13. Azacitidine Dose Modification: Nonhematologic Toxicities

Toxicity	Azacitidine Dose Instruction if Recovery[a] is Not Achieved within 14 Days		
	First Occurrence[b]	**Second Occurrence[b]**	**Third Occurrence[b]**
Grade 3 or higher nonhematologic adverse event	Dose reduce azacitidine 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.	Dose reduce azacitidine 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.	Dose reduce azacitidine 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 back to baseline level.

Following dose modifications, the cycle duration should return to 28 days. Please notify the blinded Medical Monitor of any planned dose delays.

6.8. Treatment Assignment and Bias Minimization

This is a multicenter, randomized, double-blind study. Participants who successfully complete screening will be randomized and receive either magrolimab + azacitidine (experimental arm) or azacitidine + placebo (control arm).

6.8.1. Treatment Allocation

Treatment allocation/randomization will occur centrally using an IXRS. Participants will be assigned randomly in a 1:1 ratio to either the experimental arm or the control arm.

6.8.2. Randomization Strategy and Procedure

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

Geographic region (US versus ex-US sites)

Baseline cytogenetic risk (very good/good/intermediate versus poor/very poor versus unknown) according to IPSS-R {Greenberg 2012}

Baseline bone marrow blast percentage (≥ 10% versus < 10%)

6.8.3. Extent and Maintenance of Blinding

This is a double-blind study. Azacitidine will be administered in both treatment arms. Magrolimab and azacitidine will be administered in the experimental arm. For the control arm, azacitidine + placebo will be administered. During the study, the Investigators, treatment teams, the participants, study management team, and all personnel directly involved in the conduct of the study or data cleaning will remain blinded to treatment assignment unless the criteria for unblinding at the interim analyses are met (see Section 8.3.1 and Section 8.3.2), with the exception of specified personnel who may be unblinded based on their study role as described below:

- The pharmacists at each site who prepare magrolimab or saline placebo will be unblinded to the treatment assignment and will keep this information confidential from the participants, Investigators, treatment teams, and the Sponsor's study team members or their designees (excluding the designated unblinded site monitors for investigational product accountability).

- An unblinded Medical Monitor is available to provide consultation on protocol deviations with respect to magrolimab dosing.

- Designated members of Gilead Clinical Operations who serve as liaison in communication between the Sponsor study team and the designated unblinded contract research organization (CRO) personnel (unblinded site monitors and unblinded trial managers) with respect to investigational drug management and Gilead oversight of CRO activities will be unblinded.

- The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management who facilitates the data transfer of PK files between Gilead and vendors will remain unblinded. The personnel handling RO data will also be unblinded.

- Individuals in Pharmaceutical Development and Manufacturing who have an Unblinded Inventory Manager role in the IXRS for purposes of study drug inventory management will remain unblinded.

- Individuals in Global Patient Safety who are responsible for safety signal detection, investigational new drug safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries.

- The data monitoring committee (DMC) and the independent biostatistician and statistical programmers from an independent data coordinating center (IDCC) who are responsible for preparing interim tables, listings, and graphs for DMC review remain unblinded. Controlled access to the unblinded data are described in the DMC Charter.

- The laboratories that will store and/or analyze blood samples for conducting PK, ADA, and RO analysis will be unblinded.

- The external vendor who conducts the PK/ADA merge with clinical data will be unblinded. In addition, the vendor who performs the population PK and exposure response analysis may be unblinded, if needed.

- Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting quality assurance activities and/or regulatory agency inspections.

In the event of a medical emergency that requires breaking the blind to provide medical care to the participant, the Investigator may obtain treatment assignment directly from the IXRS for that participant. Gilead recommends, but does not require, that the Investigator contact the Gilead Medical Monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine the participant's emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Gilead Medical Monitor promptly if any treatment unblinding occurs.

Data that may potentially unblind the treatment assignment (e.g., study drug plasma concentrations) will be handled with special care to ensure that integrity of the blind is maintained and the potential for bias is minimized. This may include making special provisions, such as segregating the data in question from view by the Investigators, study team, or their designees as appropriate until the study unblinding for the primary analysis.

6.9. Prior and Concomitant Medications and Therapies

6.9.1. Prohibited Therapies

Antileukemic therapies, including chemotherapy (with the exception of hydroxyurea or oral etoposide), targeted therapies, and immunotherapy, are not permitted while participants are on study treatment.

6.9.2. Permitted Therapies

Premedication, as described in Section 6.5, is permitted while on study treatment. Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates RANKL inhibitors are permitted. Red blood cell and platelet transfusions are permitted during Screening and prior to randomization to ensure adequate hemoglobin level. Blood transfusions are also permitted during the study as clinically indicated for management of cytopenias. On-study blood transfusion should be reported in the dedicated transfusion eCRF. Hydroxyurea (up to 4 g/day) can be used throughout the study to reduce the WBC to $\leq 20 \times 10^3/\mu L$. Oral etoposide (up to 200 mg orally per day) may be given as an alternative to hydroxyurea for participants who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea. In nonclinical studies, coadministration 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 participants. 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 participants who have received concomitant magrolimab and hydroxyurea or magrolimab, azacitidine, and hydroxyurea.

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

6.10. Accountability for Investigational Medicinal Product

The unblinded pharmacists at each site are responsible for ensuring adequate accountability of all used and unused study drug (vials, etc.). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to participants 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 (vials, etc.)
- The date, participant 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

6.10.1. 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 on 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 designated unblinded site monitors will review study drug supplies and associated records at periodic intervals as per the unblinded Study Monitoring Plan.

7. SAFETY MONITORING

7.1. Definitions

- **Adverse event** – An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol imposed intervention, regardless of attribution. This includes the following:

  — Adverse events not previously observed in the participant that emerge during the protocol-specified AE reporting period.

  — Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures, such as biopsies) that are assessed as related to protocol-mandated interventions. These include events that occur prior to administration of study treatment, which would otherwise be considered non-AEs.

  — Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

- **Serious adverse event** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

  — Death (For deaths attributed solely to MDS disease progression, please refer to Section 7.2.5.)

  — A life-threatening AE (An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)

  — Inpatient hospitalization or prolongation of existing hospitalization

  — A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  — A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment

  — Important medical events that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 5.0); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on event outcome or action criteria usually associated with events that pose a threat to a participant’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

Table 14. Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event	Death related to adverse event.

