CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies
Protocol Number:	5F9005
Investigational Product:	Magrolimab (previously known as Hu5F9-G4)
Indication:	Hematological Malignancies
Development Phase:	1b
Sponsor:	Gilead Sciences 333 Lakeside Drive Foster City, CA 94404 USA
Medical Monitor:	PPD Director, Clinical Development Gilead Sciences email: PPD
Lead Investigator:	PPD MRC Molecular Haematology Unit & Dept of Haematology Weatherall of Institute of Molecular Medicine University of Oxford Oxford OX3 9DS United Kingdom Telephone: PPD email: PPD
Amendment 9 Date:	21 July 2022
Amendment 8 Date:	31 March 2022
Amendment 7 Date:	25 August 2021
Amendment 6 Date:	10 February 2020
Amendment 5 Date:	18 July 2019
Amendment 4 Date:	01 August 2018 (UK only)
Amendment 3 Date:	06 March 2018
Amendment 2 Date:	20 July 2017
Amendment 1 Date:	22 May 2017
Original Protocol:	09 March 2017

Compliance Statement:

This study will be conducted in accordance with this Protocol, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

I have read the document described above, and my signature below indicates my approval:

[See appended electronic signature]	*[See appended electronic signature]*
PPD Medical Monitor, Gilead Sciences	Date

PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, my local and regional clinical trial regulatory requirements (including the Code of Federal Regulations [CFR] Title 21 for US Investigators), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Gilead Sciences

Investigational Agents: Magrolimab (previously known as Hu5F9-G4)

Protocol Number: 5F9005 Amendment 9

Study Title: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies

Scientific Rationale and Background

Acute myeloid leukemia (AML) is a common hematological malignancy whose incidence rises from 3:100,000 in young adults to greater than 20:100,000 in older adults. For patients < 60 years of age, overall survival (OS) is 40 to 50%, but is only 5% for patients > 60 years of age. The majority of newly diagnosed patients with AML are over the age of 60. In this patient population, standard induction chemotherapy is often not an option due to increased treatment-related mortality as a result of age and co-morbidities. Standard of care (SOC) for AML patients unfit for combination chemotherapy is treatment with hypomethylating agents (azacitidine or decitabine) or low dose cytarabine. Despite these frontline treatments, median OS is only about 10 months. In all types of AML, disease relapse is common despite an initial therapeutic response and is the most common reason for death. Standard chemotherapy and allogeneic stem cell transplant (when used) often fail to eradicate all tumor-propagating cells and select for chemotherapy-resistant leukemia-propagating subclones. Patients refractory to salvage therapy are treated palliatively, as current treatment options are extremely limited. These patients have a median survival of 2 months. In addition, patients with newly diagnosed intermediate or higher-risk myelodysplastic syndrome (MDS) and those who relapse after standard care have a poor prognosis and high risk of progression to AML. MDS patients who relapse or are refractory to hypomethylating agents have no SOC, and prognosis is poor. In red blood cell (RBC) transfusion-dependent low-risk MDS patients who fail erythropoiesis-stimulating agents (ESAs) or lenalidomide, no

SOC exists, and well-tolerated and effective therapies are needed. Therefore, there is an urgent need for new treatment modalities for relapsed/refractory (R/R) AML and MDS patients, newly diagnosed AML patients ineligible for induction chemotherapy based on age and co-morbidities, RBC transfusion-dependent low-risk MDS, and newly diagnosed intermediate/high/very high risk MDS patients.

Magrolimab (previously known as Hu5F9-G4) is a humanized monoclonal antibody that blocks the anti-phagocytic signal CD47, which is highly expressed on cancer cells including AML and serves as a key immune evasion signal for cancers. Magrolimab binds CD47 and blocks it from interacting with its ligand, signal regulatory protein alpha (SIRPα), on phagocytic cells, leading to phagocytic elimination of cancer cells. Magrolimab treatment in nonclinical xenograft models of human AML leads to robust elimination of leukemic disease in the peripheral blood and bone marrow which results in long term remissions in a high percentage of mice treated. Magrolimab has been tested in Phase 1 trials of solid tumors and AML. In a Phase 1 trial in R/R AML (Study SCI-CD47-002), magrolimab monotherapy has been well tolerated and a maximum tolerated dose (MTD) has not been reached. Based on nonclinical testing, it is hypothesized that magrolimab will demonstrate significant anti-leukemic activity in patients with AML or intermediate/high/very high risk MDS. Furthermore, the addition of magrolimab to standard-of-care hypomethylating agents (azacitidine) may enhance anti-leukemic activity. This trial will evaluate the anti-leukemic activity of magrolimab monotherapy in patients with relapsed or refractory AML or MDS, and will provide continued treatment for patients on a Phase 1 AML trial (Study SCI-CD47-002) who are deriving ongoing clinical benefit from magrolimab monotherapy. In addition, the safety and anti-leukemic activity of magrolimab in combination with azacitidine will be investigated in patients with R/R AML or MDS, previously untreated AML patients who are ineligible for standard induction chemotherapy, newly diagnosed intermediate/high/very high risk MDS patients, and RBC transfusion-dependent low-risk MDS patients.

Study Objectives

Primary Objectives

- To confirm the safety and tolerability of magrolimab monotherapy in R/R AML and MDS and of magrolimab in combination with azacitidine in previously untreated patients with AML or MDS and patients with R/R AML and MDS
- To evaluate the safety, tolerability, and efficacy of magrolimab monotherapy in R/R AML/MDS, and of magrolimab in combination with azacitidine in previously untreated patients with AML/MDS or R/R AML/MDS as measured by complete remission (CR) rate for patients with AML and higher-risk MDS
- To evaluate the safety, tolerability, and efficacy of magrolimab monotherapy or in combination with azacitidine in low-risk MDS patients as measured by RBC transfusion independence rate

Secondary Objectives

- To evaluate the pharmacokinetic (PK) profile of magrolimab alone and in combination with azacitidine
- To evaluate the immunogenicity of magrolimab
- To evaluate the efficacy of magrolimab alone or in combination with azacitidine as measured by duration of CR (DCR); objective response rate (ORR); CR with partial hematologic recovery; duration of response (DOR) for patients with AML; DCR for higher-risk MDS; ORR and DOR for patients with MDS; RBC transfusion independence; mean hemoglobin increase on treatment; progression-free survival (PFS); relapse-free survival (RFS), event-free survival (EFS); and OS
- To assess the level of minimal residual disease (MRD) negativity

CCI [redacted]

Overall Study Design

This trial is an open label, multicenter Phase 1b trial investigating the following:

- Magrolimab monotherapy or in combination with azacitidine in patients with R/R AML or MDS (including R/R low-risk RBC transfusion-dependent MDS patients)
- Magrolimab in combination with azacitidine in newly diagnosed intermediate/high/very high-risk MDS patients
- Magrolimab in combination with azacitidine in newly diagnosed AML patients ineligible for standard induction chemotherapy (including TP53 mutant AML)
- Magrolimab monotherapy or in combination with azacitidine for RBC transfusion-dependent low-risk MDS patients

The study includes 4 groups of patients:

- **R/R Cohorts:** R/R AML or MDS patients who have not previously received magrolimab, who will receive magrolimab monotherapy in the safety run-in cohort or magrolimab monotherapy in the R/R MDS Magrolimab Monotherapy Cohort, and who will receive magrolimab in combination with azacitidine in the R/R expansion cohort on this study. The R/R MDS Magrolimab Monotherapy Expansion Cohort has been added to further define the activity of magrolimab alone in MDS.
- **Treatment-naïve/Unfit (TN/U) Cohorts:** AML patients ineligible for standard induction chemotherapy or previously untreated intermediate/high/very high-risk MDS patients by Revised International Prognostic Scoring System (IPSS-R) (Greenberg 2012), who will receive magrolimab in combination with azacitidine on this study. A subcohort of untreated AML patients ineligible for standard induction chemotherapy that have a TP53 gene mutation is included here.

- **RBC Transfusion-dependent Low-risk MDS Cohort:** RBC transfusion-dependent very low- to low-risk MDS patients by IPSS-R who are either of the following:
    1) relapsed/refractory/intolerant to or ineligible for ESA therapy
    2) have a deletion in chromosome 5q who are relapsed/refractory/intolerant to or ineligible for lenalidomide therapy
- **Rollover Cohort:** Patients who received magrolimab in the Phase 1 R/R AML study (SCI-CD47-002), who will continue magrolimab monotherapy on this study.

Regarding magrolimab dosing for these cohorts, preliminary PK/pharmacodynamic (PD) and RO data suggest that doses higher than 20 mg/kg may be associated with greater target CD47 saturation on leukemic cells and higher free drug exposures. Higher magrolimab dose exposures may thus lead to enhanced clinical efficacy. Based on this potential benefit and the current safety profile where an MTD has not been reached, exploration of higher magrolimab dose levels represents an adequate risk-benefit profile. Therefore, a magrolimab maintenance dose of 30 mg/kg, once weekly (QW), twice weekly, every 2 weeks (Q2W), or every 4 weeks (Q4W) will be evaluated. A 60 mg/kg Q4W dosing will also be evaluated in the RBC Transfusion-dependent Low-risk MDS Cohort.

The R/R Cohorts consist of 2 cohorts: 1) an R/R Safety and Expansion Cohort, and 2) an R/R MDS Magrolimab Monotherapy Expansion Cohort. The R/R Safety and Expansion Cohort consists of an initial evaluation of magrolimab monotherapy in R/R MDS/AML patients, followed by an expansion cohort of magrolimab + azacitidine in R/R MDS/AML patients. As of Amendment 3, in the first stage, patients in the R/R Safety Cohort have been treated at the maintenance dose of 30 mg/kg twice weekly; going forward, these patients will be treated weekly at the maintenance dose of 30 mg/kg, as determined by the Clinical Trial Steering Committee (CTSC) based on clinical, PK, and PD data. This safety run-in will confirm the safety profile of magrolimab monotherapy at this dose level in an expanded R/R population. Approximately 30 days after enrollment is completed in the R/R Safety Cohort, the CTSC will assess the safety data to determine whether

enrollment may begin in the TN/U Dose Evaluation Cohort. In addition, the CTSC will also determine whether enrollment will proceed to an initial 36-patient R/R Expansion Cohort, based on safety and efficacy data, which will be conducted with magrolimab in combination with azacitidine as per Amendment 5. Based on emerging data, the CTSC may decide to enroll additional patients beyond 36 for further safety, efficacy, or dosing information.

The R/R MDS Magrolimab Monotherapy Cohort was added in Amendment 6. Per Food and Drug Administration (FDA) feedback, a magrolimab monotherapy cohort in R/R MDS will be evaluated to further define the activity of magrolimab to the contribution of magrolimab+azacitidine in MDS to support a potential single-arm approval of magrolimab+azacitidine in MDS. Patients will be enrolled in a Simon's 2-stage design to evaluate for potential futility. Patients who do not achieve an objective response with magrolimab monotherapy at the protocol-defined first response assessment may have azacitidine added by discretion of the Principal Investigator with Sponsor approval, according to the schedule of azacitidine outlined in the R/R cohorts.

The TN/U Cohort will be enrolled in 2 stages. In the first stage, the study will investigate the safety and tolerability of magrolimab and azacitidine in a 3+3 dose evaluation design, in previously untreated AML patients who are unfit for standard combination chemotherapy, and previously untreated intermediate/high/very/high risk MDS patients. The same dose level of magrolimab used in the R/R Safety Cohort will be initially evaluated in combination with the standard dose of azacitidine in the TN/U Dose Evaluation Cohort. Optional additional dose cohorts may explore higher or lower doses in increments of up to 50% of the maximum prior dose, as determined by the CTSC based on emerging PK, PD, and clinical data. A total of up to 18 patients may be treated in the TN/U Dose Evaluation Cohort. In the second stage, a recommended Phase 2 dose and schedule will be selected by the CTSC for treatment in the TN/U Expansion Cohort, which will be evaluated for efficacy of magrolimab in combination with azacitidine. As of Amendment 3, the recommended Phase 2 dose and regimen (RP2DS) and recommended dose for expansion was

determined to be magrolimab dosing at 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, and 22; and 30 mg/kg QW Cycle 2 and beyond. As of Amendment 6, the RP2DS, as selected by the CTSC in November 2019, was determined to be magrolimab dosing at 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, and 22; 30 mg/kg QW for Cycle 2; and 30 mg/kg Q2W starting Cycle 3 and thereafter. In addition, based on Amendment 5, the TN/U Expansion Cohort was expanded to a total of 122 patients, which will include at least 92 patients with MDS (see the Sample Size Justification section), including MDS patients enrolled in the original 30 TN/U Expansion (n = 30). For a higher-risk, untreated, MDS-only expansion under Amendment 6, an evaluation will occur after 36 patients have been enrolled at magrolimab Q1W C3+ and reached the first response assessment. During this evaluation, enrollment will continue, and at least 56 additional patients at a magrolimab Q2 week dosing schedule will be enrolled in the higher-risk, untreated, MDS-only expansion. Therefore, the number has increased to at least 92 patients with MDS in the TN/U Expansion Cohort. This addition is based on initial encouraging efficacy data observed in the TN/U Cohort in patients and FDA feedback for a potential single-arm approval path. The overall MDS expansion to 92 patients will be considered the MDS Registrational Cohort. The CTSC may decide to enroll additional patients beyond 92 (36 QW and 56 Q2W dosing) for further safety, efficacy, and/or dosing data. A subcohort of at least 32 TN/U AML patients with a TP53 gene mutation will be enrolled. This cohort addition is based on encouraging clinical efficacy observed with TP53 mutant AML patients in the TN/U Expansion Cohort, of which 12 slots were allotted prior to Amendment 6 by CTSC decision. Based on emerging data, the CTSC may decide to enroll additional TP53 mutant AML patients beyond the initial 32 for further safety, efficacy, and/or dosing data. In July 2020, the CTSC agreed to add an additional 30 slots (cohort n = 62) in the TN/U Expansion Cohort for TP53 mutant AML patients. This decision was based on encouraging efficacy data in this cohort. The total study numbers are adjusted in Amendment 7 to reflect this decision.

The RBC Transfusion-dependent Low-risk MDS Cohort will consist of approximately 20 patients and be based on a Q4W magrolimab dosing schedule administered

starting Cycle 2. Given that a higher dose of magrolimab (60 mg/kg) will be tested in this cohort, the first 6 patients will be treated in a safety run-in cohort. These 6 patients will be treated with magrolimab monotherapy for the first 2 cycles, followed by a response assessment. Patients who do not respond to magrolimab monotherapy by this time may have azacitidine added to their treatment regimen. Based on the initial safety and efficacy data for these 6 patients, the CTSC will determine whether the remaining 14 patients will be treated with magrolimab monotherapy or in combination with azacitidine, as well as the dose of magrolimab. After a safety evaluation of these 6 patients by the CTSC, the remaining 14 patients can be simultaneously enrolled. Based on emerging data, the CTSC may decide to enroll additional patients for further safety, efficacy, or dosing information. These additional patients may be treated with either magrolimab monotherapy or magrolimab in combination with azacitidine. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.

The Rollover Cohort will be open to all patients (maximum of 8) on the existing Phase 1 AML trial (Study SCI-CD47-002) who are deriving ongoing clinical benefit from magrolimab therapy. Patients in the Rollover Cohort may receive the same dose level and schedule (i.e., twice weekly) of magrolimab monotherapy as previously received on the Phase 1 AML study (SCI-CD47-002), or may transition to once-weekly dosing in this study at the discretion of the Investigator and with Sponsor approval. At the discretion of the CTSC for this study, rollover patients who are receiving lower doses may be escalated to a higher dose deemed to be safe by the CTSC for this study.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment (magrolimab and/or azacitidine), during which time the patient’s eligibility and baseline characteristics will be determined. Study treatment may be continued until an unacceptable drug-related toxicity occurs or until disease progression or loss of clinical benefit.

For all cohorts, response assessments will occur every 8 weeks or as otherwise detailed in the Schedule of Assessments.

Post treatment, patients will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of standard-of-care bone marrow biopsy/aspirate results will continue until documented disease progression occurs.

The end of study is defined as the date on which the last patient completes the last study visit (follow-up for safety, disease progression or survival), or when the CTSC or Sponsor decides to end the study.

Duration of Treatment

Patients enrolled in the R/R, TN/U, and Transfusion-dependent Low-risk MDS Cohorts will receive study treatment until disease progression or unacceptable toxicity. Patients enrolled in the Rollover Cohort will be treated with magrolimab until loss of clinical benefit.

Planned Number of Patients:

Total Number of Patients: Approximately 287 patients evaluable for efficacy:

- R/R Safety Cohort: 10 patients
- R/R Expansion Cohort: Up to 36 patients
- R/R MDS Magrolimab Monotherapy Cohort: 23 patients
- TN/U Dose Evaluation Cohort: Up to 18 patients
- TN/U Expansion Cohort: Up to 172 patients, including
    - Original 30 TN/U Expansion (enrolled 18 AML and 16 MDS patients, including 4 replacement patients)

- At least 92 MDS patients (including the original 16 MDS patients enrolled in original TN/U Expansion), of whom at least 56 patients will be on Q2W dosing. The overall MDS expansion to 92 patients will be considered the MDS Registrational Cohort.
- Up to 62 TP53 mutant AML patients (i.e., 12 original TP53 mutation AML patients, plus 20 additional TP53 mutant AML patients added per CTSC decision in September 2019, plus 30 additional TP53 mutant AML patients per CTSC decision July 2020)

- RBC Transfusion-dependent Low-risk MDS Cohort: Up to 20 patients
- Rollover Cohort: Up to 8 patients

Inclusion Criteria: All Patients

1. Meets the criteria below for the appropriate cohort:
   a) <u>All R/R Cohorts</u>:
      i. Pathologically confirmed AML (defined by 2017 European Leukemia Net [ELN] classification) relapsed or refractory to a prior therapy with either a hypomethylating agent (such as azacitidine or decitabine), non-intensive chemotherapy (such as low-dose cytarabine arabinoside), and/or venetoclax. Treatment is limited to 1 prior line of therapy. Hematopoietic stem cell transplant for patients in remission would not be counted as a line of therapy for AML, or
      ii. Confirmed MDS defined according to World Health Organization (WHO) classification that is either refractory to hypomethylating agent (defined as disease progression per the International Working Group [IWG] MDS response criteria at any time after initiation of a hypomethylating agent or failure to achieve an objective response by IWG 2006 criteria after 4 cycles) or is relapsed or intolerant to prior therapy with either a hypomethylating agent, non-intensive chemotherapy, or targeted therapy. Treatment is limited to 1 prior line

of hypomethylating agent therapy (including investigational hypomethylating agents) for all R/R MDS patients.

iii. R/R MDS Magrolimab Monotherapy Cohort: Inclusion criterion ii above applies.

b) All TN/U Cohorts (meets i or ii):

i. Previously untreated patients with MDS defined according to WHO classification, with an IPSS-R risk category of intermediate, high, or very high risk. Prior and concurrent therapy with hydroxyurea, oral etoposide, erythroid and/or myeloid growth factors is allowed.

ii. Previously untreated patients with histological confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity, age or other factors, or who refuse such therapy; or

c) TP53 Mutant AML Subcohort: Previously untreated patients with histological confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity, age, or other factors, or who refuse such therapy and who have presence of at least 1 TP53 gene mutation by next-generation sequencing based on local evaluation.

d) RBC Transfusion-dependent Low-risk MDS Cohort: MDS patients with very low or low risk by IPSS-R who are RBC transfusion-dependent (requiring ≥ 2 RBC units within 8 weeks prior to screening) and meet at least one of the following:

i. R/R to ESA: documented non-response or response that is no longer maintained to prior ESA-containing regimen

ii. Intolerant to ESA: documentation of discontinuation of prior ESA-containing regimen at any time after initiation due to intolerance or adverse event (AE)

iii. ESA ineligible: endogenous serum erythropoietin level > 500 U/L for patients who have not been previously treated with ESAs

iv. Have a deletion in chromosome 5q and who are relapsed/refractory/intolerant to or ineligible for lenalidomide therapy

e) Rollover Cohort: Patients on active magrolimab therapy on the Phase 1 AML (SCI-CD47-002) trial who are deriving clinical benefit by Investigator assessment.

2. White blood cell (WBC) count ≤ 20 × 10^3/mcL pre-first dose of study treatment and prior to each magrolimab dose for Cycle 1. Patients with WBC > 20 × 10^3/mcL can be treated with hydroxyurea (up to 4 g/day) throughout the trial to reduce the WBC to ≤ 20 × $10^{3/}$mcL. Oral etoposide (up to 200 mg orally [PO] /day) may be given as an alternative to hydroxyurea for patients who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.
3. Patient has provided informed consent.
4. Must be willing and able to comply with clinic visits and procedures outlined in dosing.

R/R Cohorts (including the R/R MDS Magrolimab Monotherapy Cohort), TN/U Cohorts (including the MDS Registrational Cohort and the TP53 Mutant TN/U AML Subcohort), and RBC Transfusion-dependent Low-risk MDS Cohort only (Criteria 5 through 9 DO NOT apply to the Rollover Cohort):

5. Male or female, age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2
7. Hemoglobin must be ≥ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab infusion; patient must be willing to undergo blood transfusions as deemed clinically necessary. NOTE: Transfusions are allowed to meet hemoglobin eligibility (see Section 6.2.2.1 for anemia management)
8. Pretreatment blood crossmatch completed (as detailed in Section 6.2.2.1 and Section 7.3.4)

9. Biochemical indices within the ranges shown below:

    a) Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤ 5× upper limit of normal (ULN)
    b) Bilirubin ≤ 1.5× ULN or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent
    c) Serum creatinine ≤ 1.5× ULN or calculated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2
10. Female patients 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 enrollment and within 72 hours before the first administration of study drug.
11. Female patients of childbearing potential must be willing to use 1 highly effective method of contraception during the study and continue for 6 months after the last dose of magrolimab or azacitidine, whichever ends later (Section 4.5.2 of the protocol).
12. Male patients who are sexually active with a woman of childbearing potential (WOCBP) and who have not had vasectomies must be willing to use a barrier method of contraception during the study and for 3 months after the last dose of magrolimab or azacitidine, whichever ends later (Section 4.5.4 of the protocol).
13. Willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines), unless not feasible as determined by the Investigator.

Exclusion Criteria

1. Prior treatment with CD47 or SIRPα-targeting agents (with exception of magrolimab for patients in the Rollover Cohort)
2. Prior anti-leukemic therapies including, but not limited to, chemotherapy (with the exception of hydroxyurea or oral etoposide), targeted therapies, immunotherapy, or radiotherapy within 4 weeks prior to Day 1 magrolimab

dosing. NOTE: Localized non-central nervous system (non-CNS) radiotherapy, 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.

3. TN/U Cohorts only: Any prior anti-leukemic therapy (excluding hydroxyurea or oral etoposide), prior treatment with hypomethylating agents and/or low dose cytarabine
4. R/R Expansion Cohort, R/R MDS Magrolimab Monotherapy Cohort, TN/U Cohorts, and RBC Transfusion-dependent Low-risk MDS Cohort only: Contraindications to azacitidine, including advanced malignant hepatic tumors or known hypersensitivity to azacitidine or mannitol
5. Acute promyelocytic leukemia
6. Known inherited or acquired bleeding disorders
7. Previous allogeneic hematopoietic stem cell transplant within 6 months prior to enrollment, active graft versus host disease (GVHD), or requiring transplant-related immunosuppression
8. Clinical suspicion of active CNS involvement by leukemia.
9. 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 (NYHA) Class III-IV.
10. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapy as defined in Exclusion Criterion 2.
11. History of psychiatric illness or substance abuse likely to interfere with the ability to comply with protocol requirements or give informed consent
12. Pregnancy or active breastfeeding

13. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV)

Test Product, Dose, and Mode of Administration

Magrolimab is a humanized monoclonal antibody against CD47, which is administered intravenously (IV).

- **R/R Safety and Expansion Cohorts**: In the R/R Safety Cohort, magrolimab monotherapy will be administered twice weekly on an intrapatient dose escalation schedule: 1 mg/kg twice weekly for Week 1 (Day 1 and Day 4); 15 mg/kg on Day 8; 30 mg/kg on Day 11 and Day 15; and 30 mg/kg weekly thereafter. For the R/R Expansion Cohort, magrolimab will be administered on a different dose schedule: 1 mg/kg twice weekly for Week 1 (Day 1 and Day 4); 15 mg/kg on Day 8; 30 mg/kg on Day 11 and Day 15; and 30 mg/kg weekly on Day 22 through end of Cycle 2, then 30 mg/kg Q2W starting Cycle 3 and thereafter. For R/R Expansion, azacitidine will be administered according to approved labeling, either subcutaneously (SC) or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle.
- **R/R MDS Magrolimab Monotherapy Cohort:** Magrolimab will be administered twice weekly through Cycle 1 Day 11, and then weekly beginning Cycle 1 Day 15 and thereafter using a similar intrapatient dose escalation schedule as used for the R/R Safety Cohort (1 mg/kg on Day 1 and Day 4, 15 mg/kg on Day 8, 30 mg/kg on Day 11 and Day 15, 30 mg/kg weekly through end of Cycle 2). However, for this subcohort, patients will receive magrolimab after intrapatient dose escalation at 30 mg/kg Q2W starting Cycle 3 and thereafter).
- **TN/U Dose Evaluation Cohort:** Magrolimab will be administered twice weekly through Cycle 1, Day 11, and then weekly beginning Cycle 1, Day 15, and thereafter using a similar intrapatient dose escalation schedule as used for the R/R Safety Cohort (1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11 and 15; and 30 mg/kg weekly thereafter). Azacitidine will be administered according to approved labeling, either SC or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle.

- **TN/U Expansion Cohort (including MDS Registrational Cohort):** As of Amendment 5, RP2DS for magrolimab as determined in the TN/U Dose Evaluation Cohort, is identical to that tested in the R/R Safety Cohort. Magrolimab will be administered twice weekly through Cycle 1, Day 11, and then weekly beginning Cycle 1, Day 15 and thereafter using a similar intrapatient dose escalation schedule as used for the R/R Safety Cohort (1 mg/kg on Day 1 and Day 4, 15 mg/kg on Day 8, 30 mg/kg on Day 11 and Day 15, 30 mg/kg weekly through end of Cycle 2). However, as of Amendment 6, patients will receive magrolimab after intrapatient dose escalation at 30 mg/kg Q2W starting Cycle 3 and thereafter. Azacitidine SC or IV will be administered at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle.
- **TP53 Mutant TN/U AML Subcohort:** Magrolimab will be administered as 1 mg/kg twice weekly for Week 1 (Day 1 and Day 4); 15 mg/kg on Day 8; 30 mg/kg on Day 11 and Day 15; and 30 mg/kg weekly from Day 22 through end of Cycle 2, then 30 mg/kg Q2W starting Cycle 3 and thereafter. Azacitidine will be administered according to approved labeling, either SC or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle.
- **RBC Transfusion-dependent Low-risk MDS Cohort:** Magrolimab will be administered as 1 mg/kg on Cycle 1 Day 1; at 30 mg/kg on Cycle 1 Days 8, 15, and 22; and at 60 mg/kg Q4W starting on Cycle 2 Day 1 and thereafter. Azacitidine will be administered either SC or IV at the dose of 75 mg/m^2 on Days 1 to 5 of each 28-day cycle. The dosing regimen for magrolimab and azacitidine is specific for low-risk MDS to maximize patient convenience/quality of life as well as the safety/efficacy risk/benefit. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.
- **Rollover Cohort:** Patients may continue to receive magrolimab monotherapy at the same dose level and schedule (i.e., twice weekly) they were receiving in the previous study (SCI-CD47-002), or may transition to once-weekly dosing at the discretion of the Investigator and with Sponsor approval; dose escalation up to

the highest dose deemed to be safe on this study by the CTSC may occur at the discretion of the CTSC for those rollover patients receiving a lower dose level.

Study Endpoints

Primary Endpoints

- Measurement of AEs according to NCI CTCAE Version 4.03 or customized AE severity grading as defined in the protocol (Appendix A of the protocol)
- CR rate for patients with AML as defined by the Investigator according to protocol-specified criteria (Appendix B of the protocol), which are based on European Leukemia Net (ELN) AML recommendations, CR rate for patients with MDS as defined by the IWG 2006 MDS response criteria
- 8-week RBC transfusion independence rate for patients with low-risk MDS as defined by the lack of RBC transfusions for at least an 8-week consecutive period at any time after starting therapy

Secondary Endpoints

- Magrolimab concentration versus time measurements
- Anti-drug antibodies to magrolimab
- Objective response in AML based on ELN AML recommendations and IWG AML response criteria, or ORR in MDS as defined by the IWG 2006 MDS response criteria; CRh; DCR and DOR for patients with AML; DCR and DOR for patients with MDS; RBC transfusion independence (no RBC transfusions for at least an 8-week consecutive period); 12-week RBC transfusion independence rates; mean hemoglobin increase on therapy; and, where appropriate, PFS, RFS, EFS, and OS for patients with AML or MDS
- Level of MRD negativity using a multiparameter flow cytometry-based assay for patients on therapy

CCI

[redacted]

Statistical Methods and Analyses

Time-to-event data will be analyzed by the Kaplan-Meier method. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, range, and median). Frequency counts and percentage of patients within each category will be provided for categorical data.

The safety and efficacy analysis will be conducted on all enrolled patients who receive at least 1 dose of magrolimab. An evaluable patient efficacy analysis will also be performed on all patients who receive at least 1 dose of magrolimab and have at least 1 disease response assessment or who died before the first disease response assessment.

The PK analysis set (PAS), defined as all treated patients who have at least 1 blood sample that provides evaluable PK data, will be used for summaries of PK concentration data and PK parameters.

The rate and magnitude of anti-magrolimab antibody positivity will be evaluated.

PD and correlative studies will be conducted on patient samples, and both tissue and blood samples may be biobanked for future analyses.

Sample Size Justification

A total of approximately 287 efficacy evaluable patients may be enrolled.

For the R/R Safety Cohort and Expansion Cohort, approximately 46 patients may be enrolled, including 10 patients treated in the safety run-in cohort and 36 patients treated in the expansion cohort. For the R/R Safety Cohort, 10 patients were enrolled, and this cohort was closed to further enrollment as of Amendment 3. Based on safety and efficacy data, the CTSC may decide to expand the R/R Expansion Cohort to include additional patients. An ORR of 17% has been reported in patients with R/R AML who have been treated with azacitidine (Itzykson 2015). For an estimated response rate of 33% or higher, 36 patients would provide a 95% confidence interval, with the lower bound to exclude 18.6%, the azacitidine monotherapy efficacy rate.

For the TN/U Dose Evaluation Cohort, up to 18 patients can be enrolled based on a 3+3 dose de-escalation design assuming 3 potential dose cohorts with a maximum of 6 patients treated per cohort. For the TN/U Dose Evaluation Cohort, 8 patients were enrolled, and this cohort was closed to further enrollment as of Amendment 5. For the TN/U Expansion Cohort, an initial sample size of 30 patients was proposed so that the 95% confidence interval of the desired 35% or higher CR rate would exclude a known CR rate of 17.85% for azacitidine alone. This sample size calculation was based on inclusion of both TN/U AML and higher-risk MDS patients. For the higher-risk, untreated, MDS-only Expansion Cohort added in Amendment 5 (16 originally enrolled MDS patients + 76 additional patients for n = 92), an evaluation will occur after 36 patients have reached the first response assessment (Cycle 3 Day 1); however, enrollment will continue and will not be paused in the interim. A sample size of 36 patients provides 80% power to reject the null hypothesis that the CR rate is 16.5% or lower at 2-sided 0.05 significant level, assuming the true magrolimab+azacitidine CR rate is at least 35.5% (19%

improvement). The null CR rate of 16.5% is based on the pivotal randomized trial leading to azacitidine approval in MDS reanalyzed by IWG 2000 criteria (Silverman 2006), where the upper bound of the 1-sided 95% confidence interval for azacitidine CR rate is 16.5%, with a point estimate of 10%. Based on Amendment 6, per discussion with the FDA in November 2019, the primary endpoint for this untreated, higher-risk MDS cohort was changed from CR+PR to CR rate to support a potential single-arm approval. In accordance with this CR endpoint and a transition to a Q2W magrolimab dosing regimen, a cohort of 56 patients at Q2W magrolimab dosing was added. A sample size of 56 patients provides 80% power to reject the null hypothesis that the CR rate is 16.5% or lower at a 2-sided 0.05 significant level, assuming the true CR rate is at least 31.5% (i.e., a 15% improvement). A combined planned sample size of 92 patients for the MDS Registrational Cohort will provide an 80% power to reject the updated null CR rate of 23.5% at a 2-sided 0.05 significant level, assuming the true magrolimab+azacitidine CR rate is 36.5%.

For the R/R MDS Magrolimab Monotherapy Cohort, patients will be enrolled in a Simon's 2-stage design. With 1-sided significance level of 0.05 and 80% power, the null hypothesis that the magrolimab monotherapy response rate is 9% will be tested against the alternative of 30%. In the first stage, 11 patients will be enrolled. If there are 1 or fewer responses observed in these 11 patients, the cohort will be stopped. Otherwise, 12 additional patients will be accrued, for a total of 23. This cohort was stopped after 11 patients enrolled per CTSC decision in October 2020. The null hypothesis will be rejected if 5 or more responses are observed in 23 patients. For patients who do not achieve an objective response at their first protocol-defined response assessment, azacitidine can be added on subsequent cycles at the discretion of the PI with Sponsor approval. Azacitidine will be administered in the identical dosing schedule as the R/R expansion cohort.