Source: NCI CTCAE, Version 5.0 (Appendix A)
Abbreviations: ADL = activities of daily life; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
a Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing.

7.2. Documenting Adverse Events

A consistent methodology of nondirective questioning for eliciting AEs at all participant evaluation time points should be adopted. Examples of nondirective questions include the following:

- “How have you felt since your last clinic visit?”
- “Have you had any new or changed health problems since you were last here?”

Investigators should use correct medical terminology/concepts when recording AEs and SAEs. Avoid colloquialisms and abbreviations.

A separate log line in the Adverse Event eCRF should be used for each medical concept that needs to be recorded. Causal relationship of AEs and SAEs attributed to study treatment should be recorded individually.

The Investigator is responsible for ensuring that all AEs (including SAEs) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with protocol instructions. Serious adverse events must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event.

7.2.1. Classification of Adverse Events

Seriousness, causality, and severity – Investigators will seek information on AEs and SAEs at each participant contact. All AEs and SAEs, whether reported by the participant or noted by authorized study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF. For each AE and SAE, the Investigator will make an assessment of seriousness, severity (Table 14), and causality (Table 15). For each AE and SAE, causal relationship to magrolimab/placebo and azacitidine will be assessed, as applicable. The AE grading (severity) scale NCI CTCAE, Version 5.0 (Appendix A) will be used for AE reporting as shown in Table 14. Regardless of severity, some events may also meet regulatory serious criteria (Section 7.1).

To ensure consistency of causality assessments for either study drug, Investigators should apply the following general guidelines:

Table 15. Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES /Related	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, **AND** other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO /Not Related	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Abbreviations: AE = adverse event; SAE = serious adverse event.
Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, Gilead Sciences, Inc. will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

7.2.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded as the AE term on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

7.2.3. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE on the Adverse Event eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the Adverse Event eCRF.

7.2.4. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between participant evaluation time points. Such events should only be recorded once in the Adverse Event eCRF unless their severity changes. If a persistent AE increases or decreases in severity, it should be recorded again on the Adverse Event eCRF with each change in CTCAE grade.

A recurrent AE is one that occurs and resolves between participant evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF each time they recur.

7.2.5. Deaths

Death that is attributed by the Investigator as solely due to progression of MDS, and that occurs during the protocol-specified AE reporting period (Section 7.7) should be recorded only on the Death eCRF (i.e., not collected as an SAE on the Adverse Event eCRF). All other deaths (i.e., deaths that are not due to MDS progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the Adverse Event eCRF and reported within 24 hours of awareness and no later than the next business day.

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

7.2.6. Worsening of Disease

Events that are considered to represent the expected pattern of worsening or progression of the underlying MDS should not be recorded as AE/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 must be reported as an AE/SAE.

7.2.7. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

The following hospitalization scenarios do not require reporting as an SAE unless there is the occurrence of an AE meeting a seriousness criterion other than "hospitalization/prolonged hospitalization":

- Hospitalization to perform an efficacy measurement for the study
- Hospitalization to undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Hospitalization to receive scheduled therapy for the target disease of the study
- Hospitalization for social reason (e.g., respite care, waiting for insurance authorization)

7.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

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

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, participant, 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 participant.

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 which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the Investigator has reason to suspect that the participant 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 where the results are judged to be desirable and beneficial.

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

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

7.4. Clinical Laboratory Findings

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the Adverse Event eCRF (e.g., laboratory abnormalities that require study treatment dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE on the Adverse Event eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality that require active management from visit to visit should not be repeatedly recorded as AEs or SAEs on the Adverse Event eCRF, unless their severity, seriousness, or etiology changes.

7.5. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all participants.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the participant may be discontinued from the study treatment if the Investigator determines that it is not in the participant'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 Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health and Human Services 2009} as:

- Treatment-emergent ALT or AST elevation (≥ 3 × ULN), AND
- Treatment-emergent total bilirubin elevation (> 2 × ULN), and absence of cholestasis (defined as alkaline phosphatase < 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).

7.6. Pregnancy

Female participants who become pregnant during the treatment period must stop the study treatment and inform the Investigator immediately.

Any pregnancy occurring in a participant during treatment with either study treatment or within 6 months of last study treatment administration must be reported to the Sponsor or designee per Section 7.8.2.3 by the Investigator or designee within 24 hours of the Investigator/site staff becoming aware of it.

7.7. Investigator Requirements and Instructions

7.7.1. 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 regardless of cause or relationship and any adverse events related to protocol-mandated procedures.

7.7.2. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, will be collected until 30 days after last administration of study drug and reported on the eCRFs as instructed. Adverse events occurring more than 30 days after the last dose of study drug will be reported until 70 days after the last dose of study drug or until the initiation of new anticancer therapy (including SCT), whichever is earlier.

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.

7.7.3. Serious Adverse Events

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

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 70 days of the last dose of study drug or until the initiation of new anticancer therapy (including SCT), whichever is earlier, regardless of causality, should also be reported (Refer to Section 7.2.5 for death attributed to progression of MDS).

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 GLPS.

Instructions for reporting SAEs are described in Section 7.8.1.

7.7.4. Study Drug Special Situation 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 GLPS (Section 7.8.2) Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.8.1).

7.7.5. Concomitant Therapy Reports

7.7.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug) that occurs after the participant first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.8.2.1).

7.7.5.2. 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.

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

7.8.1. 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 participant identification, maintaining the traceability of a document to the participant 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 on the concomitant medication section of the participant's eCRF and the SAE narrative section of the SAE Report Form eCRF.

7.8.1.1. 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 GLPS 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 GLPS
  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 GLPS.

7.8.2. Special Situations Reporting Process

7.8.2.1. Paper Special Situations Reporting Process for Study Drug

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

  Gilead GLPS
  Email: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

7.8.2.2. Reporting Process for Gilead Concomitant Medications

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

  Gilead GLPS
  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.

7.8.2.3. Pregnancy Reporting Process

- The Investigator should report pregnancies in female participants that are identified after initiation of study drug and throughout the study, including the follow-up period, to Gilead GLPS 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 GLPS
  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 (e.g., 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 7.8.1. 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 7.8.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead GLPS.

- The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead GLPS 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 GLPS. Gilead GLPS contact information is as follows:

  Email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

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

7.9. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union (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 (SADRs), or 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.

To minimize the possibility of exposing study participants to unusual risk, the safety information from this study will also be reviewed periodically by the DMC. The DMC may have access to partially blinded or unblinded data and will make recommendations regarding the study according to the DMC charter (Section 10.1.1).

7.10. Specific Safety Management Guidelines

7.10.1. Magrolimab/Placebo

7.10.1.1. Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBC 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 participant will receive magrolimab.

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL that is observed in the first 1 to 2 weeks of treatment. This decrease in hemoglobin level is acceptable in participants with no other significant diseases or medical conditions. However, for participants with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, complications from treatment-related anemia could be life-threatening or fatal. Significant drops (2 to 3 g/dL or higher) have been observed in early doses.

Within 24 hours prior to each of the 2 first doses of magrolimab/placebo infusion during initial treatment, all participants must have a documented hemoglobin ≥ 9 g/dL. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum hemoglobin threshold prior to each of the first 2 doses of magrolimab/placebo infusion.

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

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

For Participants After Exposure to 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 participant should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in participants with symptoms of anemia or increased risk for complications of anemia.

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 participants will not be required for this study.

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

For emergency transfusions, the blood transfusion centers may consider using emergency Group O RBCs 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}.

7.10.1.2. Management of Infusion-related Reactions

Infusion-related reactions are defined by the NCI CTCAE, Version 5.0 (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances" (Appendix A). For the purposes of this study, the time frame for infusion-related reaction assessment is the 24-hour period beginning from the start of the infusion. Premedication use described in Section 6.5 will be used to manage infusion-related reactions preemptively.

Recommendations for the management of infusion-related reactions are provided below.

- For Grade 1 infusion-related reactions, described as mild transient reaction, infusion interruption is not indicated and intervention not indicated:

— Remain at bedside and monitor participant until recovery from symptoms.

- For Grade 2 infusion-related reaction, infusion interruption is indicated, but participant responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids), and prophylactic medications are indicated for ≤ 24 hours:

— Stop the magrolimab/placebo infusion, begin an IV infusion of normal saline, and consider treating the participant with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg of oral acetaminophen.

— Remain at bedside and monitor participant 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 participant closely.

— If symptoms recur, stop infusion and disconnect participant from the infusion apparatus. No further magrolimab will be administered at that visit.

— Premedications should be considered before any future infusions.

— The amount of magrolimab infused must be recorded on the eCRF.

— Participants who experience a Grade 2 infusion-related reaction during the postinfusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 infusion-related reaction, where Grade 3 is described as prolonged infusion-related reactions (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) and Grade 4 is described as having life-threatening consequences and where urgent intervention is indicated.

  — Immediately discontinue infusion of magrolimab.

  — Begin an IV infusion of normal saline, and consider treating the participant 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 participant should be monitored until the Investigator is comfortable that the symptoms will not recur.

  — Participants who have Grade 4 infusion-related reactions occurring with the first dose (priming dose) will be permanently discontinued from study treatment.

  — Participants who experience Grade 3 or 4 infusion-related reactions must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.

  — Participants who receive premedication and still experience a Grade 3 or 4 infusion-related reaction will be permanently discontinued from the study treatment.

  — For anaphylaxis, Investigators should follow their institutional guidelines for treatment.

  — All participants with Grade 3 or greater infusion-related reactions will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

7.10.1.3. 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.

7.10.1.4. Management of Pneumonitis

Pneumonitis has been infrequently observed in participants 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 noninflammatory causes (e.g., infections, etc.). If a noninflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging, e.g. chest x-ray or computed tomography, and pulmonary consultation.

- Management of potential pneumonitis is detailed in Table 16 and follows American Society of Clinical Oncology guidelines for immune-related adverse events {Brahmer 2018}. Participants who experience Grade 3-4 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 reimaging with CT in 3-4 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 2-3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Reimage every 1-3 days. If improving to baseline, taper corticosteroids over 4-6 weeks and resume magrolimab therapy per protocol. If no clinical improvement after 48-72 hours or worsening, treat as Grade 3-4.
Grade 3-4 Severe new symptoms; new/ worsening hypoxia; life-threatening.	Discontinue magrolimab therapy. Hospitalize. Pulmonary and infectious disease consults. 1-2 mg/kg/day methylprednisolone IV or IV equivalent. Add empirical antibiotics and consider prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improving to baseline, taper corticosteroids over 4-6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

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

7.10.2. Azacitidine

Safety management guidelines for azacitidine are described in Section 6.7.2. Additional safety guidelines are provided in the azacitidine prescribing information references.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

The study will randomize approximately 520 participants in total into 2 treatment arms at a 1:1 ratio, determined by formal hypothesis testing performed on 2 primary efficacy endpoints: CR rate and OS, with family-wise Type I error controlled at a 2-sided significance level of 0.05.

The primary analysis of the CR rate will be conducted at 8 months after 348 participants are randomized. Based on the first 348 randomized participants, the study has 95% power to reject the null hypothesis that the CR rates in the 2 treatment arms are the same at the 2-sided 0.03 significance level, assuming the true CR rate is 20% in the control arm and 39% in the experimental arm (i.e., a 19% improvement).

If the null hypothesis has been rejected for CR rate, the hypothesis test on OS will be conducted at a 2-sided significance level of 0.05; otherwise, it will be conducted at a 2-sided significance level of 0.02 for the superiority test together with a futility test. Approximately 364 OS events (70% of 520 participants) in the ITT Analysis Set will allow 90% power to reject the null hypothesis that medians in OS in the 2 treatment arms are the same, assuming 18 months in the control arm and 25.4 months in the experimental arm (i.e., hazard ratio [HR] = 0.71), at a 2-sided significance level of 0.05, or at least 80% power at a 2-sided significance level of 0.02.

The sample size is determined according to the group sequential design. Assuming an enrollment rate of approximately 0.22 participants/site/month and 1% annual loss to follow-up of survival status, accrual is projected to occur over 22 months for 520 participants. The primary CR rate analysis is expected approximately 26 months after the first participant is randomized. The first interim analysis of OS will be conducted at the same time. The second interim analysis of OS will be conducted when approximately 257 deaths (71% of 364 deaths) have occurred. The final OS analysis is expected approximately 4.4 years after the first participant is randomized. The actual length of the study and the time for analyses will depend on the actual enrollment rate and the number of events that occur.