Per CTSC decision in September 2019 and Amendment 6, a subcohort of TP53 mutant TN/U AML patients was added. Initially, up to 32 patients will be enrolled. Analysis of these patients will include all TP53 mutant patients meeting subcohort

eligibility criteria enrolled prior to the Amendment/CTSC decision. A sample size of 32 patients was selected to evaluate the initial efficacy of magrolimab+azacitidine as compared to available therapies (most notably venetoclax+hypomethylating agents) in TP53 mutant AML. While venetoclax in combination with hypomethylating agents (azacitidine or decitabine) is approved in newly diagnosed AML patients who are ineligible for intensive chemotherapy, its efficacy in TP53 mutant AML patients is limited. Per a recent report, the CR+ complete remission with incomplete blood count recovery (CRi) rate of venetoclax+hypomethylating agent in TP53 mutant AML was 47% with a median duration of CR of 5.6 months and a median overall survival of 7.2 months (DiNardo 2019). In contrast, in all-comer AML patients, the CR+CRi rate was 67% with a median duration of CR of 11.3 months and a median overall survival of 17.5 months. Assuming an observed magrolimab+azacitidine ORR of 59% for a sample size of 32 patients, the 1-sided 90% confidence interval will have a lower bound of 46.5%, which excludes a control ORR of 46%. Based on emerging data, the CTSC may decide to enroll additional patients for further safety, efficacy, or dosing information. Per CTSC decision in July 2020 and captured in Amendment 7, an additional 30 TP53 mutant AML patients were enrolled for the TN/U Expansion TP53 AML Cohort.

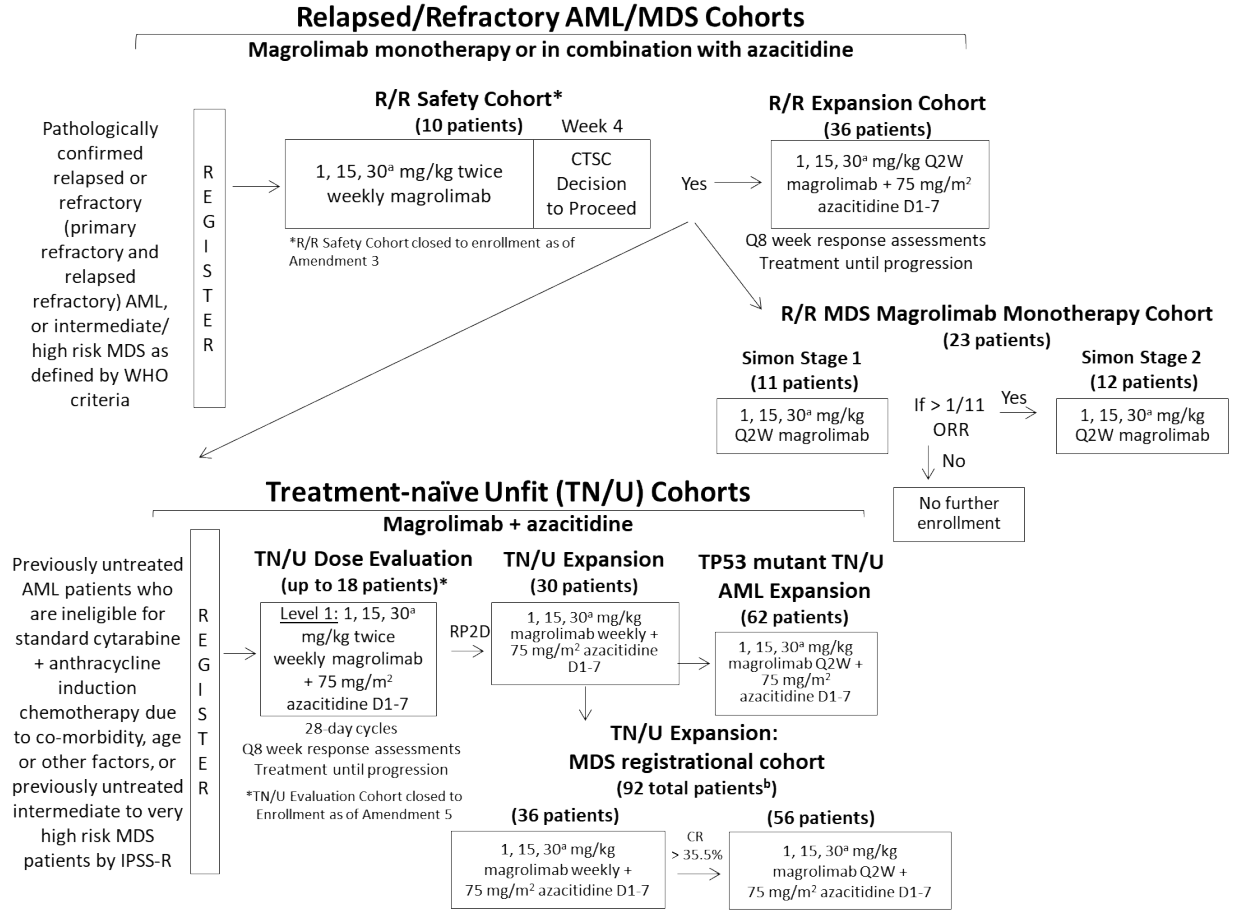
For the RBC Transfusion-dependent Low-risk MDS Cohort, approximately 20 patients will be enrolled. Initially, 6 patients will be enrolled with a safety evaluation after all 6 patients complete at least Cycle 2 Day 15 treatment. This safety evaluation is being conducted given that a 60 mg/kg dose of magrolimab will be administered starting in Cycle 2, of which this highest dose has not yet been tested in patients. However, an equivalent dose of 60 mg/kg given in 1 week (30 mg/kg twice weekly) has already been administered to MDS and AML patients in this trial and has been well tolerated. The CTSC will then evaluate based on the aggregate safety profile in these 6 patients and determine whether enrollment should proceed to the remaining 14 patients. If so, these 14 patients can be simultaneously enrolled. The sample size of 20 patients is to be enrolled to evaluate an initial efficacy signal in this population, with further enrollment based on this signal. Based on emerging data, the CTSC may decide to enroll additional patients

for further safety, efficacy, or dosing information. These may be enrolled as either magrolimab monotherapy or in combination with azacitidine. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.

For the Rollover Cohort, 1 eligible patient from the Phase 1 study (SCI-CD47-002) was enrolled in this study, and this cohort was closed to further enrollment as of Amendment 3.

STUDY DESIGN SCHEMA

Figure 1. Study Schema: Relapsed/Refractory AML and TN/U Cohorts

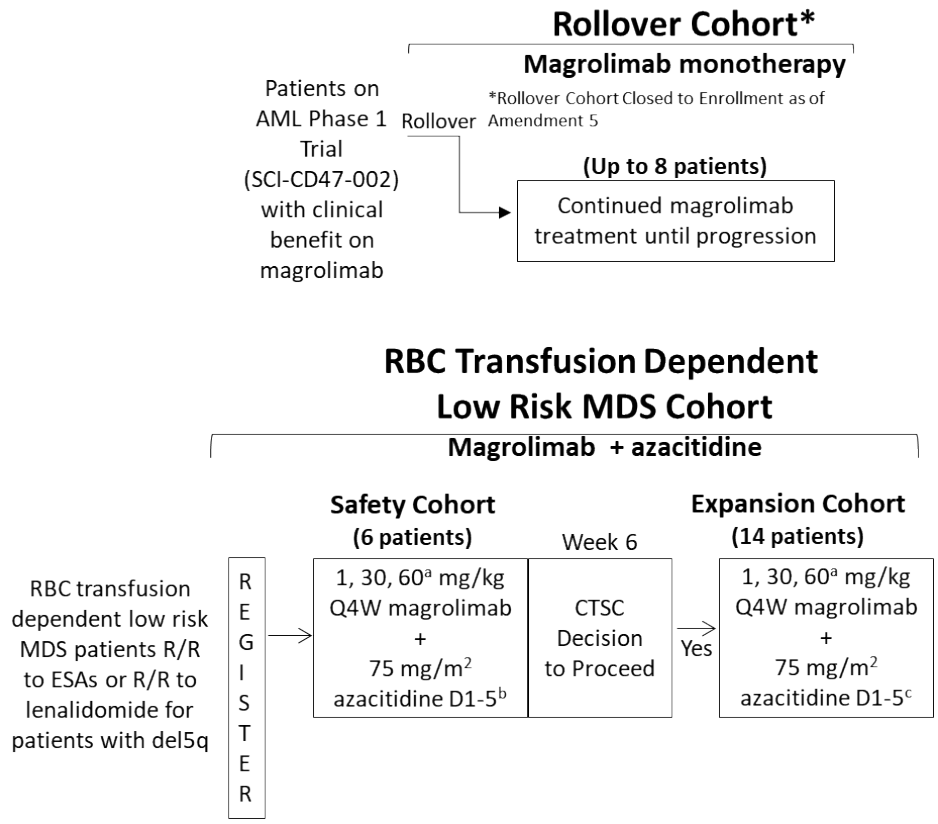


Abbreviations: AML = acute myeloid leukemia; CTSC = Clinical Trial Steering Committee; D = day; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; Q2W = every 2 weeks; Q8 week = every 8 weeks; R/R = relapsed/refractory; TN/U = treatment-naïve/unfit; WHO = World Health Organization

a Dosing will be 1 mg/kg twice weekly for 1 week (Cycle 1 Days 1 and 4) followed by 15 mg/kg on Cycle 1 Day 8; then 30 mg/kg on Cycle 1 Days 11, 15, and 22; then 30 mg/kg QW in Cycle 2 (Days 1, 8, 15, and 22); then Q2W (Days 1, 15) starting Cycle 3 and thereafter, as per dosing schedule.

b There will be 92 MDS patients in total, inclusive of those 16 MDS patients treated in the original 30-patient TN/U Expansion Cohort.

Figure 2. Study Schema: Rollover AML and RBC Transfusion-dependent Low-risk MDS Cohorts



Abbreviations: AML = acute myeloid leukemia; CTSC = Clinical Trial Steering Committee; D =day; del5q = deletion in chromosome 5q; ESA = erythropoiesis-stimulating agent; MDS = myelodysplastic syndrome; Q4W = every 4 weeks; R/R = relapsed/refractory; TN/U = treatment-naïve/unfit; RBC = red blood cell

a Dosing will be 1 mg/kg on Cycle 1 Day 1; 30 mg/kg on Cycle 1 Days 8, 15, and 22; and 60 mg/kg Q4W starting Cycle 2 and thereafter.
b The safety cohort will be treated with magrolimab monotherapy. For patients who do not respond after Cycle 2, azacitidine may be added on subsequent cycles.
c The expansion cohort will be treated with magrolimab or magrolimab+azacitidine based on CTSC evaluation of the safety cohort.

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ABBREVIATIONS AND DEFINITIONS

ABO	any of the four blood groups A, B, AB, and O comprising the ABO system
ADA	anti-drug antibodies
ADL	activities of daily life
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{tau}	the area under concentration curve during a dosing interval
Aza	azacitidine
BLA	Biologics License Application
BUN	blood urea nitrogen
CBCs	complete blood counts
CFR	Code of Federal Regulations
cCR	cytogenetic complete remission
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete remission
CRC	colorectal cancer
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete blood count recovery
CR_{MRD-}	complete remission without minimal residual disease
CSR	clinical study report
CTSC	Clinical Trial Steering Committee

CV	coefficient of variation
CyTOF	mass cytometry
DAT	direct antiglobulin test
DCR	duration of complete remission
DLT	dose-limiting toxicity
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
EGA	4-bromobenzaldehyde *N*-(2,6-dimethylphenyl)semicarbazone (a compound that protects cells from multiple toxins and viruses)
ELN	European Leukemia Net
EOT	end-of-treatment
ESA	erythropoiesis-stimulating agent
FAB	French-American-British classification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	graft versus host disease
Hgb	hemoglobin
HI	hematologic improvement
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
IPSS-R	Revised International Prognostic Scoring System

IRB	Institutional Review Board
IUD	intra-uterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWG	International Working Group
kg	kilogram
KM	Kaplan-Meier
L	liters
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
LISS	low ionic strength solution
M1	macrophages that suppress tumor progression
M2	macrophages that promote tumor progression
mAb	monoclonal antibody
mCR	molecular complete remission
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MLFS	morphologic leukemia-free state
MNS	A human blood group system based upon two genes (glycophorin A and glycophorin B) on chromosome 4
MOA	mechanism of action
MRD	minimal residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin’s lymphoma
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAS	pharmacokinetics (PK) analysis set

PBMC	peripheral blood mononuclear cell
PCD	programmed cell death
PD	pharmacodynamics
PE	physical examination
PeG	polyethylene glycol
PFS	progression-free survival
PK	pharmacokinetics
PO	*per os*; orally
PR	partial remission
PrCR	programmed cell removal
PT	prothrombin time
QW	once weekly
Q2	every 2
Q2C	every 2 cycles
Q2W	every 2 weeks
Q3C	every 3 cycles
Q4W	every 4 weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
REC	Research Ethics Committee
RFS	relapse-free survival
Rh	Rhesus factor
RNA	ribonucleic acid
RO	receptor occupancy
RP2DS	recommended Phase 2 dose and schedule
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease *or* standard deviation
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase

SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SOC	standard of care
S-P	Ser-Pro
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TN/U	treatment-naïve/unfit (for standard induction chemotherapy)
TP53	tumor protein 53
ULN	upper limit of normal
UK	United Kingdom
US	United States
V_z	volume of distribution during the terminal phase
WBC	white blood cell
WOCBP	woman of childbearing potential
WHO	World Health Organization

1. BACKGROUND

1.1. Acute Myeloid Leukemia and Myelodysplastic Syndrome

Acute myeloid leukemia (AML) is a common hematological malignancy whose incidence rises from 3:100,000 in young adults to greater than 20:100,000 in older adults. Approximately 80% of AML patients are > 60 years of age, so in an aging population, the disease is becoming more common. For patients < 60 years of age, 5-year overall survival (OS) is 40 to 50%, but is only 5% for patients > 60 years of age. Thus, most adult AML patients die of their disease. For patients who are fit for combination therapy, initial treatment consists of induction chemotherapy with cytarabine and an anthracycline (idarubicin or daunorubicin). Despite an initial therapy response, in most patients the disease relapses. Presumably, therapy often fails to eradicate all tumor-propagating cells and indeed selects for chemotherapy-resistant leukemia-propagating sub-clones. AML patients who are relapsed and/or refractory to conventional therapies have limited options for treatment. Prognosis is poor in this population with median OS of approximately 3 to 5 months (Roboz 2014; Feldman 2005). Patients refractory to salvage therapy are treated palliatively, as current treatment options are extremely limited. These patients have a median survival of 2 months and long-term survival rates of 5 to 10%. No standard of care (SOC) exists for AML patients who are either relapsed and/or refractory to therapies. Therefore, there is an urgent need for new treatment modalities for this patient population.

In the newly diagnosed setting, standard therapy is induction chemotherapy followed by either consolidation therapy or hematopoietic stem cell transplant (HSCT) based on baseline characteristics, disease risk factors, and response to initial therapy. However, a significant percentage of newly diagnosed patients are ineligible for these therapies. Due to age-related co-morbidities, these patients often are ineligible for aggressive induction chemotherapy and HSCT due to a significantly increased risk of treatment-related mortality. Instead, SOC for these patients are treatment with hypomethylating agents (e.g., azacitidine), which have a lower risk of toxicity, or supportive care measures. However, these treatments are rarely curative and provide a treatment benefit of median OS of approximately only 10 months (Dombret 2015). Thus, there is

intense interest to improve the current SOC with therapies that can be combined with azacitidine to augment anti-leukemic activity.

A growing body of evidence indicates that in AML there is a subpopulation of leukemic stem cells that are relatively resistant to therapy (Craddock 2013; Gerber 2012). Thus, novel agents that target leukemic stem cells have the potential to improve clinical outcomes compared to the current SOC (Gupta 2009; Majeti 2011). The anti-CD47 antibody magrolimab has demonstrated potent anti-leukemic stem cell activity and broad preclinical activity in AML (Liu 2015b; Majeti 2009).

Myelodysplastic syndrome (MDS) is a pre-malignant condition characterized by peripheral cytopenias 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 the untreated lower-risk MDS setting, erythropoiesis-stimulating agents (ESAs) and lenalidomide for patients with a deletion in chromosome 5q are standard of care. The main treatment goal for these patients is to improve their symptomatic cytopenias, most frequently their transfusion requirements for RBCs. For lower-risk MDS patients who fail ESAs or lenalidomide, limited options exist and achieving RBC transfusion independence is generally seen in less than a third of patients (Thepot 2016; Santini 2016). In addition, these treatment options are generally not disease modifying and only address symptomatic improvement. Thus, novel agents that are well tolerated and disease modifying are needed in lower-risk MDS patients, especially those that fail ESAs and lenalidomide. In contrast to lower-risk MDS, intermediate-, high-, and very high-risk MDS patients are generally treated with hypomethylating agents, mostly azacitidine, and carry a high risk of leukemic progression. Azacitidine is SOC for newly diagnosed MDS patients with specific high risk subtypes. However, complete remission (CR) rates are low and OS is only around 13 months (Silverman 2002). Thus, novel therapies that replace or augment the efficacy of azacitidine are needed to extend survival for MDS patients. Furthermore, no SOC exists for patients who fail frontline therapy with

hypomethylating agents. Thus, MDS patients who fail frontline therapy also have a poor prognosis with need for more effective treatment modalities.

Magrolimab has been investigated in a Phase 1 AML trial (Study SCI-CD47-002) operating in the United Kingdom (UK) and is being further investigated in this study in multiple subtypes of AML, very low/low-risk MDS, and intermediate/high/very high-risk MDS, both as monotherapy and in combination with azacitidine.

1.2. Study Drug: Magrolimab

1.2.1. Nonclinical Background

1.2.1.1. Nonclinical Introduction

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 (PCD) and programmed cell removal (PrCR; Chao 2012). Many of the steps in cancer progression subvert the multiple mechanisms of PCD, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint (Chao 2012). Increased CD47 expression was identified first on leukemic stem cells in human AML (Majeti 2009), and since then it has been found that CD47 expression is increased on the surface of cancer cells from a large number of diverse human tumor types.

In mouse xenografts, 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 (Majeti 2009; Chao 2010a; Chao 2011a; Chao 2011b; Edris 2012; Kim 2012; 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 pro-phagocytic signals expressed mainly on tumor cells and not on normal cell counterparts (Chao 2010b). In addition, the anti-CD47 antibody induces an anti-cancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis (Tseng 2013; Liu 2015a). Furthermore, CD47-blocking mAbs have shown synergistic efficacious activity with cancer-specific targeting antibodies, including anti-CD20 antibody rituximab in non-Hodgkin's lymphoma (NHL) (Chao 2010a).

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.

1.2.1.2. Nonclinical Efficacy

Magrolimab is an anti-human CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells (Liu 2015b). 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 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 2015b). 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 anti-CD47 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).

Specifically in AML, magrolimab treatment eliminated both circulating leukemic and bone marrow disease in nonclinical mouse models engrafted with human patient AML cells (Liu 2015b; Figure 1-1). The anti-leukemic effect of magrolimab was rapid, as elimination of leukemic blasts in the bone marrow occurred as early as 14 days after start of treatment. Regeneration of normal hematopoiesis in the bone marrow occurred, with 80 to 100% of mice treated achieving long term durable remissions. Furthermore, anti-CD47 antibody specifically eliminated leukemic stem cells and inhibited the ability for leukemic re-growth (Majeti 2009). The anti-leukemic effect of anti-CD47 antibody therapy is broad in AML, as efficacy is observed in nonclinical studies across cytogenetic, molecular, and morphologic AML subtypes (Liu 2015b; Majeti 2009).

Anti-CD47 antibody may also have therapeutic efficacy in MDS. 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 preclinical models, dysplastic cells from high risk MDS patients were eliminated by phagocytosis with an anti-CD47 antibody (Pang 2013).

Figure 1-1. Magrolimab Eliminates Leukemic Disease in Patient-derived AML Mouse Xenograft Models

Figure 1-1 Part A

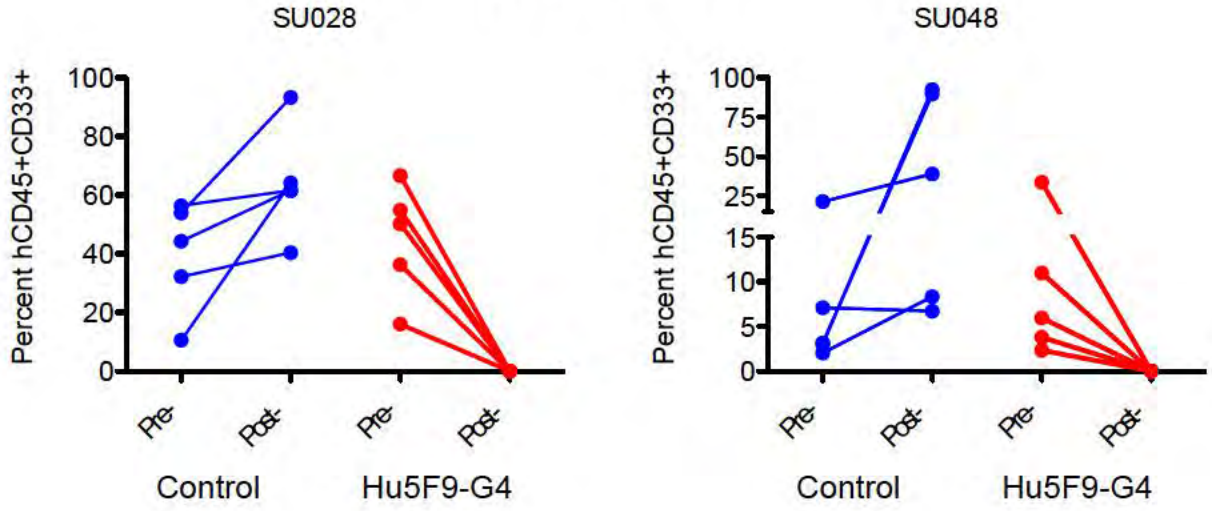
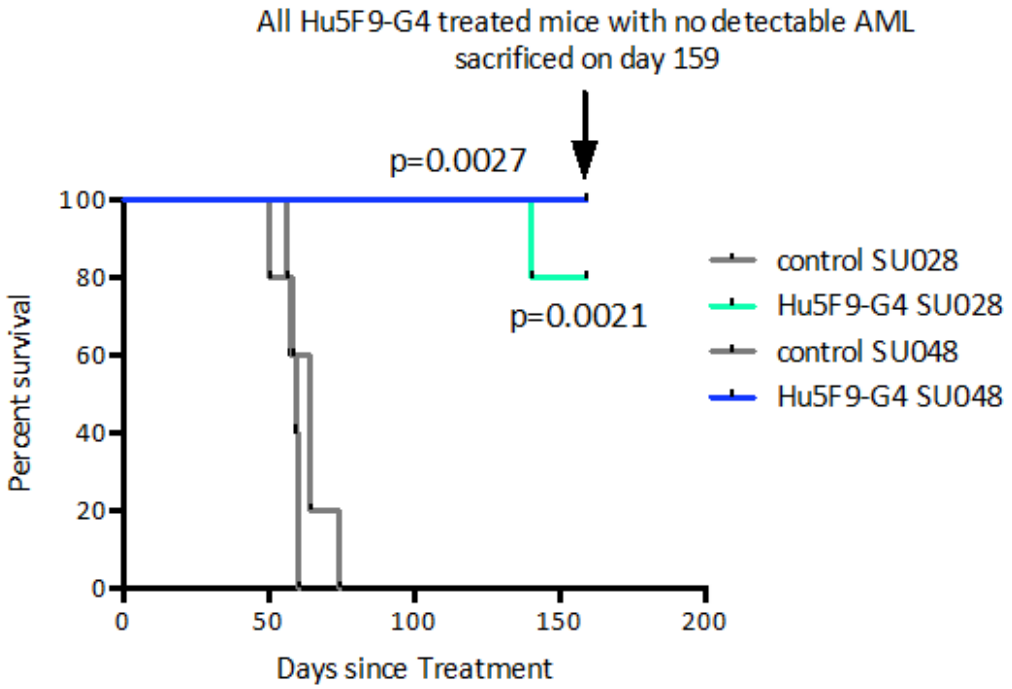


Figure 1-1 Part B

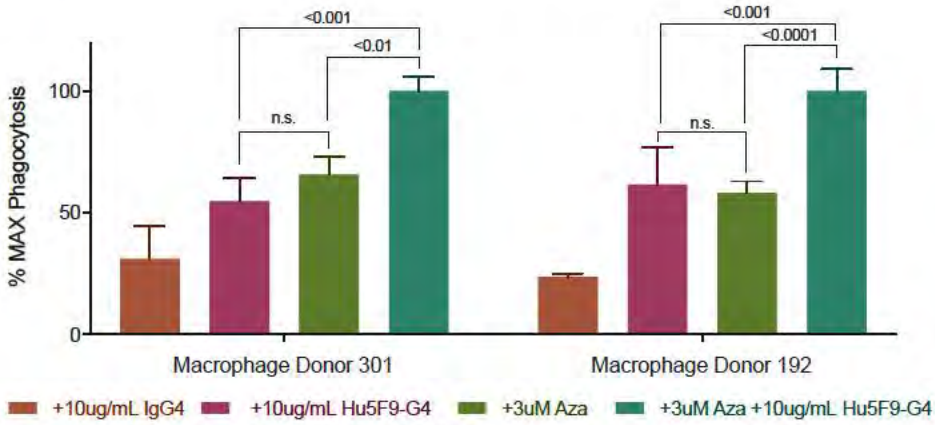


Source: Liu 2015b
Abbreviations: AML = acute myeloid leukemia

In addition to magrolimab monotherapy activity in AML, the therapeutic potential for combination with magrolimab has been explored in nonclinical studies. It has been shown that certain chemotherapies induce pro-phagocytic signal expression on tumor cells (Obeid 2007), which can potentially augment the anti-tumor activity of magrolimab through simultaneous blockade of the “don’t eat me” signal CD47 and upregulation of pro-phagocytic signals on tumor cells. Hypomethylating agents, notably azacitidine, are standard-of-care frontline therapy for AML patients who are unfit for induction chemotherapy. Since a major MOA of azacitidine is leukemic cell cytotoxicity, it is hypothesized that the addition of magrolimab to azacitidine will augment phagocytic clearance of dying leukemic cells induced by azacitidine, thereby leading to enhanced anti-leukemic activity. Thus, the therapeutic activity of combination treatment with magrolimab and azacitidine was recently explored by the Sponsor in nonclinical models. Cells from the leukemia cell line HL60 were incubated for 24 hours with human macrophages differentiated from two independent human donors in the presence of 3 μM azacitidine, 10 mcg/mL magrolimab, or control IgG4 antibody, or the combination.

The 3 µM azacitidine dose was selected since this is the approximate peak plasma concentration of azacitidine in patients (Marcucci 2005; Garcia-Manero 2008). Consistent with this hypothesis, the combination of magrolimab and azacitidine led to a statistically significant increase in leukemic cell phagocytosis in vitro compared to either monotherapy (Figure 1-2).

Figure 1-2. Combination Treatment With Azacitidine and Magrolimab Enhances Phagocytic Elimination of Acute Myelogenous Leukemia Cancer Cells by Human Macrophages



Source: Research Report FSI-2017-001.
Abbreviations: AML = acute myeloid leukemia; Aza = azacitidine.
Note: Figure represents phagocytosis of HL60 AML cells by human macrophages.

1.2.1.3. Nonclinical Toxicology

In general, magrolimab selectively eliminates tumor cells while sparing normal cell counterparts. Most normal cells lack expression of pro-phagocytic signals and are thus unaffected by magrolimab binding to and blocking CD47. RBCs are a notable exception because CD47 expression protects RBCs from elimination by splenic red pulp macrophages, as well as sinusoidal macrophages, in liver and bone marrow. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of magrolimab accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger

cells. Moreover, the potential for severe anemia in these nonclinical studies is ameliorated by administration of a low priming dose of the antibody that results in mild to moderate anemia and stimulates reticulocytosis.

The safety profile of magrolimab was specifically evaluated in nonclinical models of AML. One key AML-specific safety finding was observed in these models. In mice xenografted with high circulating leukemic disease burden, early death was observed in a fraction of mice within 1 hour of magrolimab administration. This early death exclusively occurred in cases of high burden circulating leukemia cells (> 50% of circulating peripheral white cell burden due to AML). Extensive clinical pathology and histologic analyses have failed to identify the cause of early death. There was no evidence of (i) tumor lysis and biochemical perturbations that could cause sudden death; (ii) emboli/immune complexes of AML cells/antibody in vital organs (lung, heart, endocrine organs - full autopsies were performed on the mice); (iii) bleeding, e.g., within the central nervous system (CNS); or (iv) cytokine-mediated perturbation in cardiac output, airways or gas exchange. Importantly, early death with high circulating and marrow burden of disease could be completely avoided by first lowering the circulating burden of disease with an initial low dose of magrolimab (< 0.3 mg/kg dose equivalent) and then gradual weekly intrasubject dose escalation. This intrasubject dose escalation regimen not only completed mitigated early death, but also cleared leukemic disease in the bone marrow in 100% of the mice treated. Thus, based on this nonclinical data, an intrapatient dose escalation regimen was utilized for the Phase 1 trial of magrolimab in AML (SCI-CD47-002).

1.2.2. Clinical Background

1.2.2.1. Summary of Magrolimab Clinical Safety

Magrolimab has been administered as monotherapy and in combination with other antitumor compounds in clinical trials. A summary of the clinical safety and efficacy data from ongoing human clinical trials with magrolimab is presented in the most recent magrolimab Investigator's Brochure (IB), including data from Studies SCI-CD47-001 (solid tumors), SCI-CD47-002 (AML), 5F9003 (NHL), 5F9004 (colorectal cancer [CRC]), and 5F9006 (ovarian cancer). Refer to the IB for additional information.

Based on the patient experience in trials across multiple oncology indications, magrolimab has been well tolerated. The most common treatment-associated effects across both solid tumor and AML patients are related to the targeting of CD47 on erythrocytes, with anemia and RBC agglutination being most prominent.

The recommended priming dose of 1 mg/kg of magrolimab was defined by the dose-limiting toxicities (DLTs) seen in patients with solid tumors: acute abdominal pain and headache associated with hemagglutination. However, using a priming and maintenance dose schedule in these patients has allowed for the further escalation of the maintenance dose to 10 to 30 mg/kg weekly.

In the trial in solid tumor patients (SCI-CD47-001), as expected, the most common, clinically relevant toxicity has been an acute anemia manifested as an approximately 2 g/dL fall in hemoglobin observed during the first 1 to 2 weeks of treatment. This is followed by a compensatory reticulocytosis and a gradual return to baseline by Week 3 or 4 despite continued dosing. These clinical observations are completely consistent with the known MOA of magrolimab and the physiologic role of CD47 in regulating the turnover of aging erythrocytes. The degree of anemia is mitigated by use of a priming and maintenance dose regimen. An initial low priming dose eliminates aged RBCs that are susceptible to CD47-blockade mediated clearance, which induces a reticulocytosis and shifts the RBC pool to younger cells which are not susceptible to magrolimab clearance. Subsequent higher maintenance doses can then be administered without further anemia. Other associated laboratory abnormalities including reticulocytosis, spherocytosis, transient hyperbilirubinemia (predominantly unconjugated), and decreased haptoglobin are all indicative of extravascular hemolysis consistent with phagocytic removal of RBCs due to blockade of CD47.

A second treatment-related effect on erythrocytes is hemagglutination, which is presumed to result from the direct interaction of magrolimab with CD47 on RBCs. Hemagglutination, when present, has been typically observed within 24 hours of study drug administration and is transient and reversible. Although D-dimer elevation was also common, there was no evidence of disseminated intravascular coagulation,

coagulopathy, microangiopathy, thromboembolic disease, or other clinical sequelae associated with the hemagglutination findings. Because RBC agglutination may be related to the early, rapid rise in magrolimab concentration in the blood of treatment-naïve patients, the duration of infusion of the initial two 1 mg/kg priming doses has been extended from 1 to 3 hours (± 30 minutes) in all patients starting in the maintenance dose phase of the solid tumor Phase 1 study. Hemagglutination has been observed in 21 of 36 (58%) patients treated using the 3-hour priming dose infusion. In contrast, hemagglutination was observed in 6 of 6 (100%) previous patients treated with a 1-hour priming infusion (1 mg/kg). The duration of the maintenance dose infusions remains the same at 2 hours starting at Week 2.

Other common treatment-related adverse events (AEs) in solid tumor patients include infusion-related reactions, mild headache, dizziness, fatigue, nausea, photopsia, fever, chills, urine discoloration, mild transient visual changes, low back pain, and abdominal pain. The majority of these findings have occurred following the first infusion, with very few study drug-related toxicities reported beyond the first cycle. Several patients have been treated with consecutive weekly magrolimab therapy for over 6 months without evidence of long-term toxicities.

In the Phase 1 AML trial (SCI-CD47-002), 15 patients have been treated across 5 dose cohorts. In addition, as of 31 December 2017, 10 AML and MDS patients have been treated in the R/R AML Cohort at up to 30 mg/kg of magrolimab in this study. Overall, magrolimab has been well tolerated in patients in both the Phase 1 AML trial (Study SCI-CD47-002) and this Phase 1b trial. An MTD has not been reached. Similar to the solid tumor experience, the main toxicities associated with magrolimab have been RBC-related (specifically anemia and hemagglutination).