8.2. Analysis Sets

ITT Analysis Set: The efficacy analyses will be conducted on all randomized participants according to the treatment arm to which the participants are randomized, unless otherwise specified.

Safety Analysis Set: The safety analyses will be conducted on all randomized participants who receive at least 1 dose of any study treatment, with treatment assignments designated according to the actual treatment received.

PK Analysis Set: The PK analysis will be conducted on all participants who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab. If azacitidine PK analysis is conducted, a separate azacitidine PK analysis set will consist of all participants who received any amount of azacitidine and have at least 1 measurable posttreatment serum concentration of azacitidine.

Immunogenicity Analysis Set: The immunogenicity analysis will be conducted on all participants who received at least 1 dose of magrolimab and with at least 1 reported ADA result.

8.3. Planned Analyses

8.3.1. DMC Interim Analyses

There will be 2 planned interim efficacy analyses conducted and evaluated by the DMC.

The first one will be conducted at 8 months after 348 participants have been randomized (i.e., data cutoff date), outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. First, the primary analysis of CR rate will be conducted based on the first 348 randomized participants. Second, an interim analysis of OS will be conducted based on all randomized participants by the data cutoff date. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets approach of the O'Brien-Fleming function according to the α allocated to the comparison of OS. Specifically, if the null hypothesis on CR rate is rejected at a 2-sided significance level of 0.03, $\alpha = 0.05$ (2-sided) will be allocated for OS, and there will be no formal futility testing for OS. Otherwise, if the null hypothesis on CR rate is not rejected at a 2-sided significance level of 0.03, $\alpha = 0.02$ (2-sided) will be allocated for OS and the first non-binding futility analysis with a futility boundary of HR = 0.99 will be performed. Allocation of α is applied to all subsequent interim analyses of OS (as well as the final analysis of OS). It is projected that 158 deaths (43% of 364 deaths) would have occurred at this time.

The second planned interim efficacy analyses will be conducted when approximately 257 deaths (71% of 364 deaths) have occurred in the ITT Analysis Set, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. In the case that the null hypothesis on CR rate is not rejected at a 2-sided significance level of 0.03, a non-binding futility analysis with a futility boundary of HR = 0.95 will be performed.

- If the null hypothesis on CR is rejected in the first interim analysis at a 2-sided significance level of 0.03, $\alpha = 0.05$ (2-sided) will be allocated to the analysis of OS and key secondary endpoints in the first and second interim analyses, and final analysis.

- If the null hypothesis on CR rate is not rejected in the first interim analysis at a 2-sided significance level of 0.03, $\alpha = 0.02$ (2-sided) will be allocated to the analysis of OS and key secondary endpoints in the first and second interim analyses, and final analysis.

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

The Lan-DeMets approach with O'Brien-Fleming type alpha spending function will be used for the first and second interim analyses and final analysis for OS. The stopping boundaries at each analysis time are provided in Table 17.

Table 17. Stopping Boundaries for Efficacy Superiority Analyses

Planned Analyses		Efficacy Analysis	Events (%)	Stopping Boundary	
				HR[a]	Two-sided p-value
first IA		CR	-	-	0.03
If the test of CR is rejected in first IA	first IA	OS	158 (43%)	0.600	0.0013[b]
	second IA	OS	257 (71%)	0.738	0.0148[b]
	Final Analysis	OS	364 (100%)	0.811	0.0453[b]
If the test of CR fails to be rejected in first IA	first IA	OS	158 (43%)	0.552	0.0002[b]
	second IA	OS	257 (71%)	0.700	0.0043[b]
	Final Analysis	OS	364 (100%)	0.781	0.0186[b]

HR = hazard ratio, IA = interim analysis, OS = overall survival, CR = complete remission
a HR presented in the table is the 1-sided (lower) efficacy boundary.
b The boundary p-values at each analysis timepoint will be based on the actual observed events and adjusted by using the Lan-DeMets approach with O'Brien-Fleming type alpha spending function.

The primary efficacy endpoint of OS will be tested for superiority first at the significance level specified in Table 17. If the superiority of OS is established, key secondary efficacy endpoints listed in Table 18 will be tested for superiority. To strongly control the overall type I error across the testing of the primary and key secondary efficacy endpoints, a hierarchical testing strategy will be performed with a predefined order as listed below. For each key secondary endpoint, an O'Brien-Fleming boundary will be derived based on the information fraction at each interim analysis and the remaining type I error respectively per Table 18.

Table 18. Definition of Information Fraction for Key Secondary Endpoints

Endpoint	Information Fraction at the First and Second Interim Analysis
ORR	Proportion of participants who have at least 8 months follow-up since randomization (including participants who have early discontinued, are lost to follow-up, or have died)
RBC transfusion independence rate	Proportion of participants who have at least 8 months follow-up since randomization (including participants who have early discontinued, are lost to follow-up, or have died)
EFS	43% at the first interim analysis, 71% at the second interim analysis (same with those of OS)[a]
CR rate in TP53 mutant population	Proportion of participants who have at least 8 months follow-up since randomization (including participants who have early discontinued, are lost to follow-up, or have died)
MRD-negative response rate	Proportion of participants who have at least 8 months follow-up since randomization (including participants who have early discontinued, are lost to follow-up, or have died)
Time to transformation to AML	43% at the first interim analysis, 71% at the second interim analysis (same with those of OS)[a]
PFS	43% at the first interim analysis, 71% at the second interim analysis (same with those of OS)[a]
FACT-Anemia response rate	Proportion of participants who have at least 8 months follow-up since randomization (including participants who have early discontinued, are lost to follow-up, or have died)

AML = acute myeloid leukemia; CR = complete remission; EFS = event-free survival; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; MRD = minimal residual disease; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RBC = red blood cell

a The actual information fraction at each interim analysis for time to event endpoints will be based on actual observed OS events by the time of analysis.

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

- ORR
- RBC transfusion independence rate
- Event-free survival (EFS)
- CR in TP53 mutant population
- MRD-negative response rate
- Time to transformation to AML
- Progression-free survival (PFS)
- FACT-Anemia response rate

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

At the time of the second DMC interim efficacy analysis, if the efficacy boundary of OS has been crossed, the Sponsor study team may be unblinded for the entire ITT Analysis Set and will conduct the efficacy and safety analyses.