Anemia has been observed throughout magrolimab dosing in AML patients, with an average 1 to 2 g/dL decrease in hemoglobin observed with each dose. Similar to solid tumor patients, a mild transient increase in unconjugated bilirubin has been observed which is consistent with antibody-mediated extravascular hemolysis of RBCs. In contrast to solid tumor patients, AML patients lack adequate bone marrow function.

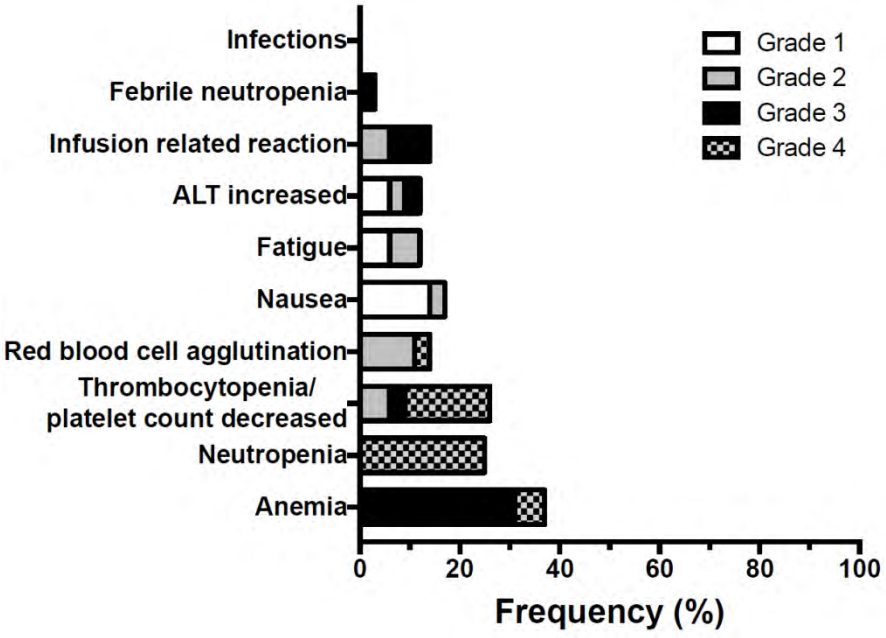
Thus, reticulocytosis post-magrolimab dosing has rarely been observed in the AML patients treated to date. However, RBC and/or platelet transfusions have been well-tolerated in all AML patients treated with magrolimab. Patients have been able to be successfully typed and crossmatched and have had no adverse safety findings during RBC transfusions while on magrolimab therapy. RBC transfusion frequencies have generally been consistent with transfusion requirements typically observed in AML patients.

Hemagglutination on peripheral smear has been observed at multiple time points and generally occurs post-magrolimab dosing in AML patients. Similar to the solid tumor experience, there has been no evidence of associated disseminated intravascular coagulation, treatment-related thrombocytopenia, coagulopathy, microangiopathy, thromboembolic disease, or other clinical sequelae associated with the hemagglutination findings. A 3-hour infusion duration of magrolimab for doses 1 mg/kg or less was used to potentially reduce frequency of hemagglutination, as observed in the solid tumor trial. In contrast to the experience in solid tumor patients, hemagglutination has been observed across multiple time points, which is likely due in part to ongoing RBC transfusions that contain a fraction of untreated, aged RBCs that are still susceptible to magrolimab-mediated clearance and agglutination. Lastly, mild infusion-related reactions manifested as fevers, chills, headache, and pain, have been observed in a less than 10% of patients during the initial first several doses of magrolimab. Apart from these expected toxicities, magrolimab treatment has been well tolerated in AML patients with no other significant treatment-related toxicities observed.

As of May 2019, 49 patients were enrolled and 46 patients with AML/MDS were treated with either magrolimab monotherapy or in combination with azacitidine in Study 5F9005 (Sallman 2019). Of the 49 patients enrolled, 21 patients had MDS and 28 patients had AML. Ten R/R AML/MDS patients were treated with magrolimab monotherapy. Thirty-six patients with AML/MDS who were treatment-naïve/unfit (TN/U) were administered magrolimab in combination with azacitidine. The safety profile of magrolimab in combination with azacitidine was well tolerated and consistent with azacitidine monotherapy, with no apparent increased toxicities in combination. No

maximum tolerated dose was reached with magrolimab dosing of 30 mg/kg weekly. The most common treatment-related AEs with magrolimab and/or azacitidine were anemia (36%), thrombocytopenia/platelet count decreased (26%), neutropenia (25%), nausea (17%), infusion-related reaction (14%), and hemagglutination (14%) (Figure 1-3).

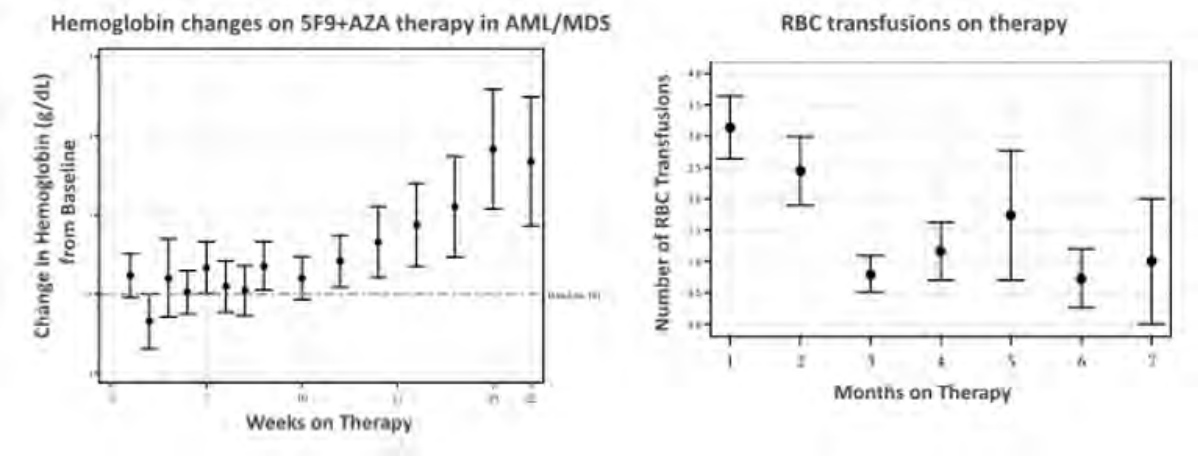
Figure 1-3. Treatment-related Adverse Events in AML/MDS Patients Treated With Magrolimab in Combination With Azacitidine in Study 5F9005



There were 36 patients treated with magrolimab in combination with azacitidine.
Abbreviations: 5F9+AZA = magrolimab in combination with azacitidine; AML = acute myeloid leukemia; ALT = alanine aminotransferase; MDS = myelodysplastic syndrome.

On-target anemia due to CD47 blockade-mediated RBC clearance was mitigated with a priming/maintenance dose strategy (Figure 1-4). The average hemoglobin drop with the first (priming) dose was 0.5 g/dL, with many patients improving their hemoglobin on therapy with a decrease in RBC transfusion requirements.

Figure 1-4. Magrolimab Priming/Maintenance Dose Regimen in AML/MDS Patients Treated With Magrolimab in Combination With Azacitidine in Study 5F9005



Abbreviations: 5F9+AZA = magrolimab in combination with azacitidine; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; RBC = red blood cell.

Only 1 of 46 (2%) patients discontinued treatment due to an AE, which was a Grade 4 DLT of hemagglutination observed in the TN/U Dose Evaluation Cohort with magrolimab in combination with azacitidine. This patient experienced an infusion-related reaction (fevers, chills, and extremity tremulousness) with the first magrolimab dose, with hemagglutination on peripheral smear. The patient underwent a full neurologic work-up including a computed tomography scan, magnetic resonance imaging, and magnetic resonance angiography of the brain, which were all negative. The patient fully recovered within 24 hours; however, the patient discontinued therapy. While hemagglutination has been observed on peripheral smear in multiple patients on study, there have been no other clinically significant sequelae that have occurred on study.

In summary, the expected adverse effects of anemia and hemagglutination have been observed in studies of solid tumor and AML patients treated with magrolimab, and the overall safety profile to date is manageable and consistent with nonclinical toxicology studies. All non-hematological magrolimab-associated toxicities have been transient and manageable. Supportive care with frequent RBC and/or platelet transfusions has been safely and successfully administered to AML patients who were concurrently

treated with magrolimab. The intrapatient dose escalation regimen of magrolimab used in AML patients has been well tolerated and has prevented acute death or related toxicities observed in nonclinical models.

1.2.2.2. Summary of Magrolimab Clinical Pharmacology

No formal clinical pharmacology trials have been completed with magrolimab; however, PK data are available for magrolimab doses from 0.1 to 45 mg/kg for patients on the ongoing solid tumor Phase 1 study (SCI-CD47-001). In the solid tumor trial, patients 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 have been observed at doses 10 mg/kg weekly and higher. Across all trials with available data, 21 out of 264 (7.95%) evaluable patients tested positive for anti-drug antibodies (ADA) against magrolimab, with no impact of ADA on PK or AE profile. In Studies SCI-CD47-002 and 5F9005 so far, 3 out of 20 (15%) and 4 out of 41 (9.76%) patients had anti-magrolimab antibodies, respectively.

1.2.2.3. Summary of Magrolimab Clinical Efficacy

In both Phase 1 clinical studies, magrolimab treatment is ongoing and efficacy data from patients with systemic magrolimab exposures in the range associated with nonclinical activity is pending. As of 31 December 2017, 2 objective responses have been observed in the solid tumor Phase 1 study. Multiple patients have had prolonged stable disease on study drug. However, the number of patients treated at the highest dose levels of 30 mg/kg evaluable for anti-tumor efficacy are relatively few.

In the AML Study SCI-CD47-002, 15 patients have been treated across 5 dose escalation cohorts as of 31 December 2017. Initial signs of biologic activity have been observed. Of 15 patients evaluable to date, no responses have been observed. However, several patients have had bone marrow blast reduction and prolonged stable

disease for up to 1 year on study treatment. In addition, biologic anti-leukemic activity has been observed in 2 patients (including 1 patient on study treatment for 1 year). These 2 patients, treated in Cohort 3, (1 mg/kg-10 mg/kg twice weekly) exhibited markedly hypocellular bone marrow, a finding similar to the magrolimab anti-leukemic activity observed in nonclinical murine xenograft models (Majeti 2009; Liu 2015b). Both of these patients have an antecedent history of MDS or dysplastic features, suggesting that magrolimab may also be effective in MDS patients. While the sample size is small, the initial response and biologic activity seen in AML patients at doses anticipated to be associated with clinical efficacy is encouraging.

Two combination trials with magrolimab have been enrolling patients, and clinical efficacy data are preliminary. In the 5F9003 trial of magrolimab in combination with rituximab for patients with B-cell NHL, 23 patients have been treated as of 31 December 2017 in a dose escalation phase. Multiple clinical responses have been observed, including both complete and partial responses. Treatment is ongoing for the majority of patients achieving responses, with at least 1 patient continuing to receive treatment for over 1 year. In the 5F9004 trial of magrolimab in combination with cetuximab in CRC, 23 patients have been treated and 1 partial response has been observed as of 31 December 2017. Enrollment is ongoing for both trials.

As of May 2019 in Study 5F9005, clinical activity was assessed for magrolimab monotherapy in R/R AML/MDS and for magrolimab in combination with azacitidine in TN/U AML/MDS (Sallman 2019). Magrolimab monotherapy induced an objective response in 1 of 10 (10%) R/R AML/MDS patients (with 1 AML patient achieving morphologic leukemia-free state [MLFS]). With magrolimab in combination with azacitidine, 11 of 11 (100%) MDS patients achieved an objective response, with a CR+partial remission (PR) rate of 55%. In untreated AML patients, magrolimab in combination with azacitidine induced an objective response in 9 of 14 (64%) of patients, with 36% achieving a CR and 14% achieving a CR with incomplete blood count recovery (CRi). Median time to response at 1.9 months for the combination treatment was more rapid than that expected for azacitidine alone (4 to 6 months). In MDS patients, 3 of 7 (43%) responding patients with abnormal cytogenetics at baseline

achieved a complete cytogenetic response, with 2 of 10 responders with minimal residual disease (MRD) assessment achieving MRD negativity by flow cytometry. In summary, in a limited sample size, magrolimab in combination with azacitidine has meaningful clinical activity that appears to be enhanced compared to azacitidine monotherapy. Further results are found in the IB.

1.3. Azacitidine

Azacitidine is a nucleoside analog, specifically a chemical analog of cytidine. Azacitidine has two known primary anti-neoplastic mechanisms of action: 1) inhibition of deoxyribonucleic acid (DNA) methyltransferase leading to hypomethylation of DNA and 2) direct cytotoxicity of malignant hematopoietic cells through cell death via its incorporation into DNA and ribonucleic acid (RNA). As a hypomethylating agent, azacitidine is a standard-of-care therapy for newly diagnosed AML patients who are ineligible for induction chemotherapy or HSCT based on age, co-morbidities, or other factors. Azacitidine is also SOC and approved in the United States (US) for treatment of subtypes of MDS including, but not limited to, MDS with refractory anemia excess blasts, a subtype that is mostly comprised of intermediate to very high risk MDS patients by IPSS-R criteria. In Europe azacitidine is approved for AML patients who are ineligible for HSCT and for intermediate-2 and high risk MDS patients according to IPSS criteria. While not approved for the indication of AML by the Food and Drug Administration (FDA) in the US, azacitidine is a recommended treatment option for AML patients 60 years or older who are not candidates for intensive chemotherapy according to the guidelines of the National Comprehensive Cancer Network (NCCN 2017). Data supporting azacitidine as SOC for this population is primarily based on a large international randomized Phase 3 study comparing azacitidine to conventional care regimens in newly diagnosed AML patients 65 years or older (Dombret 2015). Azacitidine 75 mg/m^2 per day was administered subcutaneously (SC) for 7 consecutive days per 28-day treatment cycle for at least 6 cycles. Median OS for azacitidine was 10.4 months, which was statistically significant improvement over conventional care regimens (6.5 months).

The AE profile of azacitidine primarily includes myelosuppression (anemia, leukopenia, and thrombocytopenia) and clinical sequelae of myelosuppression (neutropenic fever, infections, bleeding, and fatigue). Common non-hematologic AEs include gastrointestinal events (diarrhea, nausea, constipation, and decreased appetite), skin disorders (rash, pruritus, petechiae, ecchymosis), injection site/infusion-related reactions (injection site erythema and/or pain for 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.

1.4. Correlative Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal blocking anti-CD47 antibody leads to tumor elimination by activation of both the innate and adaptive immune system. Anti-CD47 antibody-mediated tumor elimination by the innate immune system occurs through phagocytic elimination of tumor cells by macrophage and other phagocytes. It is well known that macrophages are a common immune cell infiltrate in many tumor types, with degree of intratumoral macrophage infiltrate correlating with clinical prognosis. Correlation of macrophage infiltration to clinical disease course is often dependent on the presence of either classically activated (M1) type macrophages that suppress tumor progression or alternatively, activated (M2) type macrophages that promote tumor progression (Pollard 2004). Given the frequent infiltration of M2 macrophages in many tumor types and its role in promoting tumorigenesis, there is widespread interest in developing therapies that shift tumor macrophage polarization from the pro-tumorigenic M2 to the anti-tumorigenic M1 macrophages. In nonclinical studies, anti-CD47 antibody-mediated tumor cell phagocytosis has been demonstrated to occur through both M1 and M2 macrophages (Zhang 2016). In addition, in vivo treatment of human xenograft tumors with an anti-CD47 antibody demonstrated increased M1 intratumoral macrophages post-treatment (Zhang 2016), suggesting that an anti-CD47 antibody can also shift the phenotype of macrophages from the M2 towards the M1 phenotype in vivo. Since the

recruitment of macrophage effectors is a key mechanism for anti-tumor activity by anti-CD47 antibody, the characterization of macrophage tumor infiltration pre- and post-treatment in patients treated with anti-CD47 antibody may provide insights into patient and cancer subtypes and macrophage biomarkers that will enrich for anti-tumor efficacy.

In addition to modulating the innate immune system, anti-CD47 antibody therapy also activates the adaptive immune system towards an anti-tumor response. Phagocytosis of tumor cells by phagocytes (macrophages and/or dendritic cells) leads to cross-presentation of tumor antigens to T-cells, enabling a T-cell anti-tumor response (Tseng 2013; Liu 2015a). In one nonclinical study, anti-CD47 antibody mediated a specific CD8 T-cell anti-tumor response without proliferation of regulatory T-cells (which are generally thought to be tumor-promoting; Tseng 2013). Currently, there is intense interest in investigating the relationship between T-cell subsets that infiltrate the tumor and clinical response with the use of immune-oncology therapeutics. Indeed, increased T-cell infiltration in the tumor has been associated with clinical response in oncology patients treated with T-cell checkpoint inhibitors (Herbst 2014; Tumeh 2014). Given the role of anti-CD47 antibody in mediating an anti-tumor T-cell response, the clinical investigation of the contribution of T-cell effectors to anti-CD47 antibody-mediated efficacy is important to select for patients and tumor subtypes that respond to therapy.

1.5. Study Rationale and Risk-Benefit

SOC therapy for AML patients involves cytotoxic chemotherapies which can lead to significant treatment-related morbidity and mortality. In addition, prognosis for newly diagnosed patients and those who relapse or are refractory to these therapies is generally poor. The development of targeted leukemic therapies has the potential to improve efficacy and minimize toxicity in order to provide meaningful clinical benefit in this patient population. Monoclonal antibodies targeting leukemia-associated antigens have the potential for maximizing the efficacy to toxicity ratio through selective elimination of leukemic cells.

A monoclonal antibody targeting CD47 enables selective phagocytosis and elimination of leukemic cells, but not normal cells, and is a potentially beneficial therapy for AML as well as MDS. In murine patient xenograft studies, magrolimab has demonstrated rapid elimination of leukemic disease in the peripheral blood and bone marrow, resulting in long term and durable remissions in a high percentage of patients (Liu 2015b). The anti-leukemic activity of magrolimab and other anti-CD47 antibodies has been broadly observed across AML cytogenetic, molecular, and morphologic subtypes (Liu 2015b; Majeti 2009). In addition, recent nonclinical studies by the Sponsor demonstrated that combination therapy with magrolimab and azacitidine demonstrated enhanced anti-leukemic activity compared to either agent alone. The combination of magrolimab and azacitidine led to significantly increased macrophage phagocytosis of leukemic cells in vitro compared to monotherapy alone (Figure 1-2). Lastly, anti-CD47 antibody has been shown to induce phagocytic elimination of refractory anemia excess blast MDS patient samples, comprising both intermediate and higher-risk patients (Pang 2013). These nonclinical experiments provide the rationale for the use of magrolimab for the treatment of relapsed and/or refractory (R/R) AML and MDS patients and the use of magrolimab in combination with azacitidine for the treatment of newly diagnosed AML patients who are TN/U and newly diagnosed intermediate-/high-/very high-risk MDS patients.

AML patients who are relapsed and/or refractory to conventional therapies have limited options for treatment. Prognosis is poor in this population with median overall survival approximately 3 to 5 months (Roboz 2014; Feldman 2005). There is no SOC for patients in this setting. Thus, patients with R/R AML represent a significant unmet medical need. In the previous Phase 1 study in AML patients (SCI-CD47-002), magrolimab monotherapy has been well tolerated. The expected adverse effects of anemia and hemagglutination have been manageable and consistent with nonclinical toxicology studies, and supportive care with frequent RBC and/or platelet transfusions has been safely and successfully administered to all AML patients who were concurrently treated with magrolimab.

MDS is a pre-malignant condition characterized by peripheral cytopenias due to production of dysfunctional, dysplastic bone marrow cells. Low and very low risk patients, as defined by the IPSS-R, are often treated with erythroid and myeloid growth factor support and carry a low risk of leukemic progression. In RBC transfusion-dependent low-risk MDS patients who fail ESAs or lenalidomide, no standard of care exists, and well-tolerated and effective therapies are needed. Initial data show that patients treated with magrolimab and azacitidine can achieve RBC transfusion independence, and thus this combination has potential efficacy in this population. In contrast, intermediate, high, and very high risk MDS patients are generally treated with hypomethylating agents, mostly azacitidine, and carry a high risk of leukemic progression. However, prognosis is poor, and agents that augment the activity of azacitidine are needed. Thus, the combination of magrolimab and azacitidine may have potential clinical benefit in these MDS patients.

The majority of patients newly diagnosed with AML are over 60 years of age. However, due to age-related co-morbidities, these patients often are ineligible for aggressive induction chemotherapy and HSCT due to a significantly increased risk of treatment-related mortality. Instead, SOC for these patients is treatment with hypomethylating agents (e.g., azacitidine), which have a lower risk of toxicity. However, these treatments are rarely curative and provide a treatment benefit of a median overall survival around only 10 months (Dombret 2015). Furthermore, AML patients harboring a TP53 mutation have a particularly poor prognosis and are refractory to available therapies. To this point, median survival in TP53 mutant AML patients ineligible for induction chemotherapy is only 7 months (DiNardo 2019). Thus, there is intense interest to improve the current SOC with therapies that can be combined with azacitidine to augment anti-leukemic activity in both the general TN/U AML population as well as those patients harboring a TP53 mutation.

This study will evaluate the safety profile of magrolimab monotherapy in an expanded group of AML/MDS patients to enable a potentially broader use of magrolimab in AML and MDS patients.

Treatment with the proposed combination therapy of magrolimab and azacitidine is not anticipated to pose a significantly increased risk to patients enrolled on this trial compared to the risk of treatment with either agent alone. Based on the clinical profiles of magrolimab and azacitidine, overlapping toxicities (with the exception of anemia) are not anticipated with the combination. Based on the high frequency of disease-related anemia in AML patients and the ability to safely manage patients with anemia on magrolimab with transfusions in the previous Phase 1 trial in AML patients, the potential overlapping toxicity of anemia can be managed to ensure patient safety in this trial. In addition, specific clinical and laboratory monitoring of magrolimab and azacitidine-related toxicities will be implemented to closely monitor potential AEs.

Magrolimab alone or in combination with azacitidine will be investigated in R/R AML and MDS, newly diagnosed AML patients who are unfit for induction chemotherapy (including those with TP53 mutation), newly diagnosed intermediate-/high-/very high-risk MDS patients, and RBC transfusion-dependent low-risk MDS patients. The nonclinical evidence of magrolimab activity (alone or in combination with azacitidine), the safety profile of magrolimab in AML patients, and preliminary clinical efficacy as summarized in Section 1.2.2 suggest that magrolimab has an acceptable risk-benefit profile for both AML and MDS patients.

1.5.1. MDS Expansion Scientific Rationale

Azacitidine upregulates pro-phagocytic signals in leukemia cells and results in increased phagocytosis when combined with magrolimab's blockade of CD47, a major anti-phagocytic 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 to either single agent alone. Magrolimab in combination with azacitidine is being developed in several indications within MDS and AML, specifically in a potential pivotal single-arm study in untreated intermediate to very high risk MDS patients as assessed by IPSS-R criteria. The standard-of-care therapy for this population is hypomethylating agents (azacitidine and decitabine); however, efficacy is limited, with CR+PR rates approximately 15% to 20% with a median OS of approximately 18 months (Appendix E). Novel effective therapies that can be combined

with hypomethylating agents while maintaining an acceptable safety profile and improving durable remissions and, ultimately, survival are needed. 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 co-morbidities 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 untreated MDS patients to improve clinical activity and maintain a well-tolerated safety profile.

1.5.2. MDS Expansion Risk-Benefit Assessment

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 further development and a potential Biologics License Application (BLA) in untreated higher-risk MDS.

1.6. Dose Rationale

1.6.1. Magrolimab

Magrolimab selectively eliminates tumor cells while sparing normal cells through blockade of the CD47-SIRPα phagocytic signaling axis. Most normal cells are spared due to the expression of pro-phagocytic signals that are expressed on tumor cells, but not on normal cells (Chao 2010b). RBCs are a notable exception because CD47 expression protects RBCs from elimination by macrophages in the reticuloendothelial system. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of magrolimab accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical and clinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged

RBCs are replaced with younger cells. Nonclinical studies show that the potential for severe anemia is ameliorated by administration of a low priming dose of the antibody that results in mild to moderate anemia and stimulates reticulocytosis.

In patients with a lack of adequate bone marrow reserve and ability to produce reticulocytes, as is observed in AML patients, a priming dose to mitigate anemia may not be as effective. Furthermore, additional safety risks may be present in AML patients in contrast to solid tumor patients. Specifically, in AML nonclinical mouse models only, early death of mice was observed within 1 hour of magrolimab administration in cases with a high burden of circulating leukemia cells (> 50% of circulating blood comprised of leukemia cells). However, early death with high circulating burden of disease could be completely avoided in this nonclinical study by first lowering the circulating burden of disease with a low dose of magrolimab (< 0.3 mg/kg dose equivalent) and then proceeding with gradual intrapatient dose escalation. This intrapatient dose escalation regimen was utilized in the Phase 1 trial in R/R AML (SCI-CD47-002) and has been well tolerated with no acute death observed in any AML patients treated. No MTD has been reached on that trial. The highest dose tested to date (1 mg/kg twice weekly for Week 1, 10 mg/kg twice weekly for Week 2, and 15 mg/kg twice weekly for Week 3 and beyond) was determined to be well tolerated by the Clinical Trial Steering Committee (CTSC) in the Phase 1 trial. In addition, a dose regimen of 1 mg/kg twice weekly for Week 1, 15 mg/kg on Day 8, 30 mg/kg on Day 11, and 30 mg/kg twice weekly thereafter, has been tested in several AML patients. Preliminary safety and PK/PD data suggest that intrapatient dose escalation from 1 mg/kg twice weekly in Week 1 to 30 mg/kg on Day 11 is well tolerated and achieves potential therapeutic concentrations. Dose concentrations higher than 20 mg/kg may be associated with greater target CD47 saturation on leukemic cells and higher free drug exposures. Higher magrolimab dose exposures may thus lead to enhanced clinical efficacy. Based on this potential benefit and the current safety profile where an MTD has not been reached, exploration of higher magrolimab dose levels represents an adequate risk-benefit profile. Thus, a higher dose regimen of 1 mg/kg on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Day 11 and twice weekly thereafter has been proposed for evaluation in the Phase 1

AML trial, Study SCI-CD47-002, and will be the initial magrolimab dose regimen explored in this study.

Based on results from the Phase 1 study of magrolimab in AML, this study is designed to employ an intrapatient dose escalation regimen for both magrolimab monotherapy in R/R AML and MDS patients and for magrolimab in combination with azacitidine in TN/U AML and MDS patients. The intrapatient dose escalation regimen uses twice-weekly dosing at a starting magrolimab dose of 1 mg/kg for Week 1, with escalation to higher doses in Week 2, up to a maximum of 30 mg/kg in Week 2 and beyond. The strategy of intrapatient dose escalation was found to result in both mitigation of acute death seen in nonclinical models and in expected RBC toxicities that were manageable for this patient population.

The recommended magrolimab dose regimen has been amended based on emerging PK, PD, and clinical safety and efficacy data in the ongoing Phase 1 study in AML and MDS patients (Study SCI-CD47-002). Based on the data from ongoing clinical trials with magrolimab, including the ongoing Phase 1 trial in AML (SCI-CD47-002), twice weekly magrolimab dosing of 30 mg/kg is anticipated to exceed the target effective concentrations predicted by PK/PD modeling. Based on preliminary PK data and PK modelling, this dose is expected to result in concentrations in the range of 1000 mcg/mL, much greater than the target range of 100 to 250 mcg/mL seen in preclinical studies and the target of 200 mcg/mL predicted by PK modelling. Therefore, a maintenance dose of 30 mg/kg once weekly (QW) is proposed. As of December 2017, the 30 mg/kg dosing has been demonstrated to be safe in at least 6 AML patients treated. In the TN/U Cohort of this study, twice-weekly dose escalation from 1 mg/kg to 30 mg/kg through Week 2 will continue to be used to mitigate potential safety concerns and rapidly achieve effective drug target concentrations. Starting with Week 3, magrolimab will be dosed weekly at 30 mg/kg to enable sustained effective target concentrations while providing a less frequent and more convenient dosing schedule for patients. In the R/R Safety Cohort, the same magrolimab dose regimen as that in the TN/U Cohort was explored and was well tolerated. In the R/R Expansion Cohort, a change to magrolimab dosing was made to evaluate an every 2 week (Q2W) dosing

regimen beginning in Cycle 3 based on clinical, PK, and PD data and for evaluation of a more convenient dosing regimen. Specifically, this dose regimen is 1 mg/kg twice weekly for Week 1 (Day 1 and Day 4); 15 mg/kg on Day 8; 30 mg/kg on Day 11 and Day 15; and 30 mg/kg weekly on Day 22 through end of Cycle 2, then 30 mg/kg Q2W starting Cycle 3 and thereafter. In the Rollover Cohort, patients may continue their current dose level and maintenance schedule (i.e., twice weekly) of magrolimab monotherapy as previously received in the Phase 1 AML study (SCI-CD47-002), or patients may transition to the QW dosing schedule at the discretion of the Investigator and with Sponsor approval.

Rationale for a Magrolimab Q2W Dosing Regimen

Per Amendment 6, the magrolimab dosing regimen for all cohorts (excluding the RBC Transfusion-dependent Low-risk MDS Cohort) was transitioned to a 30 mg/kg Q2W dosing schedule starting Cycle 3 and beyond, in contrast to a 30 mg/kg weekly dosing regimen utilized in prior amendments. This change to a Q2W dosing regimen is based on clinical safety/efficacy and PK/PD data obtained in MDS/AML and other cancer types treated with magrolimab.

Based on the entirety of safety data in multiple oncology populations including the proposed study population, magrolimab doses up to 30 mg/kg twice weekly as a monotherapy and up to 45 mg/kg in combination with tumor-targeted antibodies have been found to have a safe and well-tolerated safety profile. In Studies SCI-CD47-002 and 5F9005, near-maximal CD47 receptor occupancy was observed in blood and in the bone marrow at the maintenance dose of 30 mg/kg twice weekly and QW, respectively, in AML and MDS patients. An exposure-receptor occupancy PK/PD model was built using these data. Simulations with the model predicted that >90% receptor occupancy would be achieved in the bone marrow cells after switching to 30 mg/kg Q2W from Cycle 3 onward. In addition, in NHL patients, a dose of 30 mg/kg Q2W from Cycle 3 onward was also shown to result in efficacy similar to that of a higher dose of 45 mg/kg Q2W, indicating that this is an optimal dose of magrolimab.

Transfusion-dependent Low-risk MDS Dosing Rationale:

For patients with low-risk MDS, dosing convenience and quality of life are particularly important considerations for novel treatments. In addition, the low tumor burden observed in low-risk MDS patients indicates that intrapatient dose escalation may not be required. To this effect, the following dosing regimen is proposed: priming dose of 1 mg/kg on Day 1, followed by 30 mg/kg QW for Cycle 1, followed by 60 mg/kg every 4 weeks (Q4W) from Cycle 2 onward. This dosing regimen is similar in the overall dosing rate (in mg/kg) to what is proposed above in the high-risk population. Based on existing receptor occupancy (RO) data and PK/PD modeling, it is anticipated that this Q4W dosing regimen will maintain $\geq$ 90% CD47 receptor occupancy on bone marrow cells and therefore maximize efficacy and patient convenience.

1.6.2. Azacitidine

Azacitidine has been approved in Europe for AML patients who are not eligible for HSCT using a dosing regimen of 75 mg/m^2 SC daily for Days 1 to 7 of a 28-day treatment cycle. This approval was based on a clinical trial of newly diagnosed AML patients older than or equal to 65 years of age comparing azacitidine against conventional care regimens (Dombret 2015). Median OS was increased with azacitidine versus conventional care regimens (10.4 months versus 6.5 months, respectively). Based on this result and others, azacitidine is currently SOC for newly diagnosed AML patients who are unfit for induction chemotherapy or ineligible for HSCT. While not approved in the US for this indication, azacitidine (administered either SC or IV) is approved for certain subtypes of MDS in the US, is approved for TN/U AML patients in Europe, and is considered SOC in the US for this AML population in combination with other hypomethylating agents (decitabine) or low dose cytarabine (NCCN 2017). In accordance with the azacitidine drug label, it is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression, as described in the azacitidine prescribing information. Based on these data and guidance, azacitidine will be dosed in this study at the standard clinical dose of 75 mg/m^2 on Days 1 to 7 of a 28-day cycle. Azacitidine is also approved in Europe for intermediate-2 and high-risk MDS

patients by IPSS criteria and in the US for MDS patients with refractory anemia excess blasts, among other MDS subtypes. MDS patients enrolled on this study will consist of patients in both the US- and EU-based azacitidine approval indications.

For low-risk MDS patients, patient convenience and minimizing toxicity while maintaining efficacy are important. Thus, a 5-day azacitidine schedule every cycle will be utilized specifically for the RBC Transfusion-dependent Low-risk MDS Cohort. This dose selection is based on prior data, including a randomized trial that evaluated 5-, 7-, and 10-day regimens of azacitidine and found that the efficacy was similar across regimens but the 5-day regimen had lower toxicity (Lyons 2009).

Rationale for the use of magrolimab and azacitidine in AML and MDS patients is presented in Section 1.2.1.2. Treatment with magrolimab and azacitidine may continue as long as the patient continues to benefit, until disease progression, or until unacceptable toxicities occur.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives for this study are:

- To confirm the safety and tolerability of magrolimab monotherapy in R/R AML and MDS and of magrolimab in combination with azacitidine in previously untreated patients with AML or MDS and patients with R/R AML and MDS
- To evaluate the safety, tolerability, and efficacy of magrolimab monotherapy in R/R AML/MDS, and of magrolimab in combination with azacitidine in previously untreated patients with AML/MDS or R/R AML/MDS as measured by complete remission (CR) rate for patients with AML and higher-risk MDS
- To evaluate the safety, tolerability, and efficacy of magrolimab monotherapy or in combination with azacitidine in low-risk MDS patients as measured by RBC transfusion independence rate

2.1.2. Secondary Objectives

The secondary objectives for this study are:

- To evaluate the PK profile of magrolimab alone and in combination with azacitidine
- To evaluate the immunogenicity of magrolimab
- To evaluate the efficacy of magrolimab alone or in combination with azacitidine as measured by duration of CR (DCR); objective response rate (ORR); CR with partial hematologic recovery; duration of response (DOR) for patients with AML; DCR for higher-risk MDS; ORR and DOR for patients with MDS; RBC transfusion independence; mean hemoglobin increase on treatment; progression-free survival (PFS); relapse-free survival (RFS), event-free survival (EFS); and OS
- To assess the level of MRD negativity

CCI [redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study are:

- Measurement of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 or customized AE severity grading as defined in the protocol (Appendix A)
- CR rate for patients with AML as defined by the Investigator according to protocol-specified criteria (Appendix B), which are based on European Leukemia Net (ELN) AML recommendations (Döhner 2017), CR rate for patients with MDS as defined by the IWG 2006 MDS response criteria (Cheson 2006)

- 8-week RBC transfusion independence rate for patients with low-risk MDS as defined by the lack of RBC transfusions for at least an 8-week consecutive period at any time after starting therapy

2.2.2. Secondary Endpoints

The secondary endpoints for this study are:

- Magrolimab concentration versus time measurements
- ADA to magrolimab
- Objective response in AML based on ELN AML recommendations (Döhner 2017) and IWG AML response criteria, or ORR (Cheson 2003) in MDS as defined by IWG 2006 MDS response criteria (Cheson 2006); CRh; DCR and DOR for patients with AML; DCR and DOR for patients with MDS; RBC transfusion independence (no RBC transfusions for at least an 8-week consecutive period); 12-week RBC transfusion independence rates; mean hemoglobin increase on therapy; and, where appropriate, PFS, RFS, EFS, and OS for patients with AML or MDS
- Level of MRD negativity using a multiparameter flow cytometry-based assay for patients on therapy

CCI [redacted]

[redacted]

3. STUDY DESIGN

3.1. Overall Study Design

This trial is an open label, multicenter Phase 1b trial investigating the following:

- Magrolimab monotherapy or in combination with azacitidine in patients with relapsed and/or refractory AML or MDS (including R/R low-risk RBC transfusion-dependent MDS patients)
- Magrolimab in combination with azacitidine in newly diagnosed intermediate/high/very high-risk MDS patients
- Magrolimab in combination with azacitidine in newly diagnosed AML patients ineligible for standard induction chemotherapy (including TP53 mutant AML)
- Magrolimab monotherapy or in combination with azacitidine for RBC transfusion-dependent low-risk MDS patients

The study includes 4 groups of patients:

- **R/R Cohorts:** AML or MDS patients who have not previously received magrolimab, who will receive magrolimab monotherapy in the safety run-in cohort or magrolimab in combination with azacitidine in the expansion cohort on this study, as well as an R/R MDS Magrolimab Monotherapy Cohort that will enroll up to 23 R/R MDS patients.
- **TN/U Cohorts:** AML patients ineligible for standard induction chemotherapy and previously untreated intermediate/high/very high-risk MDS patients by IPSS-R, who will receive magrolimab in combination with azacitidine on this study, with at least 92 intermediate- to very high-risk MDS patients treated (with a combination of magrolimab 30 mg/kg weekly [n = 36] and 30 mg/kg Q2W [n = 56] dosing, plus azacitidine) and approximately 62 TP53 mutant TN/U AML patients (approximately 172).
- **RBC Transfusion-dependent Low-risk MDS Cohort:** RBC transfusion-dependent very low- to low-risk MDS patients who have failed or are intolerant to ESAs or lenalidomide (for del5q patients) who will receive magrolimab monotherapy or in combination with azacitidine on this study (approximately 20).

- **Rollover Cohort:** Patients who received magrolimab in the Phase 1 R/R AML study (SCI-CD47-002), who will continue magrolimab monotherapy on this study (total N = up to 8).

The R/R Cohorts consist of 2 cohorts: 1) an R/R Safety and Expansion Cohort, and 2) an R/R MDS Magrolimab Monotherapy Expansion Cohort. The R/R Safety and Expansion Cohort consists of an initial evaluation of magrolimab monotherapy in R/R MDS/AML patients, followed by an expansion cohort of magrolimab + azacitidine in R/R MDS/AML patients. As of Amendment 3, in the first stage, patients in the R/R Safety Cohort have been treated at the maintenance dose of 30 mg/kg twice weekly; going forward, these patients will be treated weekly at the maintenance dose of 30 mg/kg, as determined by the Clinical Trial Steering Committee (CTSC) based on clinical, PK, and PD data. This safety run-in will confirm the safety profile of magrolimab monotherapy at this dose level in an expanded R/R population. Approximately 30 days after enrollment is completed in the R/R Safety Cohort, the CTSC will assess the safety data to determine whether enrollment may begin in the TN/U Dose Evaluation Cohort. In addition, the CTSC will also determine whether enrollment will proceed to an initial 36-patient R/R Expansion Cohort, based on safety and efficacy data, which will be conducted with magrolimab in combination with azacitidine as per Amendment 5. Based on emerging data, the CTSC may decide to enroll additional patients beyond 36 for further safety, efficacy, or dosing information.

The R/R MDS Magrolimab Monotherapy Cohort was added in Amendment 6. Per FDA feedback, a magrolimab monotherapy cohort in R/R MDS will be evaluated to further define the activity of magrolimab to the contribution of magrolimab + azacitidine in MDS to support a potential single-arm approval of magrolimab + azacitidine in MDS. Patients will be enrolled in a Simon's 2-stage design to evaluate for potential futility. Patients who do not achieve an objective response with magrolimab monotherapy at the protocol-defined first response assessment may have azacitidine added by discretion of the Principal Investigator with Sponsor approval, according to the schedule of azacitidine outlined in the R/R cohorts.

The TN/U Cohort will be enrolled in 2 stages. In the first stage, the study will investigate the safety and tolerability of magrolimab and azacitidine in a 3+3 dose evaluation design, in previously untreated AML patients who are unfit for standard combination chemotherapy and previously untreated intermediate/high/very high-risk MDS patients. The same dose level of magrolimab used in the R/R Safety Cohort will be initially evaluated in combination with the standard dose of azacitidine in the TN/U Dose Evaluation Cohort. Optional additional dose cohorts may explore higher or lower doses in increments of up to 50% of the maximum prior dose, as determined by the CTSC based on emerging PK, pharmacodynamic, and clinical data. A total of up to 18 patients may be treated in the TN/U Dose Evaluation Cohort. In the second stage, a recommended dose and schedule will be selected by the CTSC for treatment of up to 30 patients in the TN/U Expansion Cohort, which will be evaluated for efficacy of magrolimab in combination with azacitidine. The same dose level of magrolimab used in the R/R Safety Cohort will be initially evaluated in combination with the standard dose of azacitidine in the TN/U Dose Expansion Cohort. Per CTSC and Amendment 6, the magrolimab dosing was changed to 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, and 22; 30 mg/kg weekly for Cycle 2; and 30 mg/kg Q2W starting Cycle 3 and thereafter. In addition, based on Amendments 5 and 6, the TN/U Expansion Cohort was expanded to a total of 122 patients, which will include at least 92 patients with MDS and an additional 12 slots for TP53 AML per CTSC decision September 2019. For a higher-risk, untreated, MDS-only expansion, an evaluation will occur after 36 patients have undergone the first response assessment. If the CR rate for magrolimab+azacitidine is at least 35.5%, then subsequent enrollment can continue. After this initial efficacy evaluation (as a part of Amendment 6), at least 56 additional patients will be enrolled at a magrolimab 30 mg/kg Q2W dosing regimen in the higher-risk untreated MDS expansion. Enrollment does not need to be paused during the 36-patient evaluation prior to the additional 56-patient expansion. As part of Amendment 6, a subcohort of approximately 32 TN/U AML (12 patients plus an additional 20) patients with a TP53 gene mutation was added. This addition is based on initial encouraging efficacy data observed in the TN/U Cohort in patients with a TP53 gene mutation. Based on emerging data, the CTSC may decide to enroll additional

patients beyond the 20 patients for further safety, efficacy, and/or dosing data. Per CTSC decision in July 2020 and captured in Amendment 7, an additional 30 TP53 mutant AML patients were added to the TN/U Expansion Cohort (n = 62).

The RBC Transfusion-dependent Low-risk MDS cohort will consist of approximately 20 patients and be based on a Q4W magrolimab dosing schedule administered starting Cycle 2. Given that a higher dose of magrolimab (60 mg/kg) will be tested in this cohort, the first 6 patients will be treated in a safety run-in cohort. These 6 patients will be treated with magrolimab monotherapy for the first 2 cycles, followed by a response assessment. Patients who do not respond to magrolimab monotherapy by this time may have azacitidine added to their treatment regimen. Based on the initial safety and efficacy data for these 6 patients, the CTSC will determine whether the remaining 14 patients will be treated as magrolimab monotherapy or in combination with azacitidine, as well as the dose of magrolimab. After a safety evaluation of these 6 patients by the CTSC, the remaining 14 patients can be simultaneously enrolled. Based on emerging data, the CTSC may decide to enroll additional patients for further safety, efficacy, or dosing information. These additional patients may be treated with either magrolimab monotherapy or magrolimab in combination with azacitidine. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.

The Rollover Cohort will be open to all patients (maximum of 8) on the existing Phase 1 AML trial (study SCI-CD47-002) who are deriving ongoing clinical benefit from magrolimab therapy. Patients in the Rollover Cohort may receive the same dose level and schedule (i.e., twice weekly) of magrolimab monotherapy as previously received on the Phase 1 AML study (SCI-CD47-002), or may transition to once-weekly dosing in this study at the discretion of the Investigator and with Sponsor approval. At the discretion of the CTSC for this study, Rollover patients who are receiving lower doses may be escalated to a higher dose deemed to be safe by the CTSC for this study.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment (magrolimab and/or azacitidine), during which time the patient's eligibility and baseline characteristics will be determined. Study treatment may be continued until an unacceptable drug-related toxicity occurs or until disease progression or loss of clinical benefit. Post treatment, patients will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs.

The end of the entire study for all patients is defined as the date on which the last patient completes the last study visit (follow-up for safety, disease progression or survival), or when the CTSC or Sponsor decides to end the study.

3.2. Study Design - R/R Cohort

The R/R Cohort will be evaluated in 3 stages. As of Amendment 3, in the first stage, 10 patients (the R/R Safety Cohort) have been treated in a safety run-in to evaluate the safety profile of magrolimab monotherapy in this R/R population. Based on aggregate clinical, safety, PK, and pharmacodynamic data in the R/R Safety Cohort, the CTSC will determine whether enrollment may begin in an Expansion stage of the initial R/R Cohort, in which a total of up to 36 additional patients in the R/R Expansion Cohort will be treated to evaluate the clinical activity of magrolimab in combination with azacitidine. In the R/R Expansion Cohort, magrolimab will be administered 1 mg/kg twice weekly for Cycle 1 Week 1 (Day 1 and Day 4); 15 mg/kg on Cycle 1 Day 8, 30 mg/kg on Cycle 1 Day 11 and Day 15, 30 mg/kg weekly on Cycle 1 Day 22 through end of Cycle 2, and 30 mg/kg Q2W starting Cycle 3 and thereafter, as shown in Table 3-1, based on clinical, PK, and pharmacodynamic data and for evaluation of a more convenient dosing regimen. If a patient has only received Day 1 treatment for a cycle, the patient may transfer to the Q2W dosing regimen with that cycle, for the balance of the cycle and beyond, even if they were previously receiving magrolimab QW at Cycle 3 and beyond.

If an increased dose or frequency of dosing is explored, additional cohorts will use a standard 3+3 design. Based on emerging clinical data, the CTSC may expand this cohort beyond the initial 36 patients for further safety, efficacy, and/or dosing data. In addition, individual patients may be transitioned from a magrolimab Q2W to Q4W dosing regimen by the Investigator with approval from the Medical Monitor. As of Amendment 6, up to 23 R/R MDS patients may be enrolled in an additional R/R MDS Magrolimab Monotherapy cohort. Patients will be enrolled in this cohort in a Simon's 2-stage design. With a 1-sided significance level of 0.05 and 80% power, the null hypothesis that the magrolimab monotherapy ORR is 9% will be tested against the alternative of 30%. In the first stage, 11 patients will be enrolled. If there are 1 or fewer responses observed in these 11 patients, the cohort will be stopped. Otherwise, 12 additional patients will be accrued, for a total of 23. This cohort was stopped after 11 patients enrolled per CTSC decision in October 2020. The null hypothesis will be rejected if 5 or more responses are observed in 23 patients. R/R MDS patients who do not achieve an objective response after the first protocol response assessment may have azacitidine added to magrolimab for subsequent cycles. For patients who respond to magrolimab monotherapy and then progress, azacitidine may be added to magrolimab and patients can still be continued to be treated with the combination.

The Schedule of Assessments tables for the R/R Expansion Cohort and the R/R MDS Magrolimab Monotherapy Cohort are provided in Section 7.1. The Schedule of Assessments table for the R/R Safety Cohort, which is now closed, is provided in Appendix F.

Table 3-1. Dose and Schedule for R/R AML/MDS Cohorts

Cohort	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
R/R AML/MDS (Safety Cohort)	Magrolimab - 1 mg/kg IV	Day 1, 4	—	—
	Magrolimab - 15 mg/kg IV	Day 8	—	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 8, 15, 22	Day 1, 8, 15, 22
R/R AML/MDS (Expansion Cohort)[a]	Magrolimab - 1 mg/kg IV	Day 1, 4	—	—
	Magrolimab - 15 mg/kg IV	Day 8	—	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 8, 15, 22	Day 1 and 15
	Azacitidine - 75 mg/m^2 SC or IV[b]	Day 1-7	Day 1-7	Day 1-7
R/R MDS (Magrolimab Monotherapy Cohort)[a,c]	Magrolimab - 1 mg/kg IV	Day 1, 4	—	—
	Magrolimab - 15 mg/kg IV	Day 8	—	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 8, 15, 22	Day 1 and 15

Abbreviations: AML = acute myeloid leukemia; CTSC = Clinical Trial Steering Committee; IV = intravenous; MDS = myelodysplastic syndrome; Q2 = every 2; R/R = Relapsed/Refractory; SC = subcutaneous; UK = United Kingdom; US = United States.

a. The magrolimab maintenance dose in R/R Expansion and R/R MDS Monotherapy will be changed to Q2 weeks beginning at Cycle 3.
b. Azacitidine administered per region-specific labeling: SC in UK or US; IV in US only.
c. R/R MDS patients who do not have an objective response with magrolimab at the first protocol response assessment may have azacitidine added to magrolimab for subsequent cycles. The azacitidine dosing schedule given is identical to that of the R/R AML/MDS expansion cohort. For patients who respond to magrolimab monotherapy and then progress, azacitidine may be added to magrolimab and patients can still be continued to be treated with the combination.

3.3. Study Design - Treatment-naïve/Unfit (TN/U) Cohort

3.3.1. TN/U Cohort Dose Levels

All patients in the TN/U Cohort will receive magrolimab in combination with azacitidine. Magrolimab will be administered twice weekly through Cycle 1 Day 11; weekly beginning Cycle 1 Day 15 through end of Cycle 2; and then 30 mg/kg either weekly (for the TN/U Dose Evaluation Cohort) or Q2W (for the TN/U Expansion Cohort) starting Cycle 3 and thereafter, as shown in Table 3-2. This dose regimen was selected based on emerging clinical, PK, and pharmacodynamic data. Because dosing changed from twice weekly to weekly (beginning Week 3 of Cycle 1 and thereafter) with the previous Amendment 3, patients who are being treated under a previous Amendment may transition to the new (weekly) dosing schedule at the next cycle, or as determined by the Investigator. If a patient has only received Day 1 treatment for a cycle, the patient may transfer to the Q2W dosing regimen for the balance of the cycle and beyond. As of Amendment 6, a TP53 mutant TN/U AML subcohort was added to the TN/U Expansion Cohort. This TP53 mutant TN/U AML subcohort will have magrolimab administered on a Q2W dosing regimen starting Cycle 3 and thereafter (see Table 3-2). In addition, Amendment 6 reflects the CTSC decision to transition all TN/U Expansion Cohort patients (both existing and new) to a magrolimab dose of 30 mg/kg Q2W starting Cycle 3 and beyond.

Azacitidine will be administered according to region-specific drug labeling, either SC or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle for both dose levels. Magrolimab will be given at least 1 hour after the azacitidine infusion/injection is completed.

Dose evaluation of magrolimab will begin with the designated dose level shown in Table 3-2. Decisions related to potential dose escalation or de-escalation will be based on the first 4 weeks of treatment in the current cohort, referred to as the “Dose-Limiting Toxicity (DLT) Assessment Period,” in conjunction with ongoing assessments for patients on prior cohorts who continued therapy beyond 4 weeks. Decisions regarding additional cohorts to further refine the MTD or recommended Phase 2 dose and

schedule (RP2DS) will be made by the CTSC. The CTSC may create additional dose cohorts to be evaluated using a 3+3 design including, but not limited to, adding additional dose cohorts, adding intermediate dose steps (e.g., an additional intrapatient dose escalation step), reducing intermediate dose steps (e.g., removal of an intrapatient dose escalation step), or exploring a dose schedule of weekly or up to Q4W, if supported by emerging PK and clinical data. In addition, individual patients may be transitioned to a magrolimab Q2W to Q4W dosing regimen by the Investigator with approval from the Medical Monitor.

It should be noted that treatment with azacitidine as monotherapy is recommended for a minimum of 6 cycles (refer to the azacitidine prescribing information). All patients without evidence of treatment failure, relapse after CR or CRi, or unacceptable toxicity should continue study treatment for at least 6 cycles. Patients 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 8.1.

The Schedules of Assessments for the TN/U Dose Evaluation Cohort and the TN/U Expansion Cohort are provided in Section 7.1.

Table 3-2. Dose Level and Schedule for TN/U AML/MDS Cohorts (Including TP53 Mutant AML)

Cohort/Dose Level	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
TN/U Dose Evaluation Cohort: Level 1[b]	Magrolimab - 1 mg/kg IV	Day 1, 4	—	—
	Magrolimab - 15 mg/kg IV	Day 8	—	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 8, 15, 22	Day 1, 8, 15, 22
	Azacitidine - 75 mg/m^2 SC or IV[a]	Days 1-7	Days 1-7	Days 1-7
TN/U Expansion Cohort (including TP53 mutant AML subcohort): 30 mg/kg IV[b]	Magrolimab - 1 mg/kg IV	Day 1, 4	—	—
	Magrolimab - 15 mg/kg IV	Day 8	—	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 8, 15, 22	Day 1, 15
	Azacitidine - 75 mg/m^2 SC or IV[a]	Days 1-7	Days 1-7	Days 1-7

Abbreviations: AML = acute myeloid leukemia; IV = intravenous; MDS = myelodysplastic syndrome; R/R = Relapsed/Refractory; SC = subcutaneous; TN/U = Treatment-naïve/Unfit; UK = United Kingdom; US = United States.
a. Azacitidine administered per region-specific labeling: SC in UK or US; IV in US only.
b. As of Amendment 6, all existing and newly enrolled TN/U cohort patients are to follow 30 mg/kg Q2W magrolimab dosing starting Cycle 3 and beyond.

3.3.2. TN/U Cohort Dose Evaluation

Dose evaluation will follow a 3+3 dose evaluation design. Up to 6 evaluable patients may be enrolled in each dose cohort. If none or 1 of the first 3 patients experiences a DLT, the cohort will be expanded to 6 patients. If 2 or more patients experience DLTs, the MTD dose level will have been exceeded, enrollment to that cohort will halt. CTSC will determine whether to treat additional patients at lower or higher dose levels or evaluate alternative dose regimens. The MTD for the TN/U Cohort is the maximum dose level at which at least 6 patients are treated with magrolimab and azacitidine and less than 34% of these patients experience a DLT. The RP2DS will be determined by the CTSC (Section 11.6) based on review of all available safety, efficacy, and PK data.

Dose escalation/de-escalation and cohort expansion decisions will be reviewed and approved by the CTSC. Dose escalation or de-escalation may occur at dose increments or decrements, respectively, of up to 50% of the maximum prior dose as determined by the CTSC. The CTSC may add additional patients to any dose level to collect additional safety and PK information.

3.3.3. TN/U Cohort Dose-limiting Toxicity Evaluation

Dose evaluation decisions will be made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the "Dose-limiting Toxicity (DLT) Assessment Period." The first patient in each 3+3 dose evaluation cohort must complete at least 2 weeks of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The third patient in a cohort must complete the DLT Assessment Period prior to enrolling the next 3 patients at the same dose level. A new patient may be enrolled whenever a patient becomes nonevaluable for DLT. The CTSC may decide whether a fourth patient can be enrolled to the same cohort prior to the first 3 patients completing the DLT Assessment Period, in order to have an extra patient in case that 1 of the 3 earlier patients are not evaluable for DLT or if there is a DLT within the cohort requiring cohort expansion.

3.3.4. TN/U Cohort Definition of DLT-evaluable Patients

Patients in the TN/U Dose Evaluation cohort are considered evaluable for assessment of DLT if EITHER of the following criteria are met during the DLT Assessment Period:

- The patient experienced a DLT at any time after initiation of the first infusion/injection of magrolimab.
- The patient completed at least 4 infusions of magrolimab and 4 infusions/injections of azacitidine.

For the TN/U Dose Evaluation cohort, patients who withdraw before completing the 4-week DLT Assessment Period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

3.3.5. TN/U Cohort Definition of Dose-limiting Toxicity

All toxicities will be graded according to the NCI CTCAE, Version 4.03 (Appendix A) or protocol-specified AE severity grading scales (Appendix D). A DLT is defined as any Grade 4 or higher hematologic toxicity or Grade 3 or higher non-hematologic toxicity that has worsened in severity from pretreatment baseline during the 4-week DLT Assessment Period. These AEs will be considered DLTs unless they are clearly and incontrovertibly related to other causes, including underlying disease.

DLTs apply only to patients in the TN/U Dose Evaluation Cohort and RBC Transfusion-dependent Low-risk MDS Cohort.

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

- Myelosuppression (Grade 3 anemia, Grade 3 and 4 thrombocytopenia, and/or Grade 3 and 4 neutropenia, leukopenia, or lymphopenia) lasting no longer than 42 days from the start of study treatment. Complications within the first 4 weeks associated with myelosuppression such as fevers, infections, bleeding, and related hospitalizations will also not be considered DLTs.
  However, prolonged myelosuppression lasting longer than 42 days from the start of study treatment, without evidence of leukemia (< 5% blasts), will be considered a DLT. Absence of malignant disease must be verified by peripheral blood count and bone marrow aspirate and biopsy at Day 43 (+ 10 days).
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 7 days and is not associated with other clinically significant consequences.
- Grade 3 isolated electrolyte laboratory abnormalities that resolve to ≤ Grade 2 with supportive care within 7 days and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 7 days and is not associated with other clinically significant consequences.
- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 with supportive care within 7 days.

- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks.
- Grade 3 magrolimab infusion-related reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable non-steroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Other single laboratory values out of normal range that have no clinical correlate, and resolve to Grade ≤ 2 or to baseline within 7 days with adequate medical management.
- Transient Grade 3 nausea, vomiting, diarrhea, local reactions, influenza-like symptoms, myalgia, fever, headache, acute pain, or skin toxicity that resolves to ≤ Grade 2 within ≤ 72 hours after medical management (e.g., supportive care, including immunosuppressant treatment) has been initiated.
- Grade 3 or 4 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 14 days.

3.3.6. TN/U Expansion Cohort

Patients in the Expansion stage of the TN/U Expansion Cohort will receive the RP2DS determined in the TN/U Dose Evaluation Cohort. For the TN/U Expansion stage, patients may be enrolled simultaneously without an observation time between patients. The CTSC may alter the dosing scheme including, but not limited to, exploring a dose schedule of weekly or up to Q4W, if supported by emerging PK and clinical safety and efficacy data. Based on emerging clinical data, including efficacy data, the TN/U Expansion Cohort may be increased beyond 30 patients as determined by the CTSC.

Based on a Type B End of Phase 1 meeting with the FDA in May 2019, the TN/U Expansion Cohort was expanded in Amendment 5 to include untreated intermediate to very high-risk MDS patients, as assessed by IPSS-R, to include at least 91 patients as a single-arm trial for a potential BLA in higher-risk untreated MDS. These 91 patients are inclusive of MDS patients already treated in the TN/U Dose Evaluation and Expansion Cohorts. In a Type A meeting with the FDA in November 2019, it was agreed that the primary endpoint for potential approval can be CR rate with duration of CR.

An efficacy evaluation will be made after 36 evaluable MDS patients have undergone the first response assessment. If the CR rate for magrolimab and azacitidine is at least 35.5%, then an additional 56 patients will be treated in expansion at a magrolimab dosing regimen of Q2W. Enrollment does not need to be paused during the 36-patient evaluation prior to the additional 56-patient expansion. The 56-patient expansion would bring the total number of MDS patients in the TN/U Expansion Cohort to n = 92. The overall MDS expansion to 92 patients will be considered the MDS Registrational Cohort.

In Amendment 6, for all dosing cohorts except the RBC Transfusion-dependent Low-risk MDS Cohort, magrolimab dosing was transitioned from a 30 mg/kg weekly dosing regimen after Cycle 3 to a 30 mg/kg Q2W dosing regimen after Cycle 3 based on PK/PD and clinical data to maintain efficacy but maximize patient convenience. This dosing decision was made per CTSC recommendation on 05 November 2019. In addition, per discussion with the FDA in November 2019, the primary endpoint for this untreated higher-risk MDS cohort was changed from CR+PR to CR rate. In accordance with this CR endpoint and a transition to a Q2W magrolimab dosing regimen, a cohort of 56 patients at Q2W magrolimab dosing was added. A sample size of 56 patients provides 80% power to reject the null hypothesis that the CR rate is 16.5% or lower at a 2-sided 0.05 significance level, assuming the true CR rate is at least 31.5% (i.e., a 15% improvement). The null CR rate of 16.5% is the upper bound of the 95% confidence interval (point estimate of 10%) based on the pivotal randomized trial leading to azacitidine approval in MDS in which efficacy was reanalyzed according to the International Working Group (IWG) MDS criteria (Silverman 2006).

For more details on the expansion, refer to the scientific rationale (Section 1.5.1), clinical safety and efficacy data (Section 1.2.2), risk-benefit ratio (Section 1.5.2), and statistical analysis plan (SAP) (Section 11.8).

As per Amendment 6, a subcohort of TN/U AML patients with a TP53 gene mutation was added based on initial clinical data demonstrating activity of magrolimab + azacitidine in this patient population. As of July 2019, in 6 TP53 mutant AML patients, 5/6 (83%) achieved a CR/CRi with magrolimab + azacitidine. Based on these data, the CTSC met

in September 2019 and initiated an expansion of TN/U TP53 mutant patients with magrolimab + azacitidine. For this subcohort, magrolimab will be dosed Q2W after Cycle 2 (Table 3-2). With the exception of the magrolimab dosing regimen difference, the Schedule of Assessments for the TP53 mutant TN/U AML cohort is identical to the TN/U cohort (Table 7-2). After enrollment of up to 32 patients, additional patients may be enrolled to collect further safety, efficacy, and/or dosing data based on recommendations by the CTSC. Based on encouraging efficacy data in this cohort, the CTSC met in July 2020 and decided an additional 30 TP53 AML patients would be enrolled for the TN/U Expansion Cohort, this update is captured in Amendment 7.

It should be noted that treatment with azacitidine as monotherapy is recommended for a minimum of 6 cycles. All patients without evidence of treatment failure, relapse after CR/CRi, or unacceptable toxicity should continue study treatment for at least 6 cycles. Patients 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 8.1. The Schedule of Assessments for the TN/U Expansion Cohort is provided in Section 7.1.

3.4. Study Design - RBC Transfusion-dependent Low-risk MDS Cohort

The RBC Transfusion-dependent Low-risk MDS Cohort consists of a safety run-in phase and an expansion phase. In the safety run-in phase, 6 patients will be enrolled and will receive magrolimab monotherapy, with a safety evaluation after all 6 patients complete at least Cycle 2 Day 15 treatment. For this cohort, after the first patient is enrolled, subsequent patients in this initial 6-patient group can be enrolled simultaneously 1 week later. This safety evaluation is being conducted given that a 60 mg/kg dose of magrolimab will be administered starting in Cycle 2, of which this highest dose has not yet been tested in MDS patients. However an equivalent dose of 60 mg/kg given in 1 week (30 mg/kg twice weekly) has already been administered to MDS and AML patients in this trial and has been well tolerated. If 1 or fewer DLTs are observed in these 6 patients, then expansion may proceed.

If the DLT rate is ≥ 33% in at least 6 patients enrolled, then dose de-escalation to a lower magrolimab dosing regimen (i.e., 45 mg/kg Q4 weekly or alternative) can be explored as determined by the CTSC in an additional cohort of 6 patients with subsequent expansion. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.

3.4.1. RBC Transfusion-dependent Low-risk MDS Cohort Definition of Dose-limiting Toxicity

DLT definitions for the RBC Transfusion-dependent Low-risk MDS Cohort are similar to those for the TN/U Safety Evaluation Cohort and are defined in Section 3.3.5 with the exception that the DLT period is through the first 6 weeks (Cycle 2 Day 15). If the DLT rate is ≥ 33% in at least 6 patients enrolled, then the 60 mg/kg magrolimab dose would be considered to have exceeded the MTD. In this case, the CTSC may decide to proceed with expansion at a magrolimab dose regimen of 30 mg/kg QW for Cycle 2 followed by Q2W from Cycle 3 onward or explore a dose de-escalation to a lower magrolimab dosing regimen. The CTSC may decide to enroll additional patients in the safety run-in to further evaluate safety of the magrolimab 60 mg/kg dosing regimen or a lower dosing regimen. Patients may have their magrolimab dose interval changed (i.e., to more frequent [Q2W] or less frequent [> Q4W]) at any time on therapy based on CTSC recommendations or Sponsor requirement.

An efficacy assessment for the first 6 patients will be assessed at Cycle 3 Day 1. For patients who do not respond to magrolimab monotherapy, azacitidine can be subsequently added for continuation of therapy according to the dose schedule in Table 7-3. After the 6 patients have completed their post-Cycle 2 efficacy assessment, the CTSC will determine based on safety and efficacy data whether further expansion to 14 additional patients will occur with magrolimab monotherapy or magrolimab in combination with azacitidine. Expansion of these 14 patients can be simultaneously enrolled. Based on emerging safety, PK/PD, and/or efficacy data, the CTSC may expand this cohort to additional patients beyond the 20 total with either magrolimab monotherapy or in combination with azacitidine.

Table 3-3. Dose Level and Schedule for RBC Transfusion-dependent Low-risk MDS Cohort

Cohort/Dose Level	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)		
		Cycle 1	Cycle 2	Cycle 3+
Safety Run-in (Magrolimab 60 mg/kg)	Magrolimab - 1 mg/kg IV	Day 1	—	—
	Magrolimab - 30 mg/kg IV	Day 8, 15, 22	—	—
	Magrolimab - 60 mg/kg IV	—	Day 1	Day 1
	Azacitidine - 75 mg/m^2 SC or IV[a]	—	—	Days 1-5
Expansion	Magrolimab - 1 mg/kg IV	Day 1	—	—
	Magrolimab - 30 mg/kg IV	Day 8, 15, 22	—	—
	Magrolimab - 60 mg/kg IV[d]	—	Day 1	Day 1
	Azacitidine - 75 mg/m^2 SC or IV[a,b]	Days 1-5	Days 1-5	Days 1-5
Dose De-escalation (Magrolimab 45 mg/kg)[c]	Magrolimab - 1 mg/kg IV	Day 1	—	—
	Magrolimab - 30 mg/kg IV	Day 8, 15, 22	—	—
	Magrolimab - 45 mg/kg IV[c]	—	Day 1	Day 1
	Azacitidine - 75 mg/m^2 SC or IV[a]	—	—	Days 1-5

Abbreviations: CTSC = clinical trial steering committee; IV = intravenous; MDS = myelodysplastic syndrome; MTD = maximum tolerated dose; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

a. The first 6 patients will be treated with magrolimab monotherapy. If no response is observed after Cycle 2, then azacitidine can be added starting Cycle 3 and beyond.
b. Based on data from the safety run-in, the CTSC will decide whether the expansion cohort will receive magrolimab monotherapy or magrolimab+azacitidine.
c. If the MTD is exceeded for the safety run-in 60 mg/kg cohort, then a dose de-escalation to a magrolimab 45 mg/kg Q4W dosing regimen or alternative magrolimab dose regimen lower than 60 mg/kg (i.e., 30 mg/kg Q2W) can be explored per CTSC decision.
d. The magrolimab expansion dosing may be 60 mg/kg, 45 mg/kg, or 30 mg/kg Q4W or Q2W based on the safety run-in CTSC decision.