CCI [redacted]

[redacted]

[redacted]

8.3.3. Final Analysis

If the null hypothesis on OS will not be rejected in either of the 2 planned interim analyses, the final unblinded efficacy analyses will be conducted by the Sponsor when approximately 364 OS events (70% of 520 participants) have occurred in the ITT Analysis Set, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. Comparison of OS between the 2 treatment arms will be conducted after study unblinding.

If the null hypothesis on OS will be rejected in any planned interim analyses, the timing of the final analysis may be driven by the data maturity of all required efficacy data and the need of the safety evaluation update.

8.4. Endpoint Definitions

Response will be assessed using the criteria in Appendix B, Table 19, which are based on the 2006 IWG criteria {Cheson 2006}. In addition, hematologic improvement (HI) will be assessed by 2006 IWG criteria {Cheson 2006} and cytogenetic/molecular response by 2003 IWG criteria {Cheson 2003}.

Response assessments will be performed at the time points specified in the Schedule of Assessments in Section 4.3 and as described in Section 5.3.

The following summary measures for endpoints will be evaluated:

CR Rate: The CR rate is the proportion of participants who reach morphologic CR (morphological blast of $\leq$ 5% and recovery of ANC, platelets, and hemoglobin from CBCs as well as peripheral blast collected on the same day) based on Investigator-assessed IWG 2006 MDS criteria {Cheson 2006} prior to initiation of any new anticancer therapy, including SCT.

Duration of CR: The duration of CR is measured from the time measurement criteria are first met for CR to the first date of relapse or death, whichever occurs earlier. Those who are not observed to relapse or die will be censored at their last response assessment date with evidence of no relapse. Participants who achieve a CR and then proceed to an allogeneic SCT will continue to be followed for the response assessment posttransplant, will be included in the analysis of duration of CR, and will not be censored at the time of transplant.

Overall Survival (OS): The length of OS is measured from randomization to the date of death from any cause. Those who are not observed to die during the study will be censored at their last known alive date.

Objective Response Rate (ORR): The ORR is the proportion of participants who reach objective response including CR, PR, marrow CR, or hematologic improvement per IWG 2006 MDS criteria prior to initiation of any new anticancer therapy, including SCT.

Duration of Response (DOR): The DOR is measured from the time measurement criteria are first met for objective response to the first date of relapse, disease progression or death, whichever occurs earlier. Those who are not observed to relapse, disease progress or die will be censored at their last response assessment date with evidence of no relapse/no disease progression. Participants who achieve a response and then proceed to an allogeneic SCT will continue to be followed for the DOR posttransplant, will be included in the analysis of DOR, and will not be censored at the time of transplant.

RBC Transfusion Independence Rate: The RBC transfusion independence rate is the proportion of participants who have a 56-day or longer period with no RBC transfusions at any time between randomization and initiation of any new anticancer therapy, including SCT, among all participants who are RBC transfusion-dependent at baseline.

Progression-free Survival (PFS): The length of PFS is defined as the time from randomization to the date of documented disease progression (including treatment failure by IWG criteria or relapse after PR/CR), or death from any cause, whichever occurs first. Those who are not observed to have one of these events will be censored at their last response assessment date with evidence of no disease progression/relapse.

Event-free Survival (EFS): The length of EFS is defined as the time from randomization to transformation to AML or death from any cause, whichever occurs first. Participants who are not observed to have one of these events during the study will be censored at their last response assessment date with evidence of no transformation to AML.

MRD-negative Response Rate: The MRD-negative response rate is defined as the proportion of participants who achieve a morphologic CR or marrow CR based on Investigator-assessed IWG criteria {Cheson 2006} and reach MRD-negative disease status prior to initiation of any new anticancer therapy, including SCT. MRD-negative disease status will be assessed using a multiparameter flow cytometry-based assay performed by a central laboratory.

Time to Transformation to AML: Time to transformation to AML is defined as the time from randomization to the collection date of bone marrow sample leading to documented AML diagnosis. Participants who are not observed to have transformation to AML will be censored at their last response assessment date with evidence of no AML diagnosis.

FACT-Anemia Response Rate: The FACT-Anemia response rate is defined as the proportion of participants who showed clinically meaningful improvement in health-related quality of life (HRQoL) based on the score from the FACT-Anemia instrument prior to initiation of any new anticancer therapy, including SCT.

Duration of RBC Transfusion Independence: The duration of RBC transfusion independence is measured from the time the assessment criteria are first met for RBC transfusion independence until RBC transfusion dependence again (including assessments post SCT) or death. Those who are not observed to have one of these events will be censored at the date of their last response assessment with evidence of no RBC transfusion dependence again.

Transplantation Rate: The transplantation rate is defined as the proportion of participants who initiate transplant therapy for MDS after randomization.

Time to First Transplant: Time to first transplant is defined as the time from randomization to the initiation of first transplant therapy for MDS. Participants who are not observed to initiate transplant therapy will be censored at their last known alive date or death date if the patient died.

RBC Transfusion Independence Irrespective of RBC Transfusion-Dependence at Baseline: The RBC transfusion independence irrespective of RBC transfusion-dependence at baseline is the proportion of participants who have a 56-day or longer period with no RBC transfusions at any time between randomization and initiation of any new anticancer therapy, including SCT, among all participants irrespective of RBC transfusion-dependence at baseline.

8.5. Efficacy Analysis

8.5.1. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoints are CR rate as assessed by Investigators and OS. The analysis of CR rate will be conducted on the first 348 randomized participants in the ITT Analysis Set. The analysis of OS will be conducted on the ITT Analysis Set.

The difference in CR rates between the 2 arms will be tested using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors including region, baseline cytogenetic risk, and bone marrow blast percentage. The point estimate of the CR rate and the corresponding 2-sided exact 95% CI based on Clopper-Pearson method will be provided for each treatment arm.

Log-rank test, stratified by the randomization stratification factors including region, baseline cytogenetic risk, and bone marrow blast percentage, is the primary analysis comparing treatment differences in OS. A stratified Cox regression model will be used to estimate HR and its 2-sided 95% CI. In addition, the KM method will be used to estimate median OS with its 95% CI, and the KM plots may also be provided.