A 5-day azacitidine dosing regimen will be utilized specifically for this low-risk MDS cohort to maximize efficacy and patient convenience while minimizing toxicities in this patient population. The selection of this 5-day dosing regimen is based on a randomized trial demonstrating similar hematologic responses and RBC transfusion independence and lower AE rates for the 5-day regimen compared to a 7-day regimen (Lyons 2009). It should be noted that treatment with azacitidine as monotherapy is recommended for a minimum of 6 cycles. All patients without evidence of treatment

failure, relapse after CR/CRi, or unacceptable toxicity should continue study treatment for at least 6 cycles. Reduction of azacitidine dose frequency to a Day 1 to 3 administration per month may be considered for individual patients based on safety/efficacy or individual patient circumstances with approval by the Medical Monitor or with CTSC approval for this change for all patients. Patients 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 8.1.

3.5. Study Design - Rollover Cohort

In the Phase 1 trial of magrolimab in R/R AML (SCI-CD47-002), patients who have derived clinical benefit from magrolimab have been continuously receiving magrolimab dosing. These patients may continue to receive magrolimab therapy under this protocol in the Rollover Cohort. Patients in the Rollover Cohort may receive the same dose level and schedule (i.e., twice weekly) of magrolimab monotherapy as previously received in the Phase 1 AML study or may transition to once-weekly dosing at the discretion of the Investigator and with Sponsor approval. Patients who are receiving twice-weekly dosing may transition to the new (weekly) dosing schedule at the next cycle, or as determined by the Investigator. If a patient has only received Day 1 treatment for a cycle, the patient may transfer to the new dosing regimen with that cycle, for the balance of the cycle and beyond. Patients on the Rollover Cohort who progress on therapy, no longer derive clinical benefit, or demonstrate unacceptable toxicity to magrolimab will be taken off study treatment. (Section 8.1). The Schedule of Assessments for the Rollover Cohort is provided in Appendix F.

3.6. Number of Sites

Approximately 1 site located in the UK and 26 sites in the US will be included in this trial. Additional sites in the UK, US, and/or other countries may be included based on enrollment and study timelines.

3.7. Estimated Study Duration and End of Study

It is anticipated that this study will take approximately 5 years to complete, assuming 16 months for enrollment plus 1 month screening, 6 or more cycles of study treatment, and 1 month safety follow-up for each patient, and up to 3 years of survival follow-up after the last patient is enrolled.

Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study treatment (magrolimab and/or azacitidine), during which time the patient's eligibility and baseline characteristics will be determined. Study treatment may be continued until an unacceptable drug-related toxicity occurs or until disease progression. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs. Post treatment, patients will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

The end of study is defined as the date on which the last patient completes the last study visit (follow-up for safety, disease progression or survival), or when the CTSC or Sponsor decides to end the study.

4. PATIENT SELECTION AND ENROLLMENT

4.1. Study Entry Criteria

4.1.1. Inclusion Criteria

All Patients:

1. Meets the criteria below for the appropriate cohort:

    a. <u>All R/R Cohorts (meets i or ii)</u>:

        i. Pathologically confirmed AML (defined by 2017 ELN classification; Döhner 2017) relapsed or refractory to a prior therapy with either a hypomethylating agent (such as azacitidine or decitabine), non-intensive chemotherapy (such as low-dose cytarabine arabinoside), and/or venetoclax. Treatment is limited to 1 prior line of therapy. Hematopoietic

stem cell transplant for patients in remission would not be counted as a line of therapy for AML, or

ii. Confirmed MDS defined according to World Health Organization (WHO) classification that is either refractory to hypomethylating agent (defined as disease progression per IWG 2006 criteria [Cheson 2006] at any time after initiation of a hypomethylating agent or failure to achieve an objective response by IWG 2006 criteria after 4 cycles) or is relapsed or intolerant to prior therapy with either a hypomethylating agent, non-intensive chemotherapy, or targeted therapy. Treatment is limited to 1 prior line of hypomethylating agent therapy (including investigational hypomethylating agents) for all R/R MDS patients.

iii. R/R MDS Magrolimab Monotherapy Cohort: Inclusion criterion ii above applies.

b. All TN/U Cohorts (meets i or ii):

i. Previously untreated patients with MDS defined according to WHO classification, with an IPSS-R (Greenberg 2012) risk category of intermediate, high, or very high risk. Prior and concurrent therapy with hydroxyurea, oral etoposide, erythroid, and/or myeloid growth factors is allowed.

ii. Previously untreated patients with histological confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity, age or other factors, or who refuse such therapy.

c. TP53 Mutant AML Subcohort: Previously untreated patients with histological confirmation of AML by WHO criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity, age, or other factors, or who refuse such therapy and who have presence of at least 1 TP53 gene mutation by next-generation sequencing based on local evaluation.

d. RBC Transfusion-dependent Low-risk MDS Cohort: MDS patients with very low or low risk by IPSS-R who are RBC transfusion-dependent (requiring ≥ 2 RBC units within 8 weeks prior to screening) and meet at least one of the following:

   i. Relapsed/refractory to ESA: documented non-response or response that is no longer maintained to prior ESA-containing regimen
   ii. Intolerant to ESA: documentation of discontinuation of prior ESA-containing regimen at any time after initiation due to intolerance or adverse event
   iii. ESA ineligible: endogenous serum erythropoietin level > 500 U/L for patients who have not been previously treated with ESAs
   iv. Have a deletion in chromosome 5q and who are relapsed/refractory/intolerant to or ineligible for lenalidomide therapy

e. Rollover Cohort: Patients on active magrolimab therapy on the Phase 1 AML (SCI-CD47-002) trial who are deriving clinical benefit by Investigator assessment.

2. WBC count ≤ 20 × 10^3/mcL pre-first dose of study treatment and prior to each magrolimab dose for Cycle 1. Patients with WBC > 20 × 10^3/mcL can be treated with hydroxyurea (up to 4 g/day) throughout the trial to reduce the WBC to ≤ 20 × 10^3/mcL. Oral etoposide (up to 200 mg orally [PO] /day) may be given as an alternative to hydroxyurea for patients who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.
3. Patient has provided informed consent.
4. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

R/R Cohorts (including the R/R MDS Magrolimab Monotherapy Cohort), TN/U Cohorts (including the MDS Registrational Cohort and the TP53 Mutant TN/U AML Subcohort), and RBC Transfusion-dependent Low-risk MDS Cohort only (Criteria 5 through 9 DO NOT apply to the Rollover Cohort):

5. Male or female, age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2.
7. Hemoglobin must be ≥ 9 g/dL within 24 hours prior to the first 2 doses of magrolimab infusion; patient must be willing to undergo blood transfusions as deemed clinically necessary. NOTE: Transfusions are allowed to meet hemoglobin eligibility (see Section 6.2.2.1 for anemia management)
8. Pretreatment blood crossmatch completed (as detailed in Section 6.2.2.1 and Section 7.3.4).
9. Biochemical indices within the ranges shown below:
    a. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≤ 5× upper limit of normal (ULN)
    b. Bilirubin ≤ 1.5× ULN, or 3.0× ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent
    c. Serum creatinine ≤ 1.5× ULN or calculated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2
10. Female patients 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 enrollment and within 72 hours before the first administration of study drug.
11. Female patients of childbearing potential must be willing to use 1 highly effective method of contraception during the study and continue for 6 months after the last dose of magrolimab or azacitidine, whichever ends later (Section 4.5.1).
12. Male patients who are sexually active with a WOCBP and who have not had vasectomies must be willing to use a barrier method of contraception during the study and for 3 months after the last dose of magrolimab or azacitidine, whichever ends later (Section 4.5.4).
13. Willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines), unless not feasible as determined by the Investigator.

4.1.2. Exclusion Criteria

1. Prior treatment with CD47 or SIRPα-targeting agents (with exception of magrolimab for patients in the Rollover Cohort).
2. Prior anti-leukemic therapies including, but not limited to, chemotherapy (with the exception of hydroxyurea or oral etoposide), targeted therapies, immunotherapy, or radiotherapy within 4 weeks prior to Day 1 magrolimab dosing. NOTE: Localized non-central nervous system (non-CNS) radiotherapy, 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.
3. **TN/U Cohorts only**: Any prior anti-leukemic therapy (excluding hydroxyurea or oral etoposide), prior treatment with hypomethylating agents and/or low dose cytarabine.
4. **R/R Expansion Cohort, R/R MDS Magrolimab Monotherapy Cohort, TN/U Cohorts, and RBC Transfusion-dependent Low-risk MDS Cohort only**: Contraindications to azacitidine, including advanced malignant hepatic tumors or known hypersensitivity to azacitidine or mannitol.
5. Acute promyelocytic leukemia.
6. Known inherited or acquired bleeding disorders.
7. Previous allogeneic hematopoietic stem cell transplant within 6 months prior to enrollment, active graft versus host disease (GVHD), or requiring transplant-related immunosuppression.
8. Clinical suspicion of active CNS involvement by leukemia.
9. 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 (NYHA) Class III-IV.
10. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapy as defined in Exclusion Criterion 2.

11. History of psychiatric illness or substance abuse likely to interfere with the ability to comply with protocol requirements or give informed consent.
12. Pregnancy or active breastfeeding.
13. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).

4.2. Patient Screening and Enrollment Procedures

All patients who enter the screening period for the study, which starts when the patient signs the informed consent form (ICF), receive a unique patient identification number before any study procedures are performed. This number is used to identify the patient throughout the clinical trial and must be used on all study documentation related to that patient, including if a patient is rescreened.

Patient screening laboratory assessments may be repeated beyond the initial screening assessments within the 30-day screening period. Patients who screen fail may undergo repeated screening if the patient's medical condition has changed.

All patients who provide informed consent must be registered in the electronic data capture (EDC) system, including any screen failures.

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the Sponsor has approved the cohort or study arm assignment. After signing the ICF, eligible patients are expected to receive the first dose of study treatment (Study Day 1) within 30 days.

4.3. Informed Consent Process

All participants must be provided an ICF describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board/Research Ethics Committee (IRB/REC)-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 (in paper or electronic format) of

the consent documents must be retained in the medical record or research file. The first dose of magrolimab is to be given within 30 days of signing the ICF.

4.4. Registration Process

Patient will be assigned a patient identification number at the time of consent.

Prior to being assigned a dose cohort or treatment arm, patients must have signed the informed consent and satisfied all of the eligibility criteria. The Investigator and clinical team will determine the eligibility of the patient. Once a patient has been assigned to a dose cohort, they will be considered enrolled.

4.5. Contraception Requirements

4.5.1. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause.

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

4.5.2. Definition of Male Fertility

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

4.5.3. Female Patients

Female patients of childbearing potential who have a negative serum or urine pregnancy test before enrollment must agree to use 1 of the following highly effective forms of contraception (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly):

- Bilateral tubal occlusion
- Vasectomized partner
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Combined hormonal contraception (estrogen- and progestogen-containing) associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Abstinence

  Defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post-ovulation methods), nor is the withdrawal method (coitus interruptus), spermicides only, and lactational amenorrhea method. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Contraception must be effective at the first administration of study treatment (magrolimab or azacitidine), throughout the trial, and for 6 months after the last dose of magrolimab or azacitidine, whichever ends later.

4.5.4. Male Patients

A man who is sexually active with a woman of childbearing potential (WOCBP) and has not had a vasectomy must agree to use a barrier method of birth control (e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) during the study. A female condom and a male condom should not be used together.

Contraception must be effective at the first administration of study drug (magrolimab or azacitidine), throughout the trial, and for 3 months after the last dose of magrolimab or azacitidine, whichever ends later.

It should be explained to the patient that if his partner is pregnant or breastfeeding when he is enrolled on the trial, the patient should use barrier method contraception (condom) to prevent the unborn fetus or the baby being exposed to investigational product.

Male patients 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..

5. STUDY DRUG INFORMATION

Detailed instructions for magrolimab and azacitidine preparation and handling are provided in the Pharmacy Manual.

5.1. Magrolimab

The active pharmaceutical ingredient (API) is magrolimab, a humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) 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.

Magrolimab API is manufactured under current Good Manufacturing Practices.

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 pH of 5.0.

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

Vials containing magrolimab should be stored under refrigeration at 2 to 8°C (36°F to 46°F) in an appropriate, locked room and/or locked refrigerator, accessible only to pharmacy personnel, the Principal Investigator, or a duly designated person. Magrolimab should not be frozen. Protect from light during storage. DO NOT SHAKE.

Additional details about magrolimab are provided in the Pharmacy Manual.

5.2. Azacitidine

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.

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

Storage and handling of azacitidine should follow local prescribing information. Additional details about azacitidine are provided in the Pharmacy Manual.

6. TREATMENT PLAN

6.1. Study Drug Administration

Patients should be premedicated in accordance with Section 6.1.3. Magrolimab and azacitidine should be prepared as outlined in the Pharmacy Manual for the study.

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

Patients may continue study treatment with magrolimab and/or azacitidine until they show evidence of disease progression (treatment failure or relapse after CR/CRi), no

longer derive clinical benefit, or demonstrate unacceptable toxicity (further details about treatment discontinuation in Section 8.1). If the treating physician and Sponsor agree that it is in the best interest of the patient to continue treatment with either magrolimab or azacitidine alone, the patient may continue to participate in the study provided that other protocol stipulations are met.

6.1.1. Magrolimab

All patients will receive magrolimab administered IV as described below:

- **R/R Cohort (all stages):** Magrolimab will be dosed using an intrapatient dose escalation schedule as shown in Table 3-1.
- **TN/U Dose Evaluation Cohort:** Magrolimab will be given according to an intrapatient dose escalation schedule, with continued weekly dosing after Cycle 2 as shown in Table 3-2.
- **TN/U Expansion Cohort (including the MDS Registrational Cohort):** Magrolimab will be given according to the dose schedule with continued Q2W dosing starting Cycle 3 and thereafter, as shown in Table 3-2.
- **TP53 mutant TN/U AML Subcohort:** Magrolimab will be given according to an intrapatient dose escalation schedule with continued Q2W dosing starting Cycle 3 and thereafter, as shown in Table 3-2.
- **RBC Transfusion-dependent Low-risk MDS Cohort:** Magrolimab will be given according to the dose schedule with continued Q4W dosing starting Cycle 2 and thereafter, as shown in Table 3-3.
- **Rollover AML Cohort:** The Rollover Cohort will receive the dose and schedule of magrolimab monotherapy as shown in Appendix F. At the discretion of the CTSC for this study, patients who are receiving lower doses may be escalated to the highest dose determined to be safe by the CTSC for this study.

The duration of each magrolimab infusion will be 3 hours (± 30 minutes) for the first week of treatment in the R/R and TN/U cohorts. Starting the second week of treatment, the magrolimab infusion will be 2 hours (± 30 minutes). 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.

Magrolimab doses given twice weekly are to be at least 24 hours apart, with a window of ± 3 days for each dose; however, **magrolimab doses are not to be given on consecutive days**. Based on clinical, PK, and pharmacodynamic data, the CTSC decided to change dosing from twice weekly to weekly (beginning Week 3 of Cycle 1 and thereafter) with Amendment 3. Patients who are being treated under the previous Amendment may transition to the new (weekly) dosing schedule at the next cycle, or as determined by the Investigator. In the Rollover Cohort, the patient may continue the same twice-weekly schedule as the patient previously received in the Phase 1 AML study (SCI-CD47-002) or may transition to once-weekly dosing of magrolimab monotherapy at the discretion of the Investigator and with Sponsor approval. If a patient has only received Day 1 treatment for a cycle, the patient may transfer to the new dosing regimen with that cycle, for the balance of the cycle and beyond. In addition, patients in the R/R Expansion Cohort will transition from a magrolimab weekly dosing schedule to a Q2 week dosing schedule beginning in Cycle 3.

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

During the first cycle (Cycle 1) (28 days) of treatment, WBC count must be ≤ 20 × 10^3/mcL prior to each magrolimab dose. Patients with WBC > 20 × 10^3/mcL can be treated with hydroxyurea (up to 4 g/day) throughout the trial to reduce the WBC to ≤ 20 × 10^3/mcL. Oral etoposide (up to 200 mg PO/day) may be given as an alternative to hydroxyurea for patients who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.

All patients must have documented hemoglobin ≥ 9 g/dL within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring

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

All patients should be monitored for 1 hour post-infusion for priming, re-priming/re-escalation, and maintenance doses during Cycle 1. Post-infusion monitoring should begin after the infusion is complete. Post-infusion monitoring is not required for doses after Cycle 1, Day 22. Patients who experience any treatment-related AEs during the observation period should be further monitored, as clinically appropriate.

Re-priming/Re-escalation for Magrolimab

Given the large CD47 antigen sink on red blood cells, patients who have a long dose delay of magrolimab are required to be re-primed with magrolimab dosing to resaturate the CD47 antigen sink.

R/R and TN/U Cohorts: For patients who had a dose delay of greater than 4 weeks for magrolimab, re-priming/re-escalation is needed with magrolimab. For patients who have not received at least one 30 mg/kg dose of magrolimab (i.e., for patients who have either not received their first dose of 30 mg/kg or patients who have received doses < 30 mg/kg), a dose delay of only 2 weeks is allowed until re-priming is needed. Table 6-1 illustrates the re-priming/re-escalation magrolimab dosing regimen and schedule of assessments.

RBC Transfusion-dependent Low-risk MDS Cohort: For patients who had a dose delay of greater than 6 weeks for magrolimab, re-priming/re-escalation is needed with magrolimab. For patients who have not received at least one 30 mg/kg dose of magrolimab, a dose delay of only 2 weeks is allowed until re-priming is needed. For patients who have not received at least one 60 mg/kg dose of magrolimab, a dose delay of 4 weeks is allowed until re-priming is needed. Table 6-1 illustrates the re-priming/re-escalation magrolimab dosing regimen and schedule of assessments.

The re-priming/re-escalation dosing regimen for magrolimab is shown below in Table 6-1.

Table 6-1. Magrolimab/Azacitidine Re-priming/Re-escalation Dosing Schedule

Cohort	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)	
		Re-priming Cycle	Subsequent Cycles
R/R Cohort and TN/U Cohort (including the TP53 Mutant TN/U AML Subcohort)	Magrolimab - 1 mg/kg IV	Day 1, 4	—
	Magrolimab - 15 mg/kg IV	Day 8	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 15
	Azacitidine - 75 mg/m^2 SC or IV[b]	Day 1-7	Day 1-7
R/R MDS Magrolimab Monotherapy Cohort[c]	Magrolimab - 1 mg/kg IV	Day 1, 4	—
	Magrolimab - 15 mg/kg IV	Day 8	—
	Magrolimab - 30 mg/kg IV	Day 11, 15, 22	Day 1, 15
RBC Transfusion-dependent Low-risk Cohort	Magrolimab - 1 mg/kg IV	Day 1	—
	Magrolimab - 30 mg/kg IV	Day 8, 15, 22	—
	Magrolimab - 60 mg/kg IV[a]	—	Day 1
	Azacitidine - 75 mg/m^2 SC or IV[b]	Day 1-5	Day 1-5

Abbreviations: CTSC = Clinical Trial Steering Committee; IV = intravenous; MDS = myelodysplastic syndrome; RBC = red blood cell; R/R = relapsed/refractory; SC = subcutaneous; TN/U = treatment-naïve/unfit (for standard induction chemotherapy); UK = United Kingdom; US = United States.

a. The magrolimab dosing of 60 mg/kg, 45 mg/kg, or other alternative dose will be utilized based on the safety run-in data and CTSC decision for expansion.
b. Azacitidine will be administered per region-specific labeling: SC in UK or US; IV in US only.
c. For R/R MDS Magrolimab Monotherapy patients who require repriming, and are receiving both magrolimab and azacitidine post Cycle 3, the repriming schedule is Azacitidine - 75 mg/m^2 SC or IV, Day 1-7 of the repriming Cycle.

6.1.2. Azacitidine

Azacitidine will be administered according to region-specific drug labeling, either SC or IV, at the standard dose of 75 mg/m^2 on Days 1 to 7 of each 28-day cycle for the R/R (except the magrolimab monotherapy cohort, which will allow the addition of azacitidine after the first response assessment with Investigator and Sponsor agreement) and TN/U cohorts (including TP53 mutant cohort) for all dose levels of magrolimab when

azacitidine is scheduled to be administered (for patients assigned to combination treatment). For the RBC Transfusion-dependent Low-risk MDS Cohort, azacitidine will be administered either SC or IV at the dose of 75 mg/m^2 on Days 1 to 5 of each 28-day cycle (see Table 3-3) for all dose levels of magrolimab when azacitidine is scheduled to be administered (for patients assigned to combination treatment). When administered IV, the total dose of azacitidine (diluted in a 50-100 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 for detailed instructions for preparation and administration).

6.1.3. Premedication

Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with re-priming for all cohorts except the RBC Transfusion-dependent Low-risk Cohort, for which premedication is required for the first 2 doses of magrolimab and the first 2 doses in case of reintroduction with re-priming. Premedication for subsequent magrolimab treatments may be continued based on the treating physician's clinical judgement and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent treatments is required (Section 6.2.2.1).

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.

6.2. Dose Modifications, Dose Delays, and Safety Management Guidelines

6.2.1. Dose Modification and Delay Guidelines

6.2.1.1. Magrolimab

Dose Modifications

Magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur, which include all AEs that constitute a DLT, as defined in Section 3.3.5.

Magrolimab may be reintroduced at a 50% dose reduction if the severity has recovered to Grade $\leq$ 2 within 4 weeks and in the absence of disease progression, with approval from the Medical Monitor. A dose delay for up to 3 days may be permissible if the patient's WBC count is greater than 20 × 10^9/L (which is applicable to Cycle 1), to allow for oral hydroxyurea or etoposide treatment to reduce the WBC count. Further dose delay due to elevated WBC counts must be discussed and approved by the Medical Monitor.

Patients who experience a Grade 4 or higher AE of hemagglutination and/or microangiopathy related to magrolimab will permanently discontinue magrolimab treatment. Patients who experience Grade 3 hemagglutination and/or microangiopathy will have magrolimab dosing withheld, and may be reintroduced at a 50% dose reduction if the event severity recovers to Grade $\leq$ 1 within 4 weeks and there is no evidence of disease progression.

With one exception, patients who experience a DLT will have their treatment held for up to 4 weeks to allow sufficient time for recovery, but may restart dosing at a lower dose level if they still meet study eligibility criteria. Patients who experience a DLT of Grade 4 non-hematological toxicity will not restart magrolimab and will be withdrawn from study drug treatment. Data from patients who restart dosing after the recovery period will not contribute to the MTD evaluation at the lower dose level. Treatment delays of more than 4 weeks (such as for an unrelated medical condition with expected recovery) must be discussed with the Medical Monitor and approved by the Sponsor.

Treatment Interruption and Delays

A magrolimab treatment interruption is defined as a nonprotocol-specified interruption from treatment, assessments, and procedures. Ongoing data analysis across magrolimab + azacitidine trials shows that Q2W dosing of magrolimab without significant interruptions is important to yield optimal efficacy. Therefore, when a patient has an azacitidine treatment delay due solely to azacitidine-related toxicities, magrolimab should continue with Q2W dosing as scheduled (Table 7-4) or Q4W dosing as scheduled (Table 3-3). Re-initiation of azacitidine will start at the next cycle (which is

numerically after the azacitidine cycle which the patient most recently received azacitidine prior to the dose delay). Patients will proceed with this cycle starting on Day 1. Response assessments should occur at time points associated with cycles of azacitidine per Schedules of Assessments (Table 7-1, Table 7-2, and Table 7-3) (e.g., Cycle 3 Day 1 response assessment should only occur after a patient has received 2 cycles of azacitidine). Additionally, in the event that magrolimab dosing is decoupled from azacitidine dosing, collection of PK and ADA should always coincide with magrolimab dosing at time points specified in Table 7-4. Patients in Cycle 1 of the TN/U Expansion or RBC Transfusion-dependent Low-risk MDS Cohorts should follow dosing guidelines and collections for that cycle. Patients in Cycle 2 of TN/U Expansion Cohort should follow dosing schedule and collections for that cycle. Patients in Cycle 3 or beyond should follow Q2C collection of PK and ADA.

Patients with a magrolimab interruption of longer than 4 weeks (4 weeks is maximum allowed for an elective drug delay) or a treatment delay of longer than 4 weeks must undergo intrapatient dose escalation of magrolimab again based on their original dosing regimen (e.g., for patients on once-weekly dosing, 1 mg/kg priming dose on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Days 11, 15, and 22; or for Rollover patients who remain on twice-weekly maintenance dosing, 1 mg/kg priming dose on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Days 11, 15, 18, 22, and 25).

Any treatment delays/interruptions should be discussed with the Medical Monitor and approved by the Sponsor.

Maintenance Dose Schedule Modification

Patients in the R/R and TN/U Cohorts who have completed at least 8 weeks of therapy may stay at the same infusion dose and will have their magrolimab schedule of administration modified to weekly as decided by the CTSC based on clinical, PK, and pharmacodynamic data. Patients in the Rollover Cohort may continue the same dose level and schedule (i.e., twice weekly) of magrolimab monotherapy as previously received in the Phase 1 AML study or may transition to once-weekly dosing. Patients who are being treated under the previous Amendment may transition to the new

(weekly) dosing schedule at the next cycle, or as determined by the Investigator. If a patient has only received Day 1 treatment for a cycle, the patient may transfer to the Q2W dosing regimen with that cycle, for the balance of the cycle and beyond.

Intrapatient Dose Escalation

When the recommended dose has been determined, patients enrolled in the Rollover Cohort or TN/U Dose Evaluation Cohort of the study who have been on study for at least 8 weeks may have their current dose escalated to the dose level that has been previously determined to be safe in this study, at the discretion of the CTSC.

6.2.1.2. Azacitidine

Dose Modifications

Dose modification or dose delay of azacitidine may not occur for patients in the initial 28-day DLT Assessment Period in the TN/U Dose Evaluation Cohort or for the first cycle for patients in the TN/U Expansion Cohort. Dose modifications described below are in accordance with the azacitidine prescribing information with modifications. While the US prescribing information allows for dose escalation to 100 mg/m^2 after the first 2 cycles, a consistent azacitidine dose of 75 mg/m^2 is planned throughout this study. Azacitidine dose increases are not allowed without prior approval from the Medical Monitor. The azacitidine dose modifications described below are per prescribing information and serve as general recommendations. However, in standard clinical practice, azacitidine label instructions for dose reduction (based on nadir blood counts and bone marrow assessment) are not routinely followed in the clinical setting, and it appears that this part of the label has not been updated since the first approval of azacitidine in 2004. Recommendations from international groups underline the importance of maintaining azacitidine dose intensity in higher-risk MDS patients and AML patients and to avoid dose reductions, if possible (Fenaux 2010; Santini 2014; Wells 2014). Therefore, azacitidine dose modifications will follow the prescribing information below or institutional practice supported by international recommendations.

Azacitidine Dose Modifications Due to Non-Hematological Toxicity

Renal abnormalities ranging from elevated serum creatinine to renal failure have been reported in rare frequency in patients treated with azacitidine. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L) have 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 (BUN) 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% on the next treatment cycle. The reduced dose should be maintained during subsequent cycles unless toxicity develops.

Azacitidine Dose Modifications Due to Hematological Toxicity

Treatment with azacitidine is associated with anemia, neutropenia, and thrombocytopenia. Thus, complete blood counts (CBCs) will be performed as described in the Schedule of Assessments (Section 7.1) 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, as to not limit potential treatment benefit. In accordance to this distinction, azacitidine will not be dose-reduced if hematologic cytopenias are observed in the presence of persistent AML; i.e., evidence of:

- > 5% blasts in the bone marrow;
- blasts with Auer rods;
- circulating blasts;
- persistent cytogenetic/molecular abnormality related to AML; or
- positive minimal residual disease.

Hematologic cytopenias in this circumstance are not defined as hematologic toxicities. However, if hematologic cytopenias are observed without evidence of AML disease, this would be defined as hematologic toxicity and azacitidine dose reduced accordingly as

below. Guidance for azacitidine dose modifications due to hematologic toxicities are outlined below for 2 patient populations.

Patients without reduced baseline blood counts (i.e., WBC ≥ 3.0 × 10^9/L, absolute neutrophil count [ANC] ≥ 1.5 × 10^9/L, and platelets ≥ 75 × 10^9/L) prior to first treatment.

If hematological toxicity is observed following azacitidine treatment, the next cycle of therapy should be delayed until the platelet count and the ANC have recovered.
If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to Table 6-2. Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given unless toxicity develops.

Table 6-2. Azacitidine Dose Modification - Patients Without Reduced Baseline Blood Counts

Nadir Counts		% Dose in the Next Cycle If Recovery[a] Is Not Achieved Within 14 Days
ANC (×10^9/L)	Platelets (×10^9/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

Abbreviation: ANC = absolute neutrophil count.
a. Recovery = counts ≥ nadir count + (0.5 × [baseline count - nadir count]).

Patients with reduced baseline blood counts (i.e., WBC < 3.0 × 10^9/L or ANC < 1.5 × 10^9/L or platelets < 75.0 × 10^9/L) prior to the first treatment

Following azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 50 %, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made. If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if

recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to Table 6-3.

Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given unless toxicity develops.

Table 6-3. Azacitidine Dose Modification - Patients With Reduced Baseline Blood Counts

Bone Marrow Cellularity	% Dose in the Next Cycle if Recovery[a] Is Not Achieved Within 14 Days	
	Recovery[a] ≤ 21 days	Recovery[a] ≥ 21 days
15-50%	100%	50%
< 15%	100%	33%

a. Recovery = counts ≥ nadir count + (0.5 × [baseline count - nadir count])

Treatment Interruption and Delays

If hematological toxicity is observed following azacitidine treatment, the next cycle of therapy should be delayed until the platelet count and the ANC have recovered.
If recovery is achieved within 14 days, no dose adjustment is needed. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the azacitidine dose modification guidelines above. Additionally, azacitidine dosing may be delayed for up to 4 weeks based on an individual patient basis, which must be approved by the Medical Monitor. Following dose modifications, the cycle duration should return to 28 days.

In the event 2 or fewer doses of azacitidine are missed during the 7-day dosing period for the R/R and TN/U cohorts, dosing should continue so that the patient receives the full 7 days of therapy. In the event that 3 or more days 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.

For the RBC Transfusion-dependent Low-risk MDS Cohort, in the event that 1 dose of azacitidine is missed during the 5-day dosing period, dosing should continue so that the patient receives the full 5 days of therapy. In the event that 2 or more days are missed during the 5-day dosing period, the Investigator should contact the Sponsor and a dosing decision should be made on an individual case basis.

6.2.2. Specific Safety Management Guidelines

6.2.2.1. Magrolimab

For all cohorts except the RBC Transfusion-dependent Low-risk Cohort, premedication is required before administration of the first 4 doses of magrolimab with oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg, or comparable regimen. It is also required in case of reintroduction with re-priming. For the RBC Transfusion-dependent Low-risk Cohort, premedication is required for the first 2 doses of magrolimab and the first 2 doses in case of re-introduction with re-priming. In addition, premedications are to be used to manage infusion-related reactions as described below.

Management of Infusion-related Reactions

Infusion-related reactions are defined by the NCI CTCAE (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. 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 patient until recovery from symptoms.

- For Grade 2 infusion-related reaction , infusion interruption is indicated, but patient responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); and prophylactic medications are indicated for ≤ 24 hours:
  - Stop the magrolimab infusion, begin an IV infusion of normal saline, and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500-750 mg oral acetaminophen.
  - Remain at bedside and monitor patient until resolution of symptoms.
  - Corticosteroid therapy may also be given at the discretion of the Investigator.
  - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
  - If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
  - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit.
  - Premedications should be considered before any future infusions.
  - The amount of magrolimab infused must be recorded on the electronic Case Report Form (eCRF).
  - Patients who experience a Grade 2 infusion-related reaction during the post-infusion 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).
  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 patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
- Patients who have Grade 4 infusion-related reactions occurring with the first dose (priming dose) will be permanently discontinued from study treatment.
- Patients who experience Grade 3 infusion-related reactions must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650-1000 mg), oral or IV diphenhydramine (25-50 mg), and IV dexamethasone (4-20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.
- Patients who receive premedication (with the regimen above, including corticosteroids) and still experience a Grade 3 or 4 infusion-related reaction will be permanently discontinued from study treatment.
- For anaphylaxis, Investigators should follow their institutional guidelines for treatment.
- All patients 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.

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.

Anemia, Blood Crossmatching, and Packed RBC Transfusion Procedures

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

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

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

All patients must have documented hemoglobin $\geq$ 9 g/dL within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Prior to initiation of magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient (Section 7.3.4). Red blood cell

genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.

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

For Patients After Exposure to Magrolimab:

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines. For RBCs, phenotype/genotype matched units are preferred. However, CMV-seronegative units for CMV-seronegative patients 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 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 crossmatch 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 sample cells, pooled single donor apheresis platelets, or commercial human platelet concentrate product if required (Velliquette 2019) (Troughton 2018).

Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with magrolimab and/or azacitidine, patients will be admitted to the hospital as clinically indicated. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes in accordance with local institutional guidelines.

6.2.2.2. Azacitidine

Safety management guidelines for azacitidine are described in Section 6.2.1.2. Additional safety guidelines are provided in the azacitidine prescribing information.

6.3. Duration of Therapy

Study treatment (magrolimab and/or azacitidine) will be administered continuously until disease progression, loss of clinical benefit, or unacceptable toxicity. It should be noted that treatment with azacitidine as monotherapy is recommended for a minimum of 6 cycles. All patients in the TN/U Cohort without evidence of treatment failure, relapse after CR/CRi, or unacceptable toxicity should continue study treatment for at least 6 cycles. Patients 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 8.1.

6.4. Patient Completion of the Study

Patients are expected to remain on study treatment until at least completion of Cycle 6. Patients who have not demonstrated disease progression or unacceptable toxicity may continue to receive study treatment beyond 6 cycles.

Patients are considered to have completed the study treatment period when they finish the Safety Follow-up Visit 30 days (± 7 days) after their last dose of study treatment, unless they are experiencing ongoing serious adverse events (SAEs) or treatment-related AEs. For patients being followed for ongoing SAEs or treatment-related AEs, follow-up visits will continue at least Q4W until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer treatment. Follow-up for ongoing SAEs or treatment-related AEs after the Safety Follow-up Visit will stop if a patient begins another anti-cancer therapy.

After the Safety Follow-up Visit, patients will enter long-term follow-up for disease progression (Section 7.6) and survival follow-up (Section 7.7).

All patients, including those who discontinue study treatment early, will be followed for response until disease progression or initiation of new anti-cancer therapy, whichever happens first, and followed for survival until death or 3 years after the date of enrollment of the last patient, whichever happens first. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs. For any patient who dies during this period, the cause of death must be reported to the Sponsor. All patients must also be followed through completion of all study treatment.

Patients are considered to have completed study participation altogether when they are no longer followed for disease progression or survival (refer to Section 8 for additional details about study discontinuation).

6.5. Concomitant Therapy

Anti-leukemic therapies including chemotherapy (with the exception of hydroxyurea or oral etoposide), targeted therapies and immunotherapy are not permitted while patients are 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.

6.5.1. 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. Patients are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the patient 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 patients (receiving magrolimab/placebo + azacitidine therapy) until recovery of a neutropenic individual's ANC and determine the ideal timing of the subsequent dose of vaccine based on count recovery. If patients are neutropenic, Investigators may use clinical judgement in determining the timing of the COVID-19 vaccine. Investigators should document vaccinations. Investigators should notify patients of the risks of delaying the COVID-19 vaccination and document this along with any mitigation strategies for preventing COVID-19 infection in the source. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug(s).

7. STUDY EVALUATIONS

7.1. Schedule of Assessments

The Schedule of Assessments for the R/R Expansion Cohort is presented in Table 7-1. The Schedule of Assessments for the TN/U Expansion Cohort is provided in Table 7-2. The Schedule of Assessments for the RBC Transfusion-dependent Low-risk MDS Cohort is provided in Table 7-3. The Schedule of Assessments for all cohorts for magrolimab monotherapy during azacitidine hold(s) is provided in Table 7-4. The Schedules of Assessments for cohorts that have been completed as of Amendment 7 (the R/R Safety Cohort, the R/R MDS Magrolimab Monotherapy Cohort, the TN/U Dose Evaluation Cohort, and the Rollover Cohort) are presented in Appendix F.

Unless otherwise noted, procedures are to be completed prior to any study drug infusion/injection.

Table 7-5 details post-treatment assessments for all patients in this study. Correlative studies sample time points for all cohorts ongoing as of Amendment 7 (R/R Expansion, TN/U Expansion TP53 Mutant AML Subcohort, and RBC Transfusion-dependent Low risk MDS Cohort) are presented in Table 7-6. The time points for PK assessments are presented in Table 7-7 for the R/R Expansion Cohort (including the R/R MDS Magrolimab Monotherapy Cohort), Table 7-8 for the TN/U Expansion Cohort, Table 7-9 for all cohorts for magrolimab monotherapy during azacitidine hold(s), and Table 7-10 for the RBC Transfusion-dependent Low-risk Cohort. CD47 RO sample time points are presented in Table 7-11 for the R/R Expansion Cohort, Table 7-12 for the TN/U Expansion Cohort, and Table 7-13 for the RBC Transfusion-dependent Low-risk Cohort. The assessments required during magrolimab re-priming/re-escalation are presented in Table 7-14 and Table 7-15. Tables of PK assessments and CD47 RO sample time points for cohorts that have been completed as of Amendment 7 (the R/R Safety Cohort, the R/R MDS Magrolimab Monotherapy Cohort, the TN/U Dose Evaluation Cohort, and the Rollover Cohort) are presented in Appendix F.

Table 7-1. Schedule of Assessments, R/R Cohort (Expansion) Note: Cohort Closed to Enrollment

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohort (Expansion)**																												
Cycle (28-day Cycles)	**1**												**2**										**3+**							
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3[a]**							
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**
Informed consent	X[b]																													
Demographics	X																													
Medical and cancer history	X																													
Entry criteria	X																													
Enrollment cohort assignment	X[b]																													
Pregnancy test	X	X[c]											X										X							
Donor chimerism[d]	X																													
CBC with differential, platelets, reticulocytes[e,f]	X	X	X		X				X	X	X	X	X							X	X	X	X							X
Peripheral blood smear[e,g]	X	X	X						X		X	X	X										X							
Serum or plasma chemistry[e]	X	X	X						X		X	X	X							X	X	X	X							X
Serum uric acid, phosphorus[e]	X	X	X						X		X																			
Haptoglobin, D-dimer, thrombin, fibrinogen[e]	X	X	X						X		X		X										X							
PT/INR, aPTT[e]	X								X				X										X							
Type and screen (ABO/Rh), DAT	X																													
Urinalysis[e]	X										X																			
Correlative studies[h]		X							X		X		X										X							

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohort (Expansion)																													
Cycle (28-day Cycles)	1												2										3+							
Visit Window (Days)	-30	None		± 3[a]									± 3[a]										± 3[a]							
Cycle Day	SC	1	2	3	4	5	6	7	8	11	15	22	1	2	3	4	5	6	7	8	15	22	1	2	3	4	5	6	7	15
PK (Expansion Cohort)[i]		X						X	X		X	X	X							X			X Q2C[u]							
Anti-drug antibodies[j]		X							X				X										X Q2C[u]							
CD47 RO blood[k]		X							X	X	X		X										X Q2C-Q3C[u]							
Bone marrow aspirate/biopsy for CD47 RO/CCI [redacted]	X																						X Q2C-Q3C[q,r]							
Bone marrow biopsy and cytogenetics[p,q]	X																						X Q2C-Q3C[q,r]							
MRD monitoring[s]	X																						X Q2C-Q3C[q,r]							
Response assessment																							X Q2C-Q3C[q,r]							
ECOG[e]	X	X							X		X	X	X										X							
Vital signs[m]	X	X	X						X		X	X	X							X	X	X	X							X
Physical examination[e,n]	X	X							X		X		X								X		X							X
ECG[o]	X	X							X				X																	
Adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Study Drug Administration																														
Magrolimab premedication		X			X				X	X																				

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohort (Expansion)																													
Cycle (28-day Cycles)	1												2										3+							
Visit Window (Days)	-30	None		± 3[a]									± 3[a]										± 3[a]							
Cycle Day	SC	1	2	3	4	5	6	7	8	11	15	22	1	2	3	4	5	6	7	8	15	22	1	2	3	4	5	6	7	15
Magrolimab: Expansion Cohort[t,w]		X			X				X	X	X	X	X							X	X	X	X							X
Azacitidine[v]		X	X	X	X	X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X	X	

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MIN = minute; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2W = every 2 weeks; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; RO = receptor occupancy; R/R = relapsed/refractory; SC = screening; US = United States; W = week(s); WBC = white blood cell.

a. Note that ± 3-day visit window does not apply to specimen collection for correlative, PK, or RO assessments in Cycles 1 and 2 – refer to Table 7-6, Table 7-7, and Table 7-11 for details.
b. First dose of magrolimab must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Donor chimerism only applicable to patients with prior allogeneic hematopoietic stem cell transplant.
e. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of either study drug (magrolimab or azacitidine); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
f. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
h. Time point details for correlative studies are provided in Table 7-6.
i. Time point details for PK studies (Expansion Cohort) are provided in Table 7-7.
j. Samples to be collected before administration of either study drug (magrolimab or azacitidine), within 72 hours for initial dose and within 24 hours for subsequent doses.
k. Time point details for RO studies (Expansion Cohort, US only) are provided in Table 7-11. For visits that include bone marrow assessments, RO blood specimen (US only) should be collected on same day as RO bone marrow specimen is collected.
l. Bone marrow aspirate and biopsy required for RO/CCI [redacted] (not a response assessment) on Day 15 in US patients only; however bone marrow aspirate only is required in the UK at this time point. Bone marrow study must be done prior to magrolimab infusion. The CTSC may remove this assessment during the R/R Expansion Cohort based on emerging data.

m. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of each study drug (magrolimab or azacitidine). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
n. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
o. Single ECG at all visits for all patients within 2 hours prior to dosing and within 30 minutes of the end of magrolimab infusion. Details are provided in Section 7.3.7.
p. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
q. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
r. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
s. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
t. Magrolimab should not be given on consecutive days. On Cycle 1 Day 1 and Day 4, infuse magrolimab over 3 hours (± 30 min); starting on Cycle 1 Day 8 and thereafter, infuse over 2 hours (± 30 min).
u. RO blood samples (US only) collected on Day 1 of every other cycle during Cycles 3-7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13. Beginning at C3 Day 1, pretreatment PK and ADA samples to be collected every other cycle through Cycle 13.
v. Azacitidine administration should be completed at least 1 hour before magrolimab administration, on days when both drugs are administered.
w. Patients will have their magrolimab dosing schedule changed from weekly to Q2W beginning at Cycle 3.

Table 7-2. Schedule of Assessments, TN/U Expansion Cohort (Including TP53 TN/U AML) Note: Cohort Closed to Enrollment

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Expansion Cohort (Including TP53 TN/U AML)**																												
Cycle (28-day Cycles)	**1**												**2**										**3+**							
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3**							
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**
Informed consent	X[b]																													
Demographics	X																													
Medical and cancer history	X																													
Entry criteria	X																													
Enrollment cohort assignment	X[b]																													
Pregnancy test	X	X[c]											X										X							
CBC with differential, platelets, reticulocytes[d,e]	X	X	X		X				X	X	X	X	X							X	X	X	X							X
Peripheral blood smear[d,f]	X	X	X						X		X	X	X										X							
Serum or plasma chemistry[d]	X	X	X						X		X	X	X							X	X	X	X							X
Serum uric acid, phosphorus[d]	X	X	X						X		X																			
Haptoglobin, D-dimer, thrombin, fibrinogen[d]	X	X	X						X		X		X										X							
PT/INR, aPTT[d]	X								X				X										X							
Type and screen (ABO/Rh), DAT	X																													
Urinalysis[d]	X										X																			
Correlative studies[g]		X							X		X		X										X							

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Expansion Cohort (Including TP53 TN/U AML)**																												
Cycle (28-day Cycles)	**1**												**2**										**3+**							
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3**							
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**
PK (Expansion Cohort)[h]		X						X	X		X	X	X							X			X Q2C[u]							
Anti-drug antibodies[i]		X							X				X										X Q2C[u]							
CD47 RO blood (Expansion Cohort)[j]		X							X	X	X		X										X Q2C-Q3C[u]							
Bone marrow aspirate/biopsy for CD47 RO/[redacted]	X																						X Q2C-Q3C[l,r]							
Bone marrow biopsy + cytogenetics[k,l]	X																						X Q2C-Q3C[l,r]							
MRD monitoring[m]	X																						Q2C-Q3C[l,r]							
Response assessment																							Q2C-Q3C[l,r]							
ECOG[d]	X	X							X		X	X	X										X							
Vital signs[n]	X	X	X						X		X	X	X							X	X	X	X							X
Physical examination[d,o]	X	X							X		X		X								X		X							X
DLT assessment[p]													X																	
ECG[q]	X	X							X				X																	
Adverse events	→																													→
Concomitant medications	→																													→

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Expansion Cohort (Including TP53 TN/U AML)																												
Cycle (28-day Cycles)	**1**												**2**										**3+**							
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3**							
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**
Study Drug Administration																														
Magrolimab premedication		X			X				X	X																				
Magrolimab[s,v]		X			X				X	X	X	X	X							X	X	X	X							X
Azacitidine[t]		X	X	X	X	X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X	X	

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CR = complete remission; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2 = every 2; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; RO = receptor occupancy; SC = Screening; TN/U = treatment-naïve/unfit; US = United States; W = week(s); WBC = white blood cell.

a. Note that ± 3 day visit window does not apply to specimen collection for correlative, PK, and RO assessments in Cycles 1 and 2. Refer to Table 7-6, Table 7-8, and Table 7-12 for details.
b. First dose of magrolimab must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of either study drug (magrolimab or azacitidine); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
e. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
f. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
g. Time point details for correlative studies are provided in Table 7-6.
h. Time point details for PK studies (Expansion Group) are provided in Table 7-8.
i. Samples to be collected before administration of either study drug (magrolimab or azacitidine), within 72 hours for initial dose and within 24 hours for subsequent doses.
j. Time point details for RO studies (Expansion Group, US only) are provided in Table 7-12.

k. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
l. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, the window is ± 14 days.
m. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
n. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of each study drug (magrolimab or azacitidine). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
o. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
p. DLT will be assessed throughout the first 4 weeks of study treatment for the Dose Evaluation Cohort only.
q. Single ECG at all visits for all patients within 2 hours prior to infusion of study drug and within 30 minutes of the end of magrolimab infusion. Details are provided in Section 7.3.7.
r. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
s. Magrolimab should not be given on consecutive days. On Cycle 1 Day 1 and Day 4, infuse magrolimab over 3 hours (± 30 min); starting on Cycle 1 Day 8 and thereafter, infuse over 2 hours (± 30 min).
t. Azacitidine administration should be completed at least 1 hour before magrolimab administration, on days when both drugs are administered.
u. RO blood samples (US only) collected on Day 1 of every other cycle during Cycle 3-7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13. Beginning at Cycle 3 Day 1, pretreatment PK and ADA samples to be collected every other cycle through Cycle 13.
v. Patients may have their magrolimab dose changed from weekly to every 2 weeks at any time on therapy based on CTSC recommendations or Sponsor requirement.

Table 7-3. Schedule of Assessments, RBC Transfusion-dependent Low-risk MDS Cohort Note: Cohort Closed to Enrollment

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – RBC Transfusion-dependent Low-risk MDS Cohort**																					
Cycle (28-day Cycles)		**1**								**2**						**3+**					
Visit Window (Days)	**-30**	**None**		**± 3[a]**						**± 3[a]**						**± 3**					
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**15**	**1**	**2**	**3**	**4**	**5**	**15**
Informed consent	X[b]																				
Demographics	X																				
Medical and cancer history	X																				
Entry criteria	X																				
Enrollment cohort assignment	X[b]																				
Pregnancy test	X	X[c]								X						X					
CBC with differential, platelets, reticulocytes[d,e,x]	X	X[x]	X		X[x]		X	X	X	X			X		X	X					X[f]
Peripheral blood smear[d,g]	X	X	X				X			X						X					
Serum or plasma chemistry[d]	X	X	X				X	X		X					X	X					X[f]
Serum uric acid, phosphorus[d]	X	X	X				X	X													
Haptoglobin, D-dimer, thrombin, fibrinogen[d]	X	X	X				X			X						X					
PT/INR, aPTT[d]	X						X			X						X					
Type and screen (ABO/Rh), DAT, phenotyping/genotyping[y]	X																				
Urinalysis[d]	X							X													
Correlative studies[h]		X					X	X		X						X					
PK[i]		X					X	X		X						X Q2C-Q3C[j]					
Anti-drug antibodies[k]		X					X			X						X Q2C[j]					

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – RBC Transfusion-dependent Low-risk MDS Cohort**																				
Cycle (28-day Cycles)		**1**								**2**						**3+**					
Visit Window (Days)	**-30**	**None**		**± 3[a]**						**± 3[a]**						**± 3**					
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**15**	**1**	**2**	**3**	**4**	**5**	**15**
CD47 RO blood[l]		X					X	X		X						X Q2C, Q4C, Q6C[j]					
Bone marrow aspirate/biopsy for CD47 RO/CCI [redacted]	X															X Q2C, Q4C, Q6C[m,o]					
Bone marrow biopsy + cytogenetics[m,o]	X															X Q2C, Q4C, Q6C[m,o]					
MRD monitoring[n]	X															Q2C-Q6C[m,o]					
Response assessment[p]																Q2C-Q6C[p,o]					
ECOG[d]	X	X					X	X	X	X						X					
Vital signs[q]	X	X	X				X	X	X	X						X					
Physical examination[d,r]	X	X					X			X						X					
DLT assessment[s]															X						
ECG[t]	X									X											
Adverse events[f]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Concomitant medications[f]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Study Drug Administration																					
Magrolimab premedication		X					X														

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – RBC Transfusion-dependent Low-risk MDS Cohort																				
Cycle (28-day Cycles)		1								2						3+					
Visit Window (Days)	-30	None		± 3[a]						± 3[a]						± 3					
Cycle Day	SC	1	2	3	4	5	8	15	22	1	2	3	4	5	15	1	2	3	4	5	15
Magrolimab[u]		X[z]					X[z]	X	X	X						X					
Azacitidine[vw]		X	X	X	X	X				X	X	X	X	X		X	X	X	X	X	

Abbreviations: ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CR = complete remission; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2 = every 2; Q2C = every 2 cycles; Q2W = every 2 weeks; Q3C = every 3 cycles; Q4W = every 4 weeks; RBC = red blood cell; Rh = Rhesus factor; RO = receptor occupancy; SC = Screening; TN/U = Treatment-naïve/Unfit; US = United States; W = week(s); WBC = white blood cell.

a. Note that ± 3-day visit window does not apply to specimen collection for correlative, PK, and RO assessments in Cycles 1 and 2. Refer to Table 7-6, Table 7-10, and Table 7-13 for details.
b. First dose of magrolimab must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of either study drug (magrolimab or azacitidine); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
e. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20 × 10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
f. After Cycle 6, these laboratory tests can be omitted if the patient is clinically well and does not need Q2W CBC/chemistry lab checks as per the discretion of the PI. If C7+ D15 laboratory tests are omitted, no visit will occur on that day, and AEs and Con-Meds do not need to be collected.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
h. Time point details for correlative studies are provided in Table 7-6.
i. Time point details for PK studies are provided in Table 7-10.
j. RO blood samples (US only) collected on Day 1 of every other cycle during Cycles 3 to 7, then every 4 cycles through Cycle 19, and then starting Cycle 23 and onwards every 6 cycles (same day as bone marrow RO samples). Beginning at Cycle 3 Day 1, pretreatment PK and ADA samples to be collected every other cycle through Cycle 7 and then every third cycle to Cycle 13.

k. Samples to be collected before administration of either study drug (magrolimab or azacitidine), within 72 hours for initial dose and within 24 hours for subsequent doses.
l. Time point details for RO studies are provided in Table 7-13.
m. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
n. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
o. The first bone marrow assessment will occur at Cycle 3 Day 1 (± 3 days), approximately 8 weeks after the start of study treatment. Subsequent bone marrow assessments while on study treatment will occur every other cycle through Cycle 7 (i.e., Cycle 5 Day 1 and Cycle 7 Day 1). After Cycle 7 Day 1, bone marrow biopsies will be collected every 4 cycles through Cycle 19 (i.e., Cycle 11 Day 1, Cycle 15 Day 1, and Cycle 19 Day 1) and then starting Cycle 23 and onwards, bone marrow biopsies will be collected every 6 cycles (Cycle 23 Day 1, Cycle 29 Day 1, etc.).
p. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, the window is ± 14 days.
q. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of each study drug (magrolimab or azacitidine). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
r. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
s. DLT will be assessed throughout the first 6 weeks of study treatment for the safety run-in part only.
t. Single ECG at all visits within 2 hours prior to infusion of study drug and within 30 minutes of the end of magrolimab infusion. Details are provided in Section 7.3.7.
u. For the 1 mg/kg Cycle 1 Day 1 and Day 8 doses, infuse magrolimab over 3 hours (± 30 min); starting Cycle 1 Day 8 and for subsequent doses, infuse over 2 hours (± 30 min).
v. Azacitidine administration should be completed at least 1 hour before magrolimab administration, on days when both drugs are administered.
w. For the first 6 patients in the Safety part of the cohort on magrolimab monotherapy, azacitidine administration may begin in Cycle 3, based on patient response, and with Investigator and Sponsor agreement.
x. Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment (Days 1 and 8), all subjects must have a documented hemoglobin $\geq$ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.
y. ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (including minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient. Red blood cell genotyping instead of extended RBC phenotyping is acceptable for any patient. Red blood cell genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3 months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.
z. Hemoglobin must be checked again 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (Days 1 and 8). The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

Table 7-4. Schedule of Assessments, Magrolimab Monotherapy During Azacitidine Hold(s)

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – Magrolimab Monotherapy During Azacitidine Hold(s)**	
Visit Window (Days)	**Cycle X**	
Cycle Day	**1**	**15**
Pregnancy test	X[a]	
CBC with differential, platelets, reticulocytes[b,c]	X	X
Serum or plasma chemistry[b]	X	X
Haptoglobin, D dimer, thrombin, fibrinogen[b]	X	
PT/INR, aPTT[b]	X	
PK[d]	X Q2C[e]	
Anti-drug antibodies[f]	X Q2C[e]	
ECOG[b]	X	
Vital signs[g]	X	X[k]
Physical examination[b,h]	X	X[k]
Adverse events	X	X
Concomitant medications	X	X
Study Drug Administration		
Magrolimab[i,j]	X	X[k]

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2C = every 2 cycles; Q2W = every 2 weeks; WBC = white blood cell count.

a. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.

b. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of study drug (magrolimab); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.

c. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
d. Time point details for PK studies are provided in Table 7-9.
e. Patients in Cycle 1 of the TN/U Expansion or RBC Transfusion-dependent Low-risk MDS Cohorts should follow dosing guidelines and collections for that cycle. Patients in Cycle 2 of TN/U Expansion Cohort should follow dosing schedule and collections for that cycle. Patients in Cycle 3 or beyond should follow Q2C collection of PK and ADA.
f. Samples to be collected before administration of study drug (magrolimab), within 72 hours for initial dose and within 24 hours for subsequent doses.
g. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of study drug (magrolimab). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
h. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
i. Magrolimab should not be given on consecutive days. On Cycle 1 Day 1 and Day 4, infuse magrolimab over 3 hours (± 30 min); starting on Cycle 1 Day 8 and thereafter, infuse over 2 hours (± 30 min).
j. Patients will have their magrolimab dosing schedule changed from weekly to Q2W beginning at Cycle 3.
k. Not performed Day 15 in RBC Transfusion-dependent Low-risk MDS Cohort.

Table 7-5. Post-treatment Assessments, All Cohorts

Assessment	**Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – ALL COHORTS**			
Cycle (28-day Cycles)	**End-of-treatment Visit**	**Safety Follow-up Visit**	**Long-term Follow-up**	**Survival Follow-up**
	After last dose or within 7 Days of EOT Decision	30 Days After Last Dose	Monthly until disease progression or new anti-cancer therapy[a]	Every 2 months up to 60 months from LSE
Visit Window	**7-14 Days**	**± 7 Days**	**± 14 Days**	**± 1 Month**
Serum or urine pregnancy test		X[b]		
CBC with differential, platelet count, reticulocytes		X		
Peripheral Blood Smear		X		
Serum or plasma chemistry		X		
Haptoglobin, D-dimer, thrombin time and plasma fibrinogen		X		
PT/INR, aPTT		X		
Pharmacokinetics	X	X		
Correlative studies	X		X[c]	
Anti-drug Antibodies	X	X		
CD47 Receptor Occupancy[d]	X	X		
ECOG performance status		X		
Vital signs		X		
Physical examination (symptom-directed)		X		
Bone marrow biopsy (core and aspirates) and cytogenetics[e]	X	X[f]	Q8W	
Response assessment	X[g]	X	Q8W	
Adverse events	X[h]	X[h]	X[h]	
Concomitant medications	X	X		
New anti-cancer therapy			X	X[i]
Survival follow-up				Q2M

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CR = complete remission; EOT = end-of-treatment; LSE = last subject enrolled; M = month(s); PT/INR = prothrombin time/international normalized ratio; Q2M = every 2 months; Q8W = every 8 weeks; SAE = serious adverse event; SOC = standard of care; US = United States.

a. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs.

b. Pregnancy tests should be taken at monthly intervals until end of contraception requirement.
c. Collected at time of disease progression or relapse.
d. CD47 receptor occupancy is a US-only sub-study.
e. Conventional cytogenetic testing (per institutional standards) is required for all patients, with one exception: In the Rollover Cohort, cytogenetic assessments are required only for patients who had prior cytogenetic assessments in the previous Phase 1 study (SCI-CD47-002).
f. Required if patient discontinues treatment without documented disease progression, only if not completed within the last 4 weeks.
g. Response Assessment at EOT visit not required if performed within the last 7 days or progressive disease has been documented.
h. Report all AEs through the Safety Follow-up Visit, and any treatment-related SAEs thereafter.
i. Collect new anti-cancer therapy data following the last dose of study drug, if not documented previously.

Table 7-6. Correlative Studies Sample Time Points, R/R Cohorts (Expansion and R/R MDS Monotherapy), TN/U Cohorts (Expansion and TP53 Mutant AML Subcohort), and RBC Transfusion-dependent Low-risk MDS Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies
R/R Cohorts (Expansion and R/R MDS Monotherapy), TN/U Cohorts (Expansion and TP53 Mutant AML Subcohort), and RBC Transfusion-dependent Low-risk MDS Cohort

Phase 1b	**Cycle 1**			**Cycle 2**	**C3+**	**EOT**	**LTFU**
Day	**1**	**8**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)a	X[b]	X	X[c]	X[b]	X[b,c]	X	X[d]
1 hour (± 15 min) after end of magrolimab infusion	X	X					

Abbreviations: C = cycle; EOT = end-of -treatment; LTFU = long-term follow-up; min = minute(s); R/R = Relapsed/Refractory; TN/U = treatment-naïve/unfit.
a. Pretreatment specimens may be collected up to 72 hours before administration of either study drug (magrolimab or azacitidine).
b. Sample to be collected before azacitidine infusion.
c. When bone marrow biopsies are performed, collect blood samples ± 7 days from bone marrow collection date; otherwise, collect blood samples ± 7 days from Day 1 of each treatment cycle.
d. Obtained at the time of disease progression or relapse.

Table 7-7. Pharmacokinetic Assessments, R/R Cohorts (Expansion and MDS Monotherapy) Note: Cohorts Closed to Enrollment

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies **R/R Cohorts (Expansion and MDS Monotherapy)**										
	Cycle 1					**Cycle 2**		**C3+**	**EOT**	**SFU**
Day	**1**	**7**	**8**	**15**	**22**	**1**	**8**	**1**	**—**	**—**
Pretreatment[a]	X[b]		X	X	X	X[b]	X	X Q2C[c]	X	X
30 min (± 15 min) after end of azacitidine infusion/injection[d]	X	X				X		X Q2C[c]		
1 hour (± 15 min) after end of magrolimab infusion	X		X			X		X Q2C[c]		

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); PK = pharmacokinetic; R/R = Relapsed/Refractory; SFU = safety follow-up, Q2C = every 2 cycles.
Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or magrolimab) is started.
c. Samples to be collected every other cycle beginning with Cycle 3 through Cycle 13. No PK samples will be collected after Cycle 13.
d. Azacitidine will be given before magrolimab on days on which both treatments are to be given. For patients in the R/R MDS Magrolimab Monotherapy Cohort, post-azacitidine sampling time points are not applicable unless patients later transition to combination therapy.

Table 7-8. Pharmacokinetic Assessments, TN/U Expansion Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies
TN/U Expansion Cohort

	Cycle 1					Cycle 2		C3+	EOT	SFU
Day	**1**	**7**	**8**	**15**	**22**	**1**	**8**	**1**	**—**	**—**
Pretreatment [a]	X[b]		X	X	X	X[b]	X	X Q2C[d]	X	X
30 min (± 15 min) after end of azacitidine infusion/injection[c]	X	X				X		X Q2C[d]		
1 hour (± 15 min) after end of magrolimab infusion	X		X			X		X Q2C[d]		

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); PK = pharmacokinetic; Q2C = every 2 cycles; SFU = safety follow-up; TN/U = Treatment-naïve/Unfit.
Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or magrolimab) is started.
c. Azacitidine will be given before magrolimab on days on which both treatments are to be given.
d. Samples to be collected every other cycle beginning with Cycle 3 through Cycle 13. No PK samples will be collected after Cycle 13.

Table 7-9. Pharmacokinetic Assessments, Magrolimab Monotherapy During Azacitidine Hold(s)

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies
Magrolimab Monotherapy During Azacitidine Hold(s)

	Cycle X	
Day	**1**	**15**
Pretreatment[a]	X[b,c]	

Abbreviations: MRD = minimal residual disease; PK = pharmacokinetic; RO = receptor occupancy.
Note: PK samples are to be collected from the arm opposite from infusion site.

a. Collect pretreatment specimens within 12 hours prior to study drug (magrolimab) administration using Cycle 3+ Day 1 kits. Do NOT collect bone marrow, MRD, RO, or correlative studies.
b. Pretreatment sample to be collected before study drug (magrolimab) is started. Samples to be collected every other cycle beginning with Cycle 3 through Cycle 13. No PK samples will be collected after Cycle 13.
c. In RBC Transfusion-dependent Low-risk MDS Cohort, samples to be collected every other cycle beginning with Cycle 3 through Cycle 13. No PK samples will be collected after Cycle 13.

Table 7-10. Pharmacokinetic Assessments, RBC Transfusion-dependent Low-risk MDS Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies **RBC Transfusion-dependent Low-risk MDS Cohort**								
	Cycle 1			**Cycle 2**		**Cycle 3+**	**EOT**	**SFU**
Day	**1**	**8**	**15**	**1**	**15**	**1**	**—**	**—**
Pretreatment [a]	X[b]	X	X	X[b]		X Q2C-Q3C[d]	X	X
15 min (± 15 min) after end of magrolimab infusion				X				

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); PK = pharmacokinetic; Q2C = every 2 cycles; RBC = red blood cell; SFU = safety follow-up.
Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or magrolimab) is started.
c. Azacitidine will be given before magrolimab on days on which both treatments are to be given.
d. Samples to be collected every other cycle beginning with Cycle 3 through Cycle 7 and then every third cycle through Cycle 13. No PK samples will be collected after Cycle 13 until EOT and/or SFU.

Table 7-11. CD47 Receptor Occupancy Sample Time Points, R/R Expansion Cohort Note: Cohort Closed to Enrollment

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies **R/R Expansion Cohort**								
Phase 1b	**Cycle 1**				**Cycle 2**	**C3+**	**EOT**	**SFU**
Day	**1**	**8**	**11**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X	X	X	X[b]	X[b]	X Q2C-Q3C[b,c,d]	X	X

Abbreviations: C = cycle; EOT = end-of-treatment; RO = receptor occupancy; Q2C = every 2 cycles; Q3C = every 3 cycles; R/R = Relapsed/Refractory; SFU = safety follow-up; UK = United Kingdom; US = United States.
Note: RO is a US-only sub-study; RO specimens are not required for UK patients.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or magrolimab) is started.
c. For visits that include bone marrow assessments, RO blood specimen should be collected on the same day as RO bone marrow specimen is collected.
d. RO blood samples collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13.

Table 7-12. CD47 Receptor Occupancy Sample Time Points, TN/U Expansion Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies **TN/U Expansion Cohort**								
Phase 1b	**Cycle 1**				**Cycle 2**	**C3+**	**EOT**	**SFU**
Day	**1**	**8**	**11**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X[b]	X	X	X	X[b]	X Q2C-Q3C [a,b,c]	X	X

Abbreviations: C = cycle; EOT = end-of-treatment; Q2C = every 2 cycles; Q3C = every 3 cycles; RO = receptor occupancy; SFU = safety follow-up; TN/U = Treatment-naïve/Unfit; UK = United Kingdom; US = United States.
Note: RO is a US-only sub-study; RO specimens are not required for UK patients.
a. Pretreatment sample to be collected within 12 hours prior to administration of either study drug (azacitidine or magrolimab).
b. For visits that include bone marrow assessments, RO blood specimen should be collected on same day as RO bone marrow specimen is collected.
c. RO blood samples will be collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13.

Table 7-13. CD47 Receptor Occupancy Sample Time Points, RBC Transfusion-dependent Low-risk MDS Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies **RBC Transfusion-dependent Low-risk MDS Cohort**							
Phase 1b	**Cycle 1**			**Cycle 2**	**C3+**	**EOT**	**SFU**
Day	**1**	**8**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X[b]	X	X	X[b]	X Q2C, Q4C, Q6C [a,b,c]	X	X

Abbreviations: C = cycle; EOT = end-of-treatment; Q2C = every 2 cycles; Q3C = every 3 cycles; RO = receptor occupancy; SFU = safety follow-up; TN/U = Treatment-naïve/Unfit; UK = United Kingdom; US = United States.
Note: RO is a US-only sub-study; RO specimens are not required for UK patients.
a. Pretreatment sample to be collected within 12 hours prior to administration of either study drug (azacitidine or magrolimab).
b. For visits that include bone marrow assessments, RO blood specimen should be collected on same day as RO bone marrow specimen is collected.
c. For the TN/U Expansion Cohort, RO blood samples will be collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13. For the RBC Transfusion-dependent Low-risk Cohort, RO blood samples (US only) will be collected on Day 1 of every other cycle during Cycles 3 to 7, then every 4 cycles through Cycle 19, and then starting Cycle 23 and onwards every 6 cycles (same day as bone marrow RO samples).