8.5.2. Analysis of Secondary Efficacy Endpoint(s)

Analysis of EFS, PFS, and time to transformation to AML will be similar to that of OS.

ORR, RBC transfusion independence rate, CR rate in the TP53 mutant population, and MRD-negative response rate will be evaluated in a similar manner as the primary efficacy endpoint of CR, except that RBC transfusion independence rate will be based on a subset of all randomized participants who are RBC transfusion-dependent at baseline and CR rate in the TP53 mutant population will be based on subset of all randomized participants who have the TP53 mutation.

For the time-to-event endpoints of duration of CR and DOR, analysis will be conducted using the KM method based on the subsets on which the outcome measures are defined. Specifically, duration of CR will be based on participants who achieved CR, DOR will be based on participants who achieved OR. Median duration will be estimated with its 95% CI for each treatment arm.

Hypothesis testing of key secondary endpoints will be performed under the testing procedure described in Section 8.3 to control family-wise Type I error. No formal hypothesis testing will be conducted for any key secondary endpoint, unless the null hypothesis of OS is rejected.

8.6. Safety Analysis

The statistical analysis of safety data will be conducted in the Safety Analysis Set. Safety variables may include, but are not limited to, treatment-emergent adverse events (TEAEs; AEs occurring during or after a participant's first exposure to study treatment and up to 70 days after the last day of study treatment or initiation of new anticancer therapy, including SCT [whichever is earlier]), vital signs, physical examinations, and laboratory tests.

Data may be graphed, summarized, or listed, depending on the amount of data to be reported.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Adverse events will be coded using MedDRA Version 22.1 or later, and the NCI CTCAE, Version 5.0 (Appendix A) will be used to grade severity of AEs and clinically significant laboratory abnormalities. Participant incidence of TEAEs and treatment-related TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized using

Investigator assessment of the relationship to study treatment (related or not related). Serious adverse events, including deaths, will be summarized and/or listed for all participants. TEAEs resulting in withdrawal from study treatment will be summarized and/or listed.

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

Adverse events and SAEs that are not treatment emergent will be reported separately in data listings for the Safety Analysis Set.

8.6.3. Laboratory Evaluations

For select laboratory parameters, changes of laboratory values over time, grade shifts in laboratory value from baseline to worst on study value, and Grade 3 or higher laboratory abnormalities will be summarized. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline up to last day of treatment + 30 days, will be summarized by treatment group. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

8.6.4. Other Safety Analyses

The number and incidence of participants developing ADAs at any time will be summarized. Vital signs and physical examination findings will be summarized at select time points. Details will be provided in the statistical analysis plan (SAP).

8.7. Analysis of PRO Data

A key PRO endpoint, FACT-Anemia response rate, is defined based on the ITT Analysis Set (see Section 8.3.1). The analysis method is similar to that of the CR rate. Other indices, such as the Functional Assessment of Cancer Therapy-General (FACT-G), FACT Trial Outcome Index-Anemia scale (FACT TOI-An), and FACT Trial Outcome Index-Fatigue (FACT TOI-F), which can be derived from FACT-Anemia with published minimally clinically meaningful difference, will also be analyzed {Cella 2002, Revicki 2013}.

Additional analyses will be conducted on all PRO data, including absolute scores and changes from baseline for all items and subscales of the FACT-Anemia instrument, EQ-5D-5L instrument, and PGIS/PGIC at each assessment time point for each arm.

8.8. Pharmacokinetics Analysis

Pharmacokinetic analysis will be conducted for magrolimab on the PK Analysis Set.

The PK Analysis Set will be used for summaries of PK concentration-versus-time data. 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. Any missing PK parameter data will not be imputed.

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

If azacitidine PK data are generated, summary statistics will be provided at each time point. Descriptive graphical plots of individual serum concentration-versus-time profiles and mean concentration-versus-time profiles may be generated.

8.9. 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 antimagrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the participant population. Titer summaries may also be generated, if relevant. CCI [redacted]

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

9. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and IRB/IEC requirements.

To the extent applicable, all references to the ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between ICH and local requirements, the most stringent standard shall apply.

9.1. Investigator Responsibilities

As required by FDA regulation (21 CFR Part 56) and ICH guidelines for GCP, the Investigator at each study site must obtain IRB/IEC review and approval of the study protocol, ICFs, participant recruitment materials, and any other pertinent documents before any study-related activities involving participants are performed.

As required in 21 CFR Part 50 and ICH guidelines for GCP, the Investigator or designee must comply with the informed consent process and ensure that each participant enrolled in this clinical study understands the information presented in the IRB/IEC-approved ICF and agrees voluntarily to participate in the clinical study.

The Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended IB or safety amendments and updates) provided by the Sponsor or representative, according to the IRB/IEC-specific reporting requirements.

The Investigator must inform the IRB/IEC of the progress of the clinical study and report any nonadministrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and supervise the delegates. All persons authorized to make entries and/or corrections on eCRFs will be included on the Gilead Sciences, Inc. Delegation of Authority Form.

The clinical study report must be signed by the Investigator or, in the case of multicenter studies, the Coordinating Investigator. The Coordinating Investigator, identified by Gilead Sciences, Inc., will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible participants

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications may be made only by Gilead.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency 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). 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 5.9).

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. Ethics Review

A copy of the protocol, ICF, other written participant information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Gilead Sciences, Inc. or designee before randomization of participants in the study and shipment of magrolimab.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator is to notify the IRB/IEC of important deviations from the protocol or SAEs occurring at the site and other AE reports received from Gilead Sciences, Inc., in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval/renewal as per country-specific requirements throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Gilead Sciences, Inc.

9.4. Informed Consent

A final country level master template ICF will be provided for the Investigator to prepare the site specific ICF to be used at his or her site. However, the site level adaptation may be delegated to a clinical research organization. Updates to the template are to be communicated formally in writing from the Gilead Sciences, Inc. study monitor to the Investigator. The written ICF is to be prepared in the language(s) of the potential participant population.

Before a participant's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the participant after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The Investigator is also responsible for asking the participant if the participant has a primary care physician and if the participant agrees to have his/her primary care physician informed of the participant's participation in the clinical study. If the participant agrees to such notification, the Investigator is to inform the participant's primary care physician of the participant's participation in the clinical study. If the participant does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the participant's medical record. The acquisition of informed consent and the participant's agreement or refusal of his/her notification of the primary care physician is to be documented in the participant's medical records, and the ICF is to be signed and personally dated by the participant, and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the participant.