Table 7-14. Re-priming/Re-escalation Assessments: R/R Cohort and TN/U Cohort

Assessment	Visit Window										
	None	± 3 Days									
Cycle Day (Cycle: 28 Days)	1	2	3	4	5	6	7	8	11	15	22
CBC with differential, platelets, reticulocytes[a,b]	X	X		X				X	X	X	X
Peripheral blood smear[a,c]	X	X						X		X	
Serum or plasma chemistry[a]	X	X						X		X	X
Serum uric acid, phosphorus[a]	X	X						X		X	
Haptoglobin, D-dimer, thrombin, fibrinogen[a]	X	X						X		X	
PT/INR, aPTT[a]								X			
Anti-drug antibodies[d]	X										
CD47 RO blood[e]	X							X	X	X	
ECOG[a]	X							X		X	
Vital signs[f]	X	X						X		X	
Physical examination[a,g]	X							X		X	
Adverse events	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→
Magrolimab premedication	X			X				X	X		
Magrolimab: Re-priming/re-escalation[h]	X			X				X	X	X	X
Azacitidine[h,i]	X	X	X	X	X	X	X				

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PE = physical examination; PT/INR = prothrombin time/international normalized ratio; Rh = Rhesus factor; RO = receptor occupancy; SC = subcutaneous; US = United States; WBC = white blood cell.

a. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before study drug administration; thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
b. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20 × 10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20 × 10^3/mcL.
c. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
d. Samples to be collected before dose administration (within 72 hours for initial dose and within 24 hours for subsequent doses).
e. Time point details for RO studies (US-only sub-study) are provided in Table 7-11 and Table 7-12. Note that the ±3 day visit window does not apply to specimen collection for RO assessments.
f. Vital signs prior to infusion and within 30 minutes after the end of each infusion. Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
g. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
h. Magrolimab/azacitidine dosing for re-priming/re-escalation is shown in Table 6-1.
i. For patients on combination therapy, dosing with azacitidine should follow azacitidine 75 mg/m^2 SC or IV[a] on Days 1 to 7.

Table 7-15. Re-priming/Re-escalation Assessments: RBC Transfusion-dependent Low-risk MDS Cohort

Assessment	Visit Window							
	None	± 3 Days[a]						
Cycle Day (Cycle: 28 Days)	1	2	3	4	5	8	15	22
CBC with differential, platelets, reticulocytes[b,c]	X					X	X	X
Peripheral blood smear[b,d]	X					X	X	X
Serum or plasma chemistry[b]	X					X	X	X
Serum uric acid, phosphorus[b]	X					X	X	
Haptoglobin, D-dimer, thrombin, fibrinogen[b]	X					X	X	
PT/INR, aPTT[b]						X		
Anti-drug antibodies[e]	X							
CD47 RO blood[f]	X					X	X	
ECOG[b]	X						X	
Vital signs[g]	X					X	X	X
Physical examination[b,h]	X					X	X	
Adverse events	→	→	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	→	→	
Magrolimab premedication	X					X		
Magrolimab: Re-priming/re-escalation[i]	X					X	X	X
Azacitidine[i]	X	X	X	X	X			

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome; PE = physical examination; PT/INR = prothrombin time/international normalized ratio; RBC = red blood cell; Rh = Rhesus factor; RO = receptor occupancy; US = United States; WBC = white blood cell.

a. Note that ± 3-day visit window does not apply to specimen collection for RO assessments.
b. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before study drug administration; thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
c. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20 × 10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20 × 10^3/mcL.
d. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
e. Samples to be collected before dose administration (within 72 hours for initial dose and within 24 hours for subsequent doses).
f. Time point details for RO studies (US-only sub-study) are provided in Table 7-13.
g. Vital signs prior to infusion and within 30 minutes after the end of each infusion. Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
h. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
i. Magrolimab/azacitidine dosing for re-priming/re-escalation is shown in Table 6-1.

7.2. Assessments by Study Period

7.2.1. Screening Assessments

The following procedures are to be completed during the screening period for the R/R Cohorts and the TN/U Cohorts:

R/R Cohorts, TN/U Cohorts, and RBC Transfusion-dependent Low-risk Cohort:

- Confirmation that the ICF has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.
- Demographic data including sex, date of birth, age, race, and ethnicity.
- Relevant medical and cancer history through Day 1 (first dose of study treatment) with all findings recorded on the Medical History eCRF.
- Enrollment cohort assignment
- Urine or serum pregnancy test (in WOCBP).
- Donor chimerism, for patients with prior allogeneic hematopoietic stem cell transplant only (not applicable to the TN/U Cohort or RBC Transfusion-dependent Low-risk Cohort)
- Local laboratory values, including hematology, serum or plasma chemistry, and urinalysis (Table 7-16)
- Local laboratory peripheral blood smears (Section 7.3.3).
- Local laboratory type and screen (ABO/Rh) and DAT (Section 6.2.2.1 and Section 7.3.4).
- Physical examination (complete) and ECOG (Appendix C).
- Vital signs: blood pressure, heart rate, respiration, temperature, height and weight.
- Single electrocardiogram (ECG).
- Bone marrow core biopsy (trephine) and aspirate (within 30 days prior to first dose of drug), with conventional cytogenetic testing per institutional standard and for CD47 RO (US only)/CCI [redacted]
- MRD monitoring assessments (Section 7.12.3).

- AEs related to screening procedures or protocol-mandated interventions (e.g., AEs related to invasive procedures such as biopsies) and any SAE reporting.
- Documentation of concomitant and prior medications.

For the Rollover Cohort, assessments performed during the previous study (SCI-CD47-002) may be used as baseline values for this study as long as they meet the criteria for this study with respect to timing. Ongoing AEs and concomitant medications from the previous study will be transferred to the database for this study. The following procedures are to be completed during the screening period for the Rollover Cohort:

Rollover Cohort:

- Confirmation that the ICF has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.

Screening assessments will be completed within a 30-day screening period prior to enrollment. Patients may qualify for enrollment at any time during the 30-day screening period. Assessments performed as part of SOC prior to ICF signature may be used if they are within the required screening period.

7.3. Description of Study Procedures

Study procedure timing is provided in Section 7.1, Schedule of Assessments tables.

7.3.1. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential (WOCBP), i.e., fertile, following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless permanently sterile or has medically documented ovarian failure. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Women are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A urine or serum pregnancy test is required at Screening (except for the Rollover Cohort) and within 72 hours before study drug administration on Day 1. The Day 1 pregnancy test does not need to be repeated if the Screening pregnancy test was performed within the 72 hours before study drug administration. Pregnancy tests will be performed on Day 1 of each cycle.

7.3.2. Complete Blood Counts

Samples for CBCs should be collected per the Schedule of Assessments in Section 7.1, and must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level ≤ 20 × 10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ 20 × 10^3/mcL.

All participants must have a documented hemoglobin ≥ 9 g/dL prior to administering the first 2 doses of magrolimab. 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.

7.3.3. Peripheral Blood Smear Assessment

Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. These samples should be collected from the arm contralateral to the arm being used for drug infusion/injection, if possible. Peripheral smears will be evaluated according to the guidelines provided in Appendix D.

7.3.4. Type and Screen (ABO/Rh) and Direct Antiglobulin Test (DAT)

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC's 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 6.2.2.1.

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

7.3.5. Vital Signs

Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded during screening only (except for Rollover Cohort). Weight should be recorded during screening (except for Rollover Cohort) and on Day 1 of each cycle. Vital signs are to be recorded prior to magrolimab infusion and within 30 minutes of the end of the magrolimab infusion. On visits that include infusions of both study drugs, vital signs are to be recorded prior to infusion/injection and within 30 minutes of the end of infusion/injection of each study drug (magrolimab and azacitidine).

7.3.6. Physical Examination

Complete physical examination should be performed at screening (except for Rollover Cohort). Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and CNS. For Cycles 4 and beyond, physical examinations may be done only on Day 1 of each cycle, at the discretion of the Investigator.

7.3.7. Electrocardiographs

One ECG will be performed at screening for all patients (except for Rollover Cohort). For the R/R Safety Cohort, R/R Expansion Cohort, TN/U Dose Evaluation Cohort, and RBC Transfusion-dependent Low-risk MDS Cohort, single pre-dose ECG will be performed within 2 hours prior to dosing with either study drug (magrolimab or azacitidine) and within 30 minutes of the end of magrolimab infusion.

7.3.8. Bone Marrow Assessments

Bone marrow assessments are required for response assessments (refer to Section 7.9, Section 10, and Appendix B), including conventional cytogenetic analysis per institutional standards. In addition, bone marrow specimens may be used for

correlative studies, CD47 RO (for US patients only), MRD monitoring, CCI [redacted], and biobanking. MRD testing will be performed by 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 Schedule of Assessments in Section 7.1. For the R/R Safety the first bone marrow response assessment will occur at Cycle 2 Day 1 (± 3 days), followed by a second bone marrow assessment on Cycle 3 Day 1 (± 3 days). For the R/R Expansion Cohort, TN/U Dose Evaluation and Expansion Cohorts, and the Rollover Cohort, the first bone marrow assessment will occur at Cycle 3 Day 1 (± 3 days), approximately 8 weeks after the start of study treatment. Subsequent bone marrow assessments while on study treatment will occur for the R/R and TN/U cohorts every other cycle through Cycle 7 (i.e., Cycle 5 Day 1 and Cycle 7 Day 1), and then every 3 cycles thereafter (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.). For the RBC Transfusion-dependent Low-risk Cohort, the first bone marrow assessment will occur at Cycle 3 Day 1 (± 3 days), approximately 8 weeks after the start of study treatment. Subsequent bone marrow assessments while on study treatment will occur for the RBC Transfusion-dependent Low-risk Cohort every other cycle through Cycle 7 (i.e., Cycle 5 Day 1 and Cycle 7 Day 1). After Cycle 7 Day 1, bone marrow biopsies will be collected every 4 cycles through Cycle 19 (i.e., Cycle 11 Day 1, Cycle 15 Day 1, and Cycle 19 Day 1) and then starting Cycle 23 and onward, bone marrow biopsies will be collected every 6 cycles (Cycle 23 Day 1, Cycle 29 Day 1, etc.). An additional bone marrow assessment is required in the event of prolonged myelosuppression lasting longer than 42 days from the start of study treatment, as described in Section 3.3.5, Definition of DLT.

In addition to these response assessments, for the R/R Safety Cohort at US sites, a Day 15 bone marrow aspirate and biopsy will be required prior to magrolimab infusion to evaluate CD47 RO and other correlative studies that will aid in magrolimab dose optimization. This bone marrow procedure time point may not be performed for patient safety issues as determined by the Investigator. The Day 15 bone marrow must be

collected prior to study drug infusion; if sites do not have the capability to do a bone marrow biopsy and study drug infusion on the same day, the bone marrow may be done on the day prior to infusion (i.e., Day 15 infusion could be done on Day 16 within the allowed dosing windows). The CTSC removed this Day 15 assessment during the R/R Expansion Cohort based on emerging data. As of Amendment 3, no Cycle 1 Day 15 bone marrow will be collected in any cohort.

Bone marrow biopsies for response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, the window is ± 14 days.

For visits that include both bone marrow assessments and RO assessments, the RO blood specimen should be collected on the same day as the RO bone marrow specimen is collected.

If the patient discontinues treatment without documented progressive disease, a bone marrow assessment should be done at the Safety Follow-up visit if one has not been done within the prior 4 weeks. Bone marrow response assessments should continue during long-term follow-up approximately every 8 weeks until progressive disease is documented or the patient starts a new anti-cancer therapy.

7.3.9. Adverse Events

At each visit all AEs observed by the Investigator or reported by the patient that occur after the first dose of study drug through 30 days after the last dose of study drug, are to be reported using the applicable eCRF (Section 9). AEs that occur prior to assignment of study treatment that are assessed as related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies) must also be reported.

Following 30 days after the last dose of investigational product, Investigators should report any SAEs that are felt to be related to study treatment (magrolimab and/or azacitidine).

7.3.10. Concomitant Medication Monitoring

All concomitant medications taken by a patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after consent through the end of 30-day Safety Follow-up Period. Concomitant medication associated with procedure-related AEs will be captured from the time of informed consent on. Information to be collected includes therapy name, indication, dose, unit, frequency, route, start date, and stop date, and are to be reported using the applicable eCRF.

7.4. End-of-treatment Visit

The end-of-treatment (EOT) visit is to be completed after last dose or within 7 days of the decision to end treatment with magrolimab for all cohorts.

- PK sample collection
- Anti-drug antibodies
- CD47 RO (US only)
- Correlative studies
- Response assessment (Section 7.9), unless performed within the last 7 days or progressive disease has been documented
- Adverse events
- Concomitant medications

7.5. Safety Follow-up Visit

Safety Follow-up visit to be completed within 30 days (± 7 days) after the last dose of study drug.

- Serum or urine pregnancy test (in WOCBP)

- Local laboratory
  - CBC (with differential, platelets, reticulocytes)
  - Peripheral blood smear
  - Serum or plasma chemistry
  - Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen
  - Prothrombin time/ international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT)

- PK sample collection
- Anti-drug antibodies
- CD47 RO (US only)
- ECOG performance status (Appendix C)
- Vital signs
  - blood pressure
  - heart rate
  - respiration
  - temperature
  - weight

- Physical examination (symptom-directed)
- Bone marrow biopsy for response assessment (including cytogenetics) if patient discontinued treatment without documented disease progression and biopsy was not performed within the last 4 weeks (Section 7.3.8 and Section 7.9). For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs.
- Response assessment (± 7 days) (Section 7.9)
- Adverse events (Report all AEs through the Safety Follow-up Visit, and any treatment-related SAEs thereafter.)
- Concomitant medications

7.6. Long-term Follow-up for Disease Progression

Patient will be followed until disease progression or until they begin a new anti-cancer therapy, whichever happens first.

- Correlative studies (at time of disease progression)
- Bone marrow biopsy for response assessment (Section 7.3.8 and Section 7.9)
- Response Assessment (± 14 days), every 8 weeks (Section 7.9)

Following the Safety Follow-up Visit, patients with ongoing SAEs and study drug-related AEs will be followed for safety. If any SAEs or study drug-related AEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least Q4W until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer treatment. Follow-up will stop when a patient begins another anti-cancer treatment. For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs.

The long-term care of the patient will remain the responsibility of his/her primary treating physician.

7.7. Survival Follow-up

All patients who permanently discontinue all study treatment will be contacted during a clinic visit or by telephone to assess survival, and the commencement of new anti-cancer therapy following the last administration of study drug (if not documented previously). Patients will be contacted every 2 months (± 1 month) from the date of the Safety Follow-up Visit, until 3 years from the date that the last patient is enrolled in the study, unless there is full withdrawal of consent. The patient's primary physician or family may be contacted by the Investigator in order to obtain survival information in case the patient cannot be reached. For any patient who dies during this period, the cause of death must be reported to the Sponsor.

7.8. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 7-16.

Table 7-16. Laboratory Analyte Listing

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus [c] Glucose BUN or urea Creatinine Uric acid [c] Total bilirubin Direct bilirubin Indirect bilirubin Alkaline phosphatase LDH AST (SGOT) ALT (SGPT) Alkaline phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes Reticulocytes Haptoglobin [c] D-dimer [c] PT, aPTT, and INR [c] Thrombin [c] Plasma fibrinogen [c] Peripheral blood smear	RBC Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity	Pregnancy Correlative studies [a] Pharmacokinetics [a] CD47 receptor occupancy [a,b] Anti-drug antibodies [a] Type and screen (ABO/Rh), DAT Phenotyping/genotyping (genotyping required for patients who were transfused in the previous 3 months) Donor chimerism (for patients with prior allogeneic hematopoietic stem cell transplant) Cytogenetics Minimal residual disease (MRD)[a]

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; Rh = Rhesus factor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells; US = United States.
a. These assays may be performed at a specialty laboratory.
b. CD47 receptor occupancy is a US-only sub-study.
c. Refer to Section 7.1 Schedule of Assessments tables for collection time points.

7.9. Efficacy Assessments

Clinical response will be assessed using the guidelines in Appendix B, which are based primarily on 2017 ELN recommendations (Döhner 2017) and IWG criteria (Cheson 2003 and Cheson 2006), as described in Section 10.

Response assessments will be done in conjunction with bone marrow assessments, according to the Schedule of Assessments in Section 7.1. Accompanying laboratory results ± 2 weeks from the protocol-specified bone marrow efficacy assessment can be used to support an efficacy assessment of CR for both AML and MDS. These supporting lab results will be entered into the clinical database to capture response. Response assessments are scheduled on Day 1 of every other treatment through Cycle 7 and then every third cycle during study treatment for all cohorts, with an additional response assessment on Day 1 of Cycle 2 for the R/R Cohorts only.

If a patient achieves a CR (including morphologic CR, CR_{MRD}-, cCR, and mCR), subsequent bone marrow biopsies are still required to be performed as per the Schedule of Assessments (Section 7.1).

Response assessment will be obtained at the EOT visit (within 7 days of the decision to end treatment), unless a prior response assessment has been performed within the last 7 days or progressive disease has been documented. If the patient discontinues treatment without documented progressive disease, a response assessment should be done at the Safety Follow-up visit if one has not been done within the prior 4 weeks. Response assessments should continue during long-term follow-up approximately every 8 weeks until progressive disease is documented or the patient starts a new anti-cancer therapy.

7.10. Pharmacokinetics

The PK profile will be evaluated for magrolimab in all patients, and for azacitidine in TN/U Cohort patients receiving combination study treatment. The evaluation of PK for magrolimab and azacitidine will be conducted to investigate any potential drug-drug PK interactions, which is predicted to be unlikely. Serum magrolimab and/or azacitidine will

be measured by ELISA or other appropriate assays. At the discretion of the CTSC at any point in the study, PK studies may be eliminated or the scheduled time points may be changed if the CTSC determines that sufficient data have been generated.

Specimens will be collected for PK analysis at multiple time points during Cycles 1 and 2, at Day 1 of each subsequent cycle, and at the EOT visit, according to the Schedule of Assessments tables in Section 7.1. Residual samples used for PK and ADA analysis may also be used for CCI PK or pharmacodynamics analyses related to magrolimab treatment alone as well as combination therapy with azacitidine. This could include using leftover serum for CCI alternative PK assay development and analysis.

7.11. Immunogenicity (Anti-drug Antibodies)

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described in the Schedule of Assessments in Section 7.1 in all patients. When collected on the day of study drug dosing, the blood sample must be collected at the same time as the pre-dose PK specimen. For patients who have tested positive for ADA, the impact of ADA on PK, safety, and biologic activity will be assessed. Neutralizing antibodies to magrolimab will also be assessed for patients who test positive for ADA.

7.12. Pharmacodynamics and Biomarker Assessments

7.12.1. CD47 Receptor Occupancy

Testing for CD47 RO on select target cells enables pharmacodynamic testing of magrolimab to inform both safety and efficacy parameters. First, the degree of saturation of CD47 receptors on RBCs serves as a pharmacodynamic assessment for degree of anemia. Second, CD47 RO on WBCs and circulating or bone marrow-resident leukemia cells provides information on the level of CD47 saturation of the internal CD47 tissue sink and drug exposures on leukemia cells, respectively.

Samples for CD47 RO studies in the peripheral blood will be collected at US sites only, according to the Schedule of Assessments presented in Section 7.1. Bone marrow

aspirate samples will be collected at all bone marrow biopsy time points to assess CD47 RO in the bone marrow (US only), additional correlative study assessments, and biobanking. At the discretion of the CTSC at any point in the study, CD47 RO testing may be eliminated or the scheduled time points may be changed if the CTSC determines that sufficient data have been generated.

7.12.2. Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of magrolimab alone or magrolimab in combination with azacitidine in AML. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating T-cells, and other studies. Samples for correlative studies in the peripheral blood will be collected according to the Schedule of Assessments presented in Section 7.1. At the discretion of the CTSC at any point in the study, correlative studies may be eliminated or the scheduled time points may be changed if the CTSC determines that sufficient data have been generated.

7.12.2.1. 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. The platform allows for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity (Swartzman 1999). This predefined multiplex panel of human cytokines will be measured from a small thawed vial of plasma, detecting and quantifying the soluble proteins and peptides which 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. A specific focus on cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be explored given the nonclinical mechanism for magrolimab to engage these immune cells.

7.12.2.2. Characterization of Circulating T-Cells

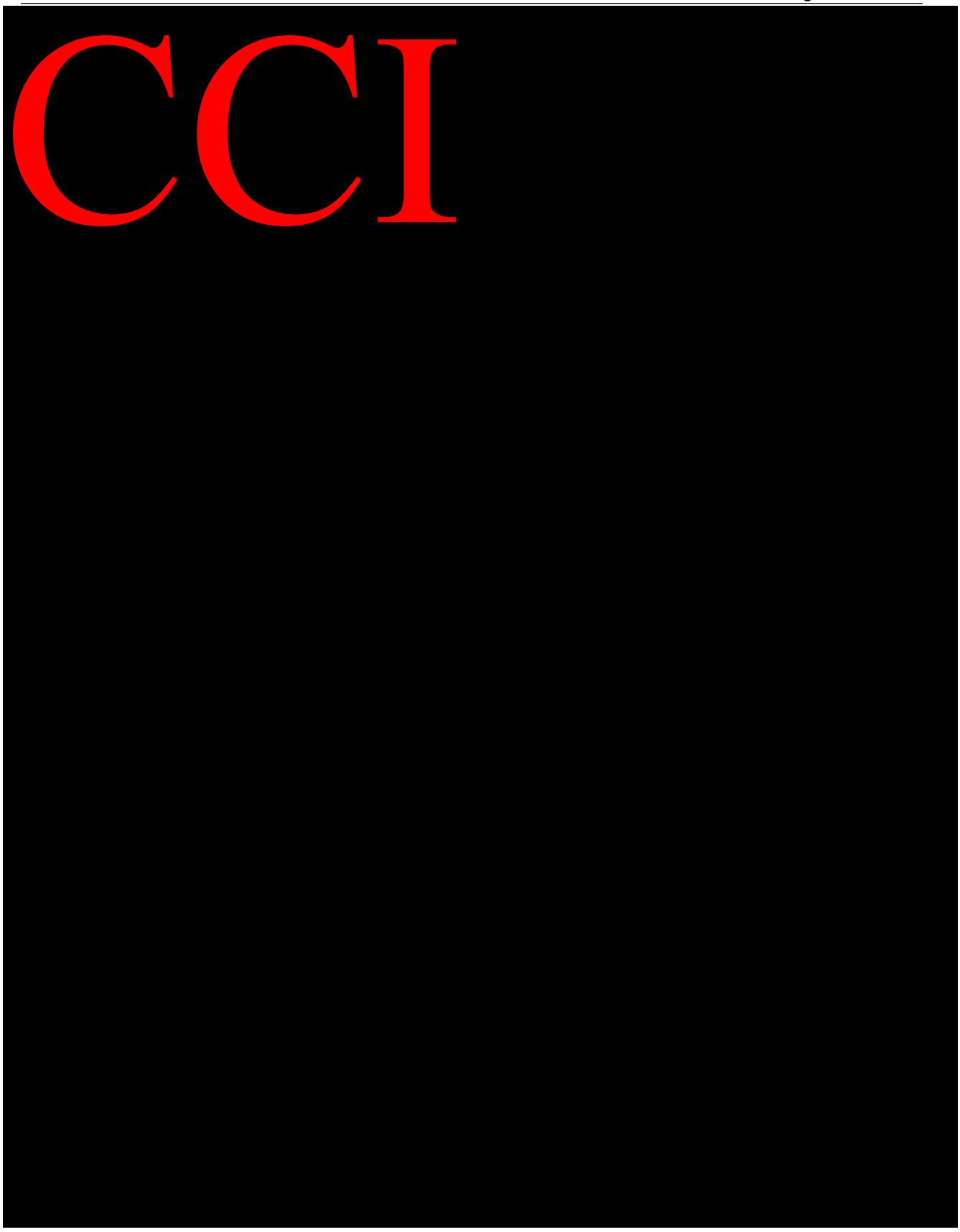
In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation (Tseng 2013). It is therefore predicted that magrolimab administration may lead to T-cell activation in patients. Peripheral blood samples will be collected and T-cell activation/repression markers/studies may be performed on CyTOF, in vitro T-cell activation assays, and T-cell receptor sequencing. CCI [redacted] CCI [redacted]

7.12.3. Minimal Residual Disease Monitoring

MRD monitoring has become a powerful prognostic factor that is beginning to play a central role in the treatment of AML patients both in the pre- and post-transplant setting. In multiple large studies of newly diagnosed AML patients, MRD positivity post-therapy was an independent poor prognostic factor and predictor of relapse (Buccisano 2012; Freeman 2013; Sievers 2003). In addition, MRD positivity also appears to be a poor prognostic factor in the post-transplant setting. In a retrospective study, patients with morphologic remission undergoing allogeneic HSCT, the presence of MRD prior to transplant was an independent predictor of relapse as 67% of patients with MRD-positive remission relapsed within 3 years post-transplant as compared to 22% in MRD-negative remission (Araki 2016). Several methods for MRD monitoring have been utilized in AML including 1) multiparameter flow cytometry for detection of aberrant hematopoietic surface antigens; 2) molecular monitoring of leukemia-specific mutational burden; 3) cytogenetic monitoring of leukemia-associated chromosomal abnormalities. MRD assessments will be performed on bone marrow aspirate specimens collected at time points as specified in the Schedule of Assessments in Section 7.1. 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. MRD 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. Using 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.

CCI [redacted]


CCI

8. STUDY DISCONTINUATION

8.1. Discontinuation of Study Drug Treatment

Patients (or a legally acceptable representative) may decline to continue receiving study drug at any time during the study, but will continue follow-up study visits unless they withdraw completely from the study (Section 8.2). The patient's health and welfare is the primary consideration in any determination to discontinue study drug treatment. Patients who discontinue study drug during the treatment period are to return for an EOT visit for evaluation of safety within 7 days of the decision to end magrolimab treatment if no evaluation was done within 7 days of the decision. In addition, patients are to return for a Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug. All patients who discontinue study drug treatment will participate in long-term follow-up for disease response until documented disease progression or initiation of new anti-cancer therapy, unless the patient withdraws consent for such follow-up and withdraws completely from the study (Section 8.2). For patients who come off study treatment to receive a bone marrow transplant, follow-up for disease progression and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs. All patients will be followed for survival until the end of the study. The assessments to be performed at each of the post-treatment visits are listed in the Schedule of Assessments, Section 7.1.

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

- Disease progression with confirmation in subsequent assessment at least 4 weeks apart (i.e., disease worsening compared to the previous assessment)
- Unacceptable toxicity
- Clinically significant change in the patient's status that precludes further treatment (e.g., pregnancy or other AE)
- Patient request, with or without a stated reason
- Bone marrow transplant
- Investigator or treating physician decision in the absence of any of the above.

Although disease progression is considered a sufficient reason for discontinuing a patient from study treatment, given the delayed treatment benefit commonly seen in immune therapies, the Investigator is advised to continue to treat the patient until the confirmation of disease progression through a subsequent response assessment at least 4 weeks apart (i.e., disease worsening compared to the previous assessment), or until the Investigator considers the study treatment to be no longer clinically beneficial to the patient or the change of disease state renders the patient unacceptable for further treatment in the judgement of the Investigator. The decision to discontinue a patient remains the responsibility of the treating Investigator, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a patient, the Investigator may contact the Medical Monitor and forward appropriate supporting documents to the Medical Monitor for review and discussion.

8.2. Withdrawal of Patients From Study

Patients have the right to withdraw completely from the study and end study data collection at any time and for any reason without prejudice to his or her future medical care. Patients (or a legally acceptable representative) may decline to continue receiving study drug 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 8.1 if possible. Patient data up to withdrawal of consent will be included in the analysis of the study. The Investigator is to discuss with the patient the appropriate procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any patient from study participation.

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

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

8.3. Termination of the Study

Gilead Sciences reserves the right to terminate the study at any time. Both Gilead Sciences 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/independent ethics committee (IEC) in writing of the study's completion or early termination and send a copy of the notification to Gilead Sciences.

The study may also be terminated for safety reasons, as described in Section 11.10 (Interim Safety Review).

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters and Definitions

Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Gilead Sciences or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive, and/or local regulatory requirements.

Gilead Sciences or its designee is responsible for reporting, in writing, all unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. Gilead Sciences or its designee will report other relevant SAEs associated with the use of the study medication to the regulatory agencies and competent authorities within 15 calendar days of notification.

9.1.1. 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:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with a patient's cancer that were not present prior to the AE reporting period (Section 9.2.1).
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies), including AEs that occur prior to assignment of study treatment that are related to protocol-mandated interventions.
- 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.

9.1.2. Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death at the time of the event; it does not refer to an event which might hypothetically have caused death if more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the Investigator (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’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.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the eCRF and that SAEs are recorded on the SAE report form and reported to the Sponsor in accordance with protocol instructions. SAEs must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event.

9.2.1. Adverse Event Reporting Period

After signing of informed consent, but prior to initiation of study medications, all events deemed by the Investigator as caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) will be collected as AEs (or SAEs if any of the serious criteria apply).

After initiation of the study treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or the Safety Follow-up Visit, whichever occurs later, or the patient begins an alternate anti-cancer therapy. After this period, Investigators are to report only SAEs that they assess to be related to study treatment (magrolimab and/or azacitidine received as part of this study).

Refer to Section 9.6 for post-treatment AE reporting.

9.2.2. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.2.3. Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF and on the SAE report form, if applicable.

For each AE and SAE, the Investigator will make an assessment of seriousness (Section 9.1.2), severity (Table 9-1), and causality. For each AE and SAE, causal relationship to magrolimab and to azacitidine will be assessed, as applicable. Table 9-2 provides guidance for assessing the causal relationship to the study drug(s).

The AE grading (severity) scale NCI CTCAE v4.03 (Appendix A) will be used for AE reporting as shown in Table 9-1. A customized severity grading for hemagglutination and microangiopathy AEs is described in Section 6.2.2.1. Regardless of severity, some events may also meet regulatory serious criteria (Section 9.1.2).

Table 9-1. 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: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (Appendix A).
Abbreviation: ADL = activities of daily life.
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.

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

Table 9-2. 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	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	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 or its designee, 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.

9.3. Procedures for Recording Adverse Events

9.3.1. Recording Adverse Events on the eCRF

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 each treatment (magrolimab, azacitidine) should be recorded individually.

9.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the 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 an AE on a separate eCRF. If a diagnosis is subsequently established, it should be reported to Gilead Sciences by subsuming the symptoms under the reported diagnosis according to the CRF Completion Guidelines.

9.3.1.2. 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 eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

9.3.1.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the 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 patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF each time they occur.

9.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug 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 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 “hyperkalemia.”

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

9.3.1.5. Deaths

All deaths that occur during the protocol-specified AE reporting period (Section 9.2.1), regardless of attribution, will be recorded on an eCRF and SAE Report Form and reported to the Sponsor within 24 hours of awareness and not later than the next business day. This includes death attributed to progression of disease.

If the death is attributed to progression of disease, especially in the absence of other signs and symptoms, record “[specific disease type] progression” as the SAE term on the SAE Report Form.

When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept whenever possible.

9.3.1.6. Worsening of Disease

Worsening of and/or progression of disease should not routinely be recorded as an AE or SAE if it does not result in death. These data will be captured as efficacy assessment data. However, worsening and/or progression of disease must be recorded as an AE/SAE if the investigator assesses the disease progression to be related to study treatment.

9.3.1.7. 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.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

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

9.3.1.7.1. Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

9.3.1.7.1.1. Pregnancy

Female patients who become pregnant during the treatment period must be withdrawn from study treatment immediately.

Any pregnancy occurring in a patient or a patient's partner during treatment with either study drug or within 6 months of last study drug administration must be reported to the Sponsor or designee (Section 9.4) within 24 hours of the site staff becoming aware of it, using a Pregnancy Notification Form (provided in the Investigator Trial File). It is the Investigator's responsibility to obtain consent for follow-up from the patient or the patient's partner. The Sponsor or designee will follow-up on all pregnancies for the pregnancy outcome through the Investigator, using a Pregnancy Outcome Form. Data will be collected about the pregnancy, fetal status, and neonate status. In the event that the neonate has abnormalities at birth, additional data will be collected about those abnormalities. Spontaneous abortion should always be classified as serious (as the Sponsor considers this medically significant), recorded on a Serious Adverse Event Form (SAE Form), and expeditiously reported to the Sponsor or designee, as described in Section 9.4. Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be recorded and reported as an SAE within 24 hours of awareness of the event.

9.3.1.7.1.2. Overdose

An overdose is a dose higher than that indicated in the protocol, with or without an AE.

9.3.1.7.1.3. Abuse or Misuse

Abuse or misuse of a study drug is use for nonclinical reasons, with or without experiencing an AE.

9.3.1.7.1.4. Special Situations

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

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

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

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

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

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

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

Unexpected benefit is defined as an unintended therapeutic effect 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 is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

Site personnel will record all special situations report (SSR) data on the special situations report form and transmit the SSR information by emailing or faxing the report form within 24 hours of the Investigator's knowledge of the event to the attention of Gilead Global Patient Safety from study drug initiation throughout the duration of the study, including the protocol required post-treatment follow up period.

9.4. Expedited Reporting Requirements for Serious Adverse Events

Investigators will submit reports of all SAEs, regardless of attribution, within 24 hours of awareness according to the instructions provided by the Sponsor. All SAEs will be recorded on the SAE 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 Global Patient Safety.

Gilead Global Patient Safety:

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

Medical Monitor Contact Information for Sites:

Medical Monitor: PPD
Email: PPD

The Sponsor or designee will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, Investigators/institutions, and central IRBs/IECs in compliance with reporting requirements according to local regulations and Good Clinical Practice (GCP) guidelines.