If a potential participant is illiterate or visually impaired, the Investigator must provide an impartial witness to read the ICF to the participant and must allow adequate time for questions. Thereafter, both the participant and the witness must sign the ICF to attest that informed consent was freely given and understood. If a participant has questions during the conduct of the study, the Investigator or site staff must provide assistance.

The informed consent form will inform participants about genomic testing and/or planned sample retention. Genomic testing is not optional and is a requirement for study participation. In addition to the study-specific informed consent form to be signed by each participant participating in the study, participants will be required to document agreement to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. The results of the tests done on the samples will not be given to the participant or the Investigator.

9.5. Data Privacy and Confidentiality

The Investigator must ensure that the participant's confidentiality is maintained for documents submitted to Gilead Sciences, Inc., including the following:

- Participants are to be identified by a unique patient identification number.
- Where permitted, birth year is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique patient identification number, the age at time of randomization is to be included.
- For SAEs reported to Gilead Sciences, Inc., participants are to be identified by their unique patient identification number, and birth year (in accordance with local laws and regulations).

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Documents that are not submitted to Gilead Sciences, Inc. (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with the CFR/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IRB/IEC direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the participant to permit such individuals to have access to his/her study-related records, including personal information.

9.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The study may continue with the urgent safety measures in place. **The Investigator must inform the IRB/IEC and Gilead Sciences, Inc. *immediately* if the study site initiates an urgent safety measure**.

The notification must include:

- date of the urgent safety measure;
- who made the decision; and
- why the action was taken.

The Investigator will provide any other information that may be required to enable Gilead Sciences, Inc. to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

9.7. Disclosure

A description of this clinical study will be available on http://www.ClinicalTrials.gov, as well as other country-specific registries, as required by US law and/or other country laws.

9.8. Biological Specimens and Data

Blood and bone marrow specimens will be cryopreserved and biobanked for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the informed consent.

Any blood, tissue, or biomarker sample collected according to the Schedule of Assessments (Section 4.3) may be analyzed prior to or after study unblinding for any tests outlined in the protocol. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure data integrity and control. Samples may be retained for up to 15 years.

If permitted by local law and if informed consent is provided by the participant, Gilead Sciences, Inc. may do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand MDS and the dose response and/or prediction of response to magrolimab, to characterize antibody response, and to characterize aspects of the molecule (e.g., MOA/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study.

Since the evaluations are not expected to benefit the participant directly or to alter the participant's treatment course, the results of these exploratory studies are not placed in the participant's medical record and are not to be made available to the participant, members of the participant's family, the participant's personal physician, or other third parties, except as specified in the ICF.

The participant retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the participant, the Investigator is to provide the Sponsor with the required study and patient number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures have been completed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the participant through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The participant has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

9.8.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (e.g., 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.

10. OVERSIGHT

10.1. Independent Monitoring

10.1.1. DMC

The DMC will review the unblinded data generated during the clinical study. The mandate of the DMC is to serve as an independent committee with pertinent clinical and study conduct expertise to monitor and ensure the safety of the therapies for participants on study. The composition, structure, and function of the DMC and the scope of data for review are defined in the DMC Charter. The timing of such data review will be predefined in the DMC Charter.

10.2. Quality Control and Assurance

10.2.1. Monitoring

The Gilead Sciences, Inc. representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., eCRFs and other pertinent data) provided that participant confidentiality is respected.

The Gilead Sciences, Inc. representative(s) are responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Gilead Sciences, Inc. representative(s) are to have access to participant medical records and other study-related records needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the Gilead Sciences, Inc. representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

10.2.2. Audits

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor or regulatory agency may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including eCRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours if requested.

10.2.3. Records

10.2.3.1. Data Capture and Management

The Investigator is responsible for complying with the requirements for all assessments and data collection (including participants not receiving protocol-required therapies), as stipulated in the protocol for each participant in the study. For participants who discontinue from the study prior

to completion of all protocol-required visits for study assessments or survival follow-up as described in Section 4.3, the Investigator may search publicly available records (where permitted by local laws and regulations) to ascertain survival status. This ensures reduced risk of missing critical efficacy data.

The Investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. Data collection will involve the use of the EDC system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. 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. Detailed instructions are provided in the other study-specific documents.

All entries made on the eCRF may require verification against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure participant confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the Sponsor or designee for destruction.

10.2.3.2. Source Documentation

As stipulated by 21 CFR §312.57 and ICH E6 GCP Consolidated Guidance Section 8, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of participants.

The source data for this study may be obtained from EDC and central or local laboratory reports. Source documents are original documents, data, and records from which the participant's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.2.3.3. Study Files

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Gilead Sciences, Inc. and/or applicable regulatory authorities.

10.2.3.4. Records Retention

The Investigator must retain all essential documents for this clinical study until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of magrolimab. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. A Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. Before destroying any records, the Investigator must notify the Sponsor and reach agreement on record destruction, or the Sponsor may request an additional retention period.

10.3. Serious Breaches or Fraud

A serious breach is defined as "A breach of GCP or the study protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the participants of the study; or
- the scientific value of the study"

Investigators or designee must notify Gilead Sciences, Inc. immediately if any serious breach of GCP is suspected and prior to notifying IRB/IECs.

If there is any proof of fraud, this must also be reported to Gilead Sciences, Inc. If any additional local or national reporting is required, this must also be done.

10.4. Study Termination or Study Site Closure

Gilead Sciences, Inc. reserves the right to terminate the study at any time. Both Gilead Sciences, Inc. and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The Investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Gilead Sciences, Inc.

The study may also be terminated for safety reasons.

11. FINANCIAL DISCLOSURE AND INSURANCE

The Sponsor maintains clinical study insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

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 participant completes the protocol-defined activities.

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13. APPENDICES

Appendix A. National Cancer Institute Common Terminology Criteria for Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 5.0

Publication date: 27 November 2017 (v5.0)
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Accessed 18 February 2020

Appendix B. Disease Response Assessment Based on International Working Group Criteria

Response will be assessed in myelodysplastic syndrome (MDS) patients using the 2006 International Working Group (IWG) criteria {Cheson 2006} as shown in Table 19. In addition, complete remission (CR) with partial hematologic recovery (CRh) will be assessed for MDS, defined as patients who achieve a CR per IWG 2006 MDS criteria {Cheson 2006}, with the exception of requiring partial hematologic recovery as defined by a platelet count of $> 50 \times 10^9$/L and an absolute neutrophil count of > 500/μL.

In addition, HI will be assessed by 2006 IWG criteria {Cheson 2006} (Table 21) and cytogenetic/molecular response by 2003 IWG criteria {Cheson 2003} (Table 20).

Table 19. Response Criteria in MDS (IWG 2006 Criteria With Modifications)

Category	Response Criteria
CR	Bone marrow ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] Hgb ≥ 11 g/dL Platelets ≥ 100×10^9/L Neutrophils ≥ 1.0×10^9/L[b] Blasts 0%
PR	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR[b]	Bone marrow ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment[b] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable Disease	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence[d]
Cytogenetic Response	Complete: Disappearance of chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease Progression	For patients with: Less than 5% blasts: ≥ 50 increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL[d] Transfusion dependence[d]

Source: {Cheson 2006}
Abbreviations: CR = complete remission; FAB = French-American-British classification; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndrome; PR = partial remission.
a Dysplastic changes should consider the normal range of dysplastic changes.
b Modification to IWG response criteria.
c Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.
d Impact of anemia must be deemed disease-related and not due to study treatment.

Table 20. Additional Response Definitions Used in This Study (2003 IWG Criteria)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
cCR	$\geq 1.0 \times 10^9$/L	$\geq 100 \times 10^9$/L	< 5%	Cytogenetics normal and no evidence of extramedullary disease
mCR	$\geq 1.0 \times 10^9$/L	$\geq 100 \times 10^9$/L	< 5%	Molecular investigations normal and no evidence of extramedullary disease
Treatment Failure[a]	Lack of response/Progressive Disease + loss of clinical benefit			

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

Table 21. Response Criteria for Hematologic Improvement

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

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

Appendix C. Functional Assessment of Cancer Therapy – Anemia

Available online:
FACT-An (facit.org)

Appendix D. 5-Level EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Available online:
EQ-5D-5L – EQ-5D (euroqol.org)Sample_UK-English-EQ-5D-5L-Paper-Self-Complete-v1.2-ID-24700.pdf

Appendix E. Patient Global Impression of Severity and Patient Global Impression of Change

Publication:
Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976

Available online:
PGI-C, PGI-I, PGI-S - Patient Global Impressions scale - Change, Improvement, Severity (mapi-trust.org)

PGI-C_TS1.0_eng-USori_review copy (1).pdf

Appendix F. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Scale of Performance Status

Publication:
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 G. 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 participant is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless permanently sterile or with 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 any age with amenorrhea of > 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

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

b. Definition of Male Fertility

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

2. Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a malformative effect has been demonstrated/suspected or is unknown taking into consideration class effect and/or strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on 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 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.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information regarding the potential risks of treatment with azacitidine.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants 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 at the beginning of each cycle thereafter (described in the protocol) until the end of the contraception requirement.

The duration of required contraception for female participants in this clinical trial should start from the Screening Visit until 6 months after the last dose of azacitidine or magrolimab/placebo, whichever is later.

Female participants 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 participant's preferred and usual lifestyle.

Or

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

- Hormonal or non-hormonal intrauterine device (IUD)
- Subdermal contraceptive implant
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

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

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

- 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 participants 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 participants should be advised to seek advice about egg donation and cryopreservation prior to treatment.

3. Contraception Requirements for Male Participants

Male participants with female partners of childbearing potential must use condoms during treatment and until 3 months after the last dose of azacitidine or magrolimab/placebo, whichever is later. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive method should also be considered.

Male participants must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male participants 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 (e.g., calendar, ovulation, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). A female condom and a male condom should not be used together.

5. Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the Investigator immediately if they become pregnant at any time during the study or if they become pregnant within 6 months of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. Participants whose partner has become pregnant or suspects she is pregnant during the study must report the information to the Investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.8.2.3.

Appendix H. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These potential risks & mitigation plans can be summarized as follows:

1) Schedule of assessments:

    a) Physical Exam:

        i) For all assessments where a physical exam is indicated, this portion of the visit can be conducted virtually. While samples will need to be collected, and dosing will need to occur on dosing days in clinic.

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

    b) Dosing:

        i) For the priming and repriming period, magrolimab/placebo can be administered on Day 7 with azacitidine with collection of Day 8 assessments (i.e. labs, PK) on Day 7 in order to minimize an extra participant visit.

        ii) Dosing with azacitidine:

            (1) If needed under specific circumstances, sites can allow for administration of azacitidine locally nearer to participant's residence, with proper documentation (i.e., name of site, name of MD overseeing transfusion, name of laboratory used including accreditation certificate, etc.)

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

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

            (4) This should be reserved only in cases where participants will not be able to get azacitidine dosing otherwise.

c) Sample Collection:

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

ii) MRD testing should be collected and shipped. If real time shipping is not possible then add RPMI no more than 1:1 ratio if shipment is delayed more than 24 hours but not exceed 48 hours and store at room temperature.

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 mononuclear cells (e.g. 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 participant selection guidance:

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

2) Participant safety monitoring and follow-up:

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

Mitigation plan: For participants 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 participant within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

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

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

iii) If applicable, confirm that patient-reported outcome questionnaires have been completed and transmitted.

b) Participants may be unable or unwilling to travel to the site for planned assessments (e.g., safety blood draws); hence, samples may not be sent for central laboratory analyses.

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

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

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if 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 participants 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 participant 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. Participants with a COVID-19 infection while participating in a clinical trial will have this event documented as an adverse event in the clinical database.

3) Protocol and monitoring compliance:

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

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

b) Monitors may be unable to carry out source data review (SDR), 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. Remote SDV may be arranged if allowed. 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 participants on site must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

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

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

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternative methods that will ensure the evaluation and assessment of the safety of participants 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 participants remains unchanged. In case these potential risks cannot be mitigated due to the escalation of a pandemic, randomization of new participants will be placed on hold until the pandemic outbreak is under control by following local regulatory guidelines.

amd-8-prot 5F9009

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	PPD