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

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

The Investigator is to notify the appropriate local IRB/IEC of SAEs occurring at the site and other AE reports received from the Sponsor or designee in accordance with local procedures and statutes.

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

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

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's eCRF.

9.5. Type and Duration of Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved SAEs and study-related AEs until the events are resolved or stabilized, the events are determined to be irreversible by the Investigator, the patient initiates new anti-cancer therapy, or the patient is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF, the SAE report form, and in the patient's medical record to facilitate source data verification (SDV).

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9.6. Post-treatment Adverse Events

For patients who discontinue the study treatment and have completed the 30-day Safety Follow-up visit, Investigators are to report any death or other SAE occurring beyond 30 days following the last administration of study treatment (magrolimab and/or azacitidine) that the Investigator assesses as related to study treatment.

Investigators are to report these events as described in Section 9.4.

10. MEASUREMENT OF EFFECT

Assessment of response will be conducted by the Investigator using the criteria in Appendix B, which are based primarily on the 2017 ELN recommendations for AML (Döhner 2017) and the 2003 IWG criteria (Cheson 2003) for AML patients. Response classifications include: complete remission (CR) rate, morphologic CR, complete remission without minimal residual disease (CR_{MRD}-), cytogenetic complete remission (cCR), molecular complete remission (mCR), complete remission with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), marrow complete remission (CR), morphologic leukemia-free state (MLFS), PR, and stable disease (SD).

In addition, hematologic improvement (HI) will be assessed by 2006 IWG criteria (Cheson 2006) to compare with disease response assessed by 2017 ELN criteria (Döhner 2017) and 2003 IWG criteria (Cheson 2003).

Response will be assessed in MDS patients using the criteria in Appendix B Table 14-4, which are based on the 2006 IWG criteria (Cheson 2006) with the added caveat that the impact of anemia must be deemed disease-related and not due to study treatment.

Response assessments will be performed at the time points specified in the Schedule of Assessments in Section 7.1 and as described in Section 7.9.

The following summary measures for endpoints will be evaluated:

Objective Response Rate for Patients with AML: The ORR is the proportion of patients who reach CR (including morphologic CR, CR_{MRD}-, cCR, and mCR), CRi, CRh, PR, or MLFS while on study.

CR Rate for Patients with AML: The CR rate is the proportion of patients who achieved CR, as defined by the Investigator based on ELN AML recommendations (Döhner 2017; Appendix B).

CR Rate for Patients with MDS: The CR rate is the proportion of MDS patients who reach morphologic CR while on study per IWG 2006 criteria (Cheson 2006).

Duration of Complete Remission (DCR) for AML: The DCR is measured from the time measurement criteria are first met for CR (including morphologic CR, CR_{MRD}-, cCR, and mCR) until the first date that recurrent disease or death with evidence of no disease recurrence is objectively documented. Those who are not observed to have recurrent disease or die with evidence of no recurrence during the trial active period will be censored at their last response assessment date with evidence of no progression/recurrence.

Duration of Response (DOR) for Patients with AML: The duration of response is measured from the time measurement criteria are met for CR (including morphologic CR, CR_{MRD}-, cCR, and mCR), CRi, CRh, PR, marrow CR, or MLFS, whichever is first recorded, until the first date that recurrent or progressive disease, or death with evidence of no disease progression is objectively documented. Those who are not observed to have recurrent or progressive disease or die with evidence of no disease progression during the trial active period will be censored at their last response assessment date with evidence of no progression/recurrence.

Duration of CR for Patients with MDS: The duration of CR for MDS patients is measured from the time measurement criteria are first met for CR until the first date that recurrent disease or death with evidence of no disease recurrence is objectively documented. Patients who are not observed to have recurrent disease or die with

evidence of no recurrence during the trial active period will be censored at their last response assessment date with evidence of no progression/recurrence.

Duration of Response for Patients with MDS: The DOR for MDS patients is measured from the time measurement criteria are first met for objective response (including CR, PR, marrow CR, and HI) as assessed by IWG MDS criteria (Cheson 2006) until the first date that recurrent disease or death with evidence of no disease recurrence is objectively documented. Those who are not observed to have recurrent disease or die with evidence of no recurrence during the trial active period will be censored at their last response assessment date with evidence of no progression/recurrence.

Overall Survival (OS): The length of OS is measured from the date of study treatment initiation until the date of death from any cause. Those who are not observed to die during the trial active period will be censored at their last known alive date from survival follow-up.

Progression-free Survival (PFS): The length of PFS is defined as the time from the date of study treatment initiation until the date of documented disease progression or relapse or death from any cause, whichever occurs first (Cheson 2003). Those who are not observed to have one of these events during the time the overall trial remains active will be censored at their last known progression-free follow-up date.

Event-free Survival (EFS): For AML, the length of EFS is defined as the time from the date of study treatment initiation until the date of documented disease progression, death from any cause, or treatment failure (defined as failure to achieve CR/CRi by Cycle 5 Day 1), whichever occurs first (Cheson 2003). For MDS, EFS is defined as the time from the date of study treatment initiation to transformation to AML or death from any cause, whichever occurs first. Those who are not observed to have one of these events during the time the overall trial remains active will be censored at their last known progression-free follow-up date.

11. STATISTICAL CONSIDERATIONS

The final analysis will be based on patient data collected through study discontinuation. The statistical analyses will be based on all patients who receive at least 1 dose of magrolimab. In general, data will be described and summarized as warranted by the sample size, and listings will be used in place of tables when the sample sizes are small. All summaries will be presented by indication (AML or MDS) and cohort (R/R or TN/U), and by treatment, when appropriate.

11.1. Safety Analysis

All patients who receive at least 1 dose of magrolimab will be included in the safety analysis.

The DLT analysis will be conducted in the TN/U Dose Evaluation Cohort in patients who completed either at least 4 infusions of magrolimab or 4 infusions/injections of azacitidine and have been followed for the 4-week DLT Assessment Period or have experienced a DLT within 4 weeks after initiating study drug treatment.

Safety will be assessed through summaries of deaths, DLTs, AEs, changes in laboratory test results, and exposure to magrolimab.

Adverse events leading to treatment discontinuation will be listed. AEs leading to the declaration of DLTs will be listed.

11.2. Efficacy Analysis

All patients who receive at least 1 dose of magrolimab will be included in the efficacy analysis except for those endpoints that are applicable only to patients who achieved a response. In addition, an evaluable patient efficacy analysis will also be performed on all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 disease response assessment or who died before the first disease response assessment.

11.3. Pharmacokinetics Analysis

The PK analysis will be conducted on all enrolled patients treated with magrolimab (and/or azacitidine if appropriate) whose PK blood samples are collected during the study and who have measurable concentrations of magrolimab (and/or azacitidine if appropriate).

11.4. Sample Size Determination

The number of patients planned for inclusion in this trial is up to a total of approximately 287 patients evaluable for efficacy, as follows:

- R/R Safety Cohort: 10 patients
- R/R Expansion Cohort: Up to 36 patients
- R/R MDS Magrolimab Monotherapy Cohort: 23 patients
- TN/U Dose Evaluation Cohort: Up to 18 patients
- TN/U Expansion Cohort: Up to 172 patients, including
    - Original 30 TN/U Expansion (enrolled 18 AML and 16 MDS patients, including 4 replacement patients)
    - At least 92 MDS patients (including the original 16 MDS patients enrolled in the original TN/U Expansion), of whom at least 56 patients will be on Q2W dosing. The overall MDS expansion to 92 patients will be considered the MDS Registrational Cohort.
    - Up to 62 TP53 mutant AML patients (i.e., 12 original TP53 mutation AML patients, plus 20 additional TP53 mutant AML patients added per CTSC decision in September 2019, plus 30 additional TP53 mutant AML patients per CTSC decision July 2020)
- RBC Transfusion-dependent Low-risk MDS Cohort: Up to 20 patients
- Rollover Cohort: Up to 8 patients

For the R/R Safety Cohort, 10 patients have been enrolled as of the approval of Amendment 5 for evaluation of safety of magrolimab monotherapy.

For the R/R Safety Cohort and Expansion Cohort, approximately 46 patients may be enrolled, including 10 patients treated in the safety run-in cohort and 36 patients treated in the expansion cohort. For the R/R Safety Cohort, 10 patients were enrolled and this cohort was closed to further enrollment as of Amendment 3. Based on safety and efficacy data, the CTSC may decide to expand the R/R Expansion Cohort to include additional patients. An ORR of 17% has been reported in patients with R/R AML who have been treated with azacitidine (Itzykson 2015). For an estimated response rate of 33% or higher, 36 patients would provide a 95% confidence interval, with the lower bound to exclude 18.6%, the azacitidine monotherapy efficacy rate.

Per FDA feedback, a magrolimab monotherapy cohort in R/R MDS will be evaluated to further define the activity of magrolimab to the contribution of magrolimab+azacitidine in MDS to support a potential single-arm approval of magrolimab+azacitidine in MDS. Patients will be enrolled in a Simon's 2-stage design. With a 1-sided significance level of 0.05 and 80% power, the null hypothesis that the magrolimab monotherapy ORR is 9% will be tested against the alternative of 30%. In the first stage, 11 patients will be enrolled. If there are 1 or fewer responses observed in these 11 patients, the cohort will be stopped. Otherwise, 12 additional patients will be accrued, for a total of 23. This cohort was stopped after 11 patients enrolled per CTSC decision in October 2020. The null hypothesis will be rejected if 5 or more responses are observed in 23 patients.

For the TN/U Dose Evaluation Cohort, up to 18 patients can be enrolled based on a 3+3 dose de-escalation design, assuming 3 potential dose cohorts with a maximum of 6 patients treated per cohort. For the TN/U Dose Evaluation Cohort, 8 patients were enrolled and this cohort was closed to further enrollment as of Amendment 5.

For the TN/U Expansion Cohort, a total of up to 172 patients may be enrolled. An initial sample size of 30 patients was proposed so that the 95% confidence interval of the desired 35% or higher CR rate would exclude a known CR rate of 17.85% for azacitidine alone. This sample size calculation was based on inclusion of both TN/U AML and higher-risk MDS patients. For the higher-risk, untreated, MDS-only Expansion Cohort, an evaluation will occur after 36 patients have reached the first response

assessment (Cycle 3 Day 1); however, enrollment will continue and not be paused in the interim. A sample size of 36 patients provides 80% power to reject the null hypothesis that the CR rate is 16.5% or lower at 2-sided 0.05 significant level, assuming the true magrolimab + azacitidine CR rate is at least 35.5% (19% improvement). The null CR rate of 16.5% is based on the pivotal randomized trial leading to azacitidine approval in MDS reanalyzed by IWG 2000 criteria (Silverman 2006), where the upper bound of the 1-sided 95% confidence interval for azacitidine CR rate is 16.5%, with a point estimate of 10%. Based on Amendment 6 and FDA feedback for a single-arm trial to support a potential BLA, the sample size of the TN/U MDS-only Expansion Cohort for untreated, higher-risk MDS patients was further increased to include a cohort of 56 patients with MDS at a magrolimab Q2W dosing regimen. A sample size of 56 patients provides 80% power to reject the null hypothesis that the CR rate is 16.5% at a 2-sided 0.05 significant level, assuming the true magrolimab+azacitidine CR rate is at least 31.5%. The null CR rate of 16.5% is based on the same assumption for azacitidine monotherapy as above. A combined planned sample size of 92 patients for the MDS Registrational Cohort will provide an 80% power to reject the updated null CR rate of 23.5% at a 2-sided 0.05 significant level, assuming the true magrolimab+azacitidine CR rate is 36.5%.

Per the CTSC decision in September 2019 and Amendment 6, a subcohort of TP53 mutant TN/U AML patients was added. Initially, 12 patients and then an additional 20 patients will be enrolled. Analysis of these patients will include all TP53 mutant patients meeting subcohort eligibility enrolled prior to the Amendment/CTSC decision. A sample size of 32 patients was selected to evaluate the initial efficacy of magrolimab+azacitidine as compared to available therapies (most notably venetoclax+hypomethylating agents) in TP53 mutant AML. While venetoclax in combination with hypomethylating agents (azacitidine or decitabine) is approved in newly diagnosed AML patients who are ineligible for intensive chemotherapy, their efficacy in TP53 mutant AML patients is limited. Per a recent report, the CR+CRi rate of venetoclax+hypomethylating agent in TP53 mutant AML was 47%, with a median duration of CR of 5.6 months and a median overall survival of 7.2 months (DiNardo 2019). In contrast, in all-comer AML patients, the CR+CRi rate was 67% with

a median duration of CR of 11.3 months and a median overall survival of 17.5 months. Assuming an observed magrolimab+azacitidine ORR of 59% for a sample size of 32 patients, the 1-sided 90% confidence interval will have a lower bound of 46.5%, which excludes a control ORR of 46%. Based on emerging data, the CTSC may decide to enroll additional patients for further safety, efficacy, or dosing information. Per CTSC decision in July 2020 and captured in Amendment 7, an additional 30 TP53 mutant AML patients were enrolled for the TN/U Expansion Cohort (n = 62).

For the RBC Transfusion-dependent Low-risk MDS Cohort, approximately 20 patients will be enrolled. Initially, 6 patients will be enrolled with a safety evaluation after all 6 patients complete at least Cycle 2 Day 15 treatment. This safety evaluation is being conducted given that a 60 mg/kg dose of magrolimab will be administered starting in Cycle 2, of which this highest dose has not yet been tested in MDS patients. However, an equivalent dose of 60 mg/kg given in 1 week (30 mg/kg twice weekly) has already been administered to MDS and AML patients in this trial and has been well tolerated. The CTSC will then evaluate based on the aggregate safety profile in these 6 patients and determine whether enrollment should proceed to the remaining 14 patients. If so, these 14 patients can be simultaneously enrolled. Based on emerging data, the CTSC may decide to enroll additional patients for further safety, efficacy, or dosing information. These may be enrolled as either magrolimab monotherapy or in combination with azacitidine.

For the Rollover Cohort, 1 eligible patient from the Phase 1 study (SCI-CD47-002) is now enrolled in this study, and this cohort was closed to further enrollment as of Amendment 3.

11.5. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC.
The CTSC will have representation from each participating site in the study. The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments,

expansion of cohorts, using higher or lower dose levels or different dosing schedules, defining any new dose cohorts, and identification of the recommended dose and schedule for Phase 2 trials. The CTSC will meet at a minimum at the completion of each dosing cohort during safety run-in and dose evaluation phase of the trial and when emergent critical safety data are reported. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

CTSC decisions in this study are included in the following sections of this document: Section 3.1 Overall Study Design; Section 3.2 Study Design - R/R Cohort; Section 3.3 Study Design - TN/U Cohort; Section 3.4 Study Design – RBC Transfusion-dependent Low-risk MDS Cohort; Section 3.5 Study Design - Rollover Cohort; Section 3.7 Estimated Study Duration and End of Study; Section 6.1 Study Drug Administration; Section 6.2.1.1 Dose Modification and Delay Guidelines, magrolimab; Section 7.3.8 Bone Marrow Assessments; Section 7.10 Pharmacokinetics; Section 7.12 Pharmacodynamic and Biomarker Assessments; and Section 11.8.2 Additional Secondary Endpoints.

11.6. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 11.5.

11.7. Analysis of the Conduct of the Study

The CTSC, in conjunction with the Sponsor, will be the main body responsible for the analysis of the conduct of the study, as outlined in the CTSC Charter.

11.8. Statistical Methods

All analyses will be conducted separately for patients by indication in the R/R Cohorts, the TN/U Cohorts, and the Rollover Cohort, unless otherwise mentioned. Additional analyses may be conducted separately for the R/R Safety Cohort alone and TN/U Dose Evaluation Cohorts. Combined safety analyses may be conducted for patients in both monotherapy cohorts (the R/R Safety Cohort, R/R MDS Cohort, and Rollover Cohort, where applicable), as well across the study on all treated patients. Statistical analyses

will be performed separately for the patients treated with magrolimab in combination with azacitidine in the TP53 TN/U AML Cohort and RBC Transfusion-dependent Low-risk MDS Cohort, as well as in the untreated higher-risk MDS cohort as a potential pivotal single-arm study to support a potential BLA in higher-risk untreated MDS.

For continuous variables, the mean, standard deviation, median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided, along with 95% confidence intervals for primary and secondary efficacy endpoints. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding 2-sided 95% confidence intervals for the median will be provided, when appropriate. The KM plots may also be provided. Details regarding the statistical analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the SAP.

11.8.1. Efficacy Analyses

11.8.1.1. Primary Efficacy Endpoint: CR Rate

The primary efficacy endpoint for both AML and MDS is CR rate as assessed by Investigators. The analysis of CR rate will be conducted on all enrolled patients who receive at least 1 dose of the investigational drug magrolimab. In addition, an evaluable patient efficacy analysis will be performed on all enrolled patients who receive at least 1 dose of magrolimab and have at least 1 disease response assessment or who died before the first post-treatment disease response assessment. The point estimate of the CR rate and the corresponding 2-sided 95% confidence interval will be generated.

For the primary analysis of TN/U higher-risk MDS patients, the percentage of patients achieving a CR will be estimated based on all TN/U higher-risk MDS patients who received at least 1 dose of magrolimab, with exact 95% CI using the Clopper and Pearson method. Formal hypothesis testing will be performed to test the statistical hypothesis of:

H_0: CR rate = 23.5%; vs.
H_1: CR rate ≠ 23.5%.
The Chi-square test will be performed at 2-sided 0.05 significance level.

11.8.1.2. Secondary Efficacy Endpoints

Additional parameters of objective response, including CRh, will be evaluated in a similar manner as the primary efficacy endpoints. For the time-to-event endpoints listed here, the Kaplan-Meier (KM) estimates and corresponding 95% intervals for the median will be provided when appropriate. The KM plots may also be provided when appropriate. RBC transfusion independence is defined as no transfusions for at least an 8-week consecutive period. The percent of patients who become RBC transfusion-independent will be estimated based on the number of patients who received at least 1 dose of HuF59-G4 and are RBC transfusion-dependent at baseline.

Duration of Complete Remission (DCR)

The analysis of DCR will be conducted using the Kaplan-Meier method.

Progression-free Survival (PFS)

The analysis of PFS will be conducted on all treated patients.

Overall Survival (OS)

The analysis of OS will be conducted on all treated patients.

Objective Response Rate (ORR) and Duration of Response (DOR)

Analysis of ORR and DOR will be conducted in the R/R MDS Magrolimab Monotherapy Cohort.

11.8.2. Additional Secondary Endpoints

Pharmacokinetic Analyses

PK analysis will be conducted for magrolimab on the PK analysis set (PAS). Based on the distinct MOAs of magrolimab and azacitidine, overlapping drug PK interactions are not expected. Thus, samples for PK analysis for azacitidine will be banked and will be conducted based on CTSC recommendation.

The PAS consists of all treated patients who have at least 1 blood sample that provides evaluable PK data. The PAS will be used for summaries of PK concentration data, and PK parameters. Individual patients may be removed from the estimation of particular PK parameters based on the number of available blood samples for them. These patients will be identified at the time of analysis.

Depending on availability of data, the following PK parameters after the first and after multiple doses may be calculated using noncompartmental analysis:

- AUC_{tau} (the area under concentration curve during a dosing interval)
- C_{max} (maximum observed serum concentration)
- CL (clearance)

Additional PK parameters may also be calculated, if relevant.

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics.

Descriptive statistics of all PK parameters will include arithmetic and geometric mean, median, SD, CV, geometric coefficient of variation (CV), minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since time to maximum concentration (T_{max}) is generally evaluated by a nonparametric method, median values and ranges will be provided for this parameter.

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.

Immunogenicity Analyses

The rate and magnitude of anti-magrolimab antibody incidence and prevalence will be evaluated for individual patients, for all patients in each of the study cohorts, and for the pooled patient population. CCI [redacted]

Immunogenicity analysis may also be performed for azacitidine. However, it is not expected that magrolimab will impact the immunogenicity of azacitidine and vice versa.

Immunogenicity: Exposure and/or Adverse Event Relationship

The concentration-versus-adverse event/immunogenicity relationship will be explored graphically, tabulated, and, if appropriate, evaluated by a mixed effects model in order to characterize a relationship between the changes from screening immunogenicity presence and serum concentration of magrolimab.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy, and biomarker parameters) may be evaluated. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between immunogenicity change from screening values and major safety, efficacy, and biomarker parameters. Second, for any potential correlation identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

11.8.3. Safety Analyses

The statistical analysis of safety data will be conducted in patients who received at least 1 dose of magrolimab. Safety variables may include, but are not limited to: DLTs, treatment-emergent adverse events (TEAEs; AEs worsening or occurring during or after a patient's first exposure to study drug), vital signs, physical examinations, laboratory tests, RO (US only), and anti-drug antibody assessments.

Data will be presented by cohort (R/R or TN/U) and by treatment, when appropriate, as well as all cohorts combined. Some safety data may be summarized across multiple study cohorts or over all cohorts. Data may be graphed, summarized, or listed, depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

11.8.3.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later and the NCI CTCAE v 4.03 (Appendix A) will be used to grade severity of AEs and laboratory toxicities. Patient 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 drug (related or not related). SAEs, including deaths, will be summarized and/or listed for each cohort and for all cohorts combined. TEAEs resulting in withdrawal from study drug or further study participation will be tabulated and/or listed. DLTs will also be listed.

Adverse events that occurred during screening, but before exposure to study drug will be reported in the AE line listings and appropriately identified as non-TEAEs.

Adverse events and SAEs occurring during screening will be reported separately for patients who were screened, but not entered in the study, with line listings and/or summary tables, along with relevant demographic data collected.

11.8.3.2. Analysis of Other Safety Endpoints

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 toxicities will be summarized. The number and incidence of patients developing RO (US only) and ADAs at any time will be summarized. Vital signs and physical examination will be summarized at select time points. Details will be provided in the SAP.

11.9. Handling of Missing Data

Details regarding the handling of missing data will be described in the SAP.

11.10. Interim Safety Review

An interim safety review will be performed for patients in the R/R Cohort, TN/U AML Expansion Cohort, and the RBC Transfusion-dependent Low-risk MDS Cohort. After the first 10 patients are enrolled in each cohort, if >33% of patients experience an AE that qualifies as a DLT and results in permanent study drug discontinuation, withdrawal, or death, then that cohort will be stopped for unacceptable toxicity. If a study drug-related death occurs on study, a safety review will be conducted by the CTSC to determine whether enrollment should be interrupted. The trial may also be stopped at any time if the CTSC deems that there is an unacceptable safety risk to patients with the study treatment.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the protocol and with US FDA and the ICH GCP guidelines, the Declaration of Helsinki, and any applicable local health authority and IRB/ IEC requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, CFR, 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 FDA, ICH, and local requirements, the most stringent standard shall apply.

12.2. 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, patient recruitment materials, and any other pertinent documents before any study-related activities involving patients 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 patient 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 non-administrative 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. All persons authorized to make entries and/or corrections on CRFs will be included on the Gilead Sciences. Delegation of Authority Form.

The clinical study report must be signed by the Investigator or, in the case of multi-center studies, the Coordinating Investigator. The Coordinating Investigator, identified by Gilead Sciences, 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 patients.

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to patients must be returned to the site and/or destroyed.

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug
- The date, patient number, and the study drug number dispensed
- The date, quantity of used and unused study drug destroyed on site or returned, along with the initials of the person recording the information

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed ICF, other written patient 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 before recruitment of patients in the study and shipment of magrolimab.

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Gilead Sciences. 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 deviations from the protocol or SAEs occurring at the site and other AE reports received from Gilead Sciences, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval/renewal as applicable 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.

12.4. Informed Consent and Human Subject Protection

An initial sample ICF is provided for the Investigator to prepare the ICF to be used at his or her site. Updates to the template are to be communicated formally in writing from the Gilead Sciences. Study Monitor to the Investigator. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative 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. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The Investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient, or a legally acceptable representative, 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 patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the ICF to attest that informed consent was freely given and understood.

12.5. Confidentiality

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

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For SAEs reported to Gilead Sciences, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Gilead Sciences (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(s), and the IRB/IEC direct access to review the patient'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 patient to permit such individuals to have access to his/her study-related records, including personal information.

12.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place. **The Investigator must inform Gilead Sciences 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 to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

12.7. Serious Breaches and Fraud

Within the UK, the Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the Medicines and Healthcare products Regulatory Agency (UK) (MHRA) within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial”

Investigators must notify Gilead Sciences immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to Gilead Sciences. All instances of confirmed clinical trial fraud occurring at sites in the UK will be treated according to the procedure for dealing with a serious breach and must be reported to the MHRA within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

The Gilead Sciences 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/CRFs and other pertinent data) provided that patient confidentiality is respected.

The Gilead Sciences representative(s) are responsible for verifying the CRFs 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 representative(s) are to have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

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

12.9. Audits and Inspections

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including CRFs 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.

12.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies), as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the schedule of study assessments (as described in Section 7.1), the Investigator may search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients 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/or paper CRFs and source documentation as part of the case histories. Gilead Sciences will supply the eCRF, which will be completed in English.

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

All entries made on the eCRF/CRFs must be verifiable 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 patient 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.

12.11. Maintenance of Source Documents and Record Retention

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 patients as described in the study manual.

Source documents are original documents, data, and records from which the patient's CRF 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.

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 and/or applicable regulatory authorities.

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.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.13. Financing and Insurance

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

12.14. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.7).
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.

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14. 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 4.03

Publication date: 28 May 2009 (v4.03: 14 June 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Accessed 7 June 2016

Hemagglutination and microangiopathy will be graded using the scale below, which is adapted from the CTCAE Version 4.03 general guidance:

AE Severity Grading for Hemagglutination and Microangiopathy

Grade 1: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are asymptomatic or mild, not requiring intervention

Grade 2: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that require medical intervention

Grade 3: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily living

Grade 4: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are life threatening or require urgent intervention

Grade 5: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that result in death

Appendix B: Disease Response Assessment Based On European Leukemianet And International Working Group Criteria

Assessment of leukemia response in AML patients will be conducted primarily using the European Leukemia Net (ELN) 2017 recommendations for AML (Döhner 2017) (Table 14-1) and the 2003 IWG criteria (Cheson 2003) (Table 14-2). Response classifications include: complete remission (CR), complete remission without minimal residual disease (CR_{MRD}-), cytogenetic complete remission (cCR), molecular complete remission (mCR), complete remission with incomplete hematologic recovery (CRi), partial remission (PR) and stable disease (SD).

Accompanying laboratory results ± 2 weeks from the protocol-specified bone marrow efficacy assessment can be used to support an efficacy assessment of CR for both AML and MDS.

In addition, CR with partial hematologic recovery will be assessed for AML and MDS, defined as patients who achieve a CR per AML ELN 2017 recommendations (Döhner 2017) or MDS IWG 2006 criteria (Cheson 2006), with the exception of requiring partial hematologic recovery as defined by a platelet count of > 50 × 10^9/L and an absolute neutrophil count of > 500/μL.

In addition, hematologic improvement (HI) will be assessed by 2006 IWG criteria (Cheson 2006) (Table 14-3) to compare with disease response assessed by 2017 ELN criteria (Döhner 2017) and 2003 IWG criteria (Cheson 2003).

Response will be assessed in MDS patients using the 2006 IWG criteria (Cheson 2006) as shown in Table 14-4, with the added caveat that the impact of anemia must be deemed disease-related and not due to study treatment.

Table 14-1. Response Criteria in AML (ELN 2017 Recommendations)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Complete Remission without minimal residual disease (CR_{MRD-})	≥ 1.0 × 10^9/L	≥ 100 × 10^9/L	< 5%	If studied pretreatment, CR with negativity for a genetic marker by real-time quantitative polymerase chain reaction (RT-qPCR) or similar modality or CR with negativity by multi-color flow cytometry
Complete Remission (CR)	≥ 1.0 × 10^9/L	≥ 100 × 10^9/L	< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; MRD positive or unknown
Complete Remission with Incomplete Hematologic Recovery (CRi)	Neutrophils ≥ 1.0 × 10^9/L or Platelets ≥ 100 × 10^9/L		< 5%	Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; MRD positive or unknown (All CR criteria except residual neutropenia [< 1.0 × 10^9/L] or thrombocytopenia [< 100 × 10^9/L])
Morphologic Leukemia-Free State (MLFS)			< 5%	Absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required; marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial Remission (PR)	≥ 1.0 × 10^9/L	≥ 100 × 10^9/L	Decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Blasts < 5% with Auer rods may also be considered a PR
Stable Disease (SD)	Absence of CR_{MRD-}, CR, CRi, PR, MLFS; and criteria for progressive disease not met			
Progressive Disease (PD)	• Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: ○ > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 10^9/L [500/μL]), and/or platelet count to > 50 × 10^9/L (50,000/μL) non-transfused]; or ○ > 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L (> 25,000/μL) (in the absence of differentiation syndrome); or • New extramedullary disease			

Source: Döhner 2017
Abbreviations: AML = acute myeloid leukemia; ANC = absolute neutrophil count; CR = complete remission; MRD = minimal residual disease; WBC = white blood cell count.

Table 14-2. Additional Response Definitions Used in This Trial (2003 IWG Criteria)

Response Criteria	Definitions			
	Neutrophils	Platelets	Bone Marrow Blasts	Other
Cytogenetic CR (cCR)	≥ 1.0 × 10^9/L	≥ 100 × 10^9/L	< 5%	Cytogenetics normal and no evidence of extramedullary disease
Molecular CR (mCR)	≥ 1.0 × 10^9/L	≥ 100 × 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: IWG = International Working Group.
a. Treatment failure defined for this protocol

Table 14-3. 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)	• Pre-transfusion 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 post-treatment period
Platelet Response (HI-P) (pretreatment < 100 × 10^9/L)	• Absolute increase of ≥ 30 × 10^9/L for patient starting with a platelet count > 20 × 10^9/L pretreatment or • Increase from < 20 × 10^9/L pretreatment to > 20 × 10^9/L post-treatment and by at least 100%
Neutrophil Response (HI-N) (pretreatment < 1.0 × 10^9/L)	At least 100% increase and an absolute increase of > 0.5 × 10^9/L
Progression/relapse after Hematological Improvement[b]	One or more of the following • ≥ 50% decrement from maximum response in neutrophils or platelets • Reduction in hemoglobin by ≥ 15 g/L • Transfusion dependence

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

Table 14-4. Response Criteria in MDS (IWG 2006 Criteria With Modifications)

Category	Response Criteria
Complete Remission	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%
Partial Remission	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 = myelodysplastic syndrome French-American-British classification; Hgb = hemoglobin; 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.

Appendix C: ECOG 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 7 June 2016

Appendix D: Peripheral Smear Assessment

Peripheral smears will be assessed by the designated hematopathology service using the following guidelines:

RBC Agglutination	
0-9%	Not reported
10-19%	1+
20-50%	2+
51-75%	3+
> 75%	4+
Spherocytes	
0-1 cells/100 RBCs	Not reported
2-5 cells/100 RBCs	1+
> 5-10 cells/100 RBCs	2+
> 10-30 cells/100 RBCs	3+
> 30 cells/100 RBCs	4+
RBC Fragments/Schistocytes	
0 cells/100 RBCs	Not reported
1-2 cells/100 RBCs	1+
> 2-5 cells/100 RBCs	2+
> 5-10 cells/100 RBCs	3+
> 10 cells/100 RBCs	4+

All other observed findings: report according to local laboratory hematopathology standard procedures.

These guidelines are based on the Stanford Health Care Peripheral Blood Slide Review Manual, Version 3.0, 2015, modified by Gilead Sciences for clarification of the following items in the original manual:

- RBC agglutination, 1+ = 10%, 3+ = 60-75%
- Spherocytes, 2+ = 5-10 cells/100 RBCs, 3+ = 10-30 cells/100 RBCs
- RBC Fragments/Schistocytes, 2+ = 2-5 cells, 3+ = 5-10 cells

If sites are not able to quantify the degree of peripheral smear findings noted above, then the presence or absence of RBC agglutination, spherocytes, and/or RBC fragments/schistocytes must be reported at a minimum.

Appendix E: Decitabine Prescribing Information

Decitabine for injection - prescribing information

Available online:
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c155d6ba-9a16-406c-919e-65a149689ab9&type=display

Accessed 9 July 2019

Appendix F: Schedules Of Dosing And Assessments For Completed Cohorts

This appendix contains schedules of dosing and assessments for completed cohorts. These tables are maintained here for archival purposes but should not be followed for any patients currently enrolled.

Table 14-5. Dose and Schedule for Rollover AML Cohort

Cohort	Drug/Dose/Route	Dose Schedule (Day per 28-day Cycle)
		All Cycles
Rollover AML	Magrolimab - continue same dose level as previous study (up to 30[a] mg/kg) IV	Dosing schedule may be twice weekly (Day 1, 4, 8, 11, 15, 18, 22, and 25), once weekly (Day 1, 8, 15, 22), or in accordance with a modified recommended Phase 2 dose and schedule determined by the CTSC.

Abbreviations: AML = acute myeloid leukemia; CTSC = Clinical Trial Steering Committee; IV = intravenous.

a. At the discretion of the CTSC, patients who are receiving lower doses may be escalated to a higher dose deemed to be safe on this study by the CTSC.

Table 14-6. Schedule of Assessments, R/R Cohort (Safety)

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohorts (Safety)																								
Cycle (28-day Cycles)	1												2									3+			
Visit Window (Days)	-30	None		± 3[a]									± 3[a]									± 3			
Cycle Day	SC	1	2	4	8	11	15	16	17	18	22	25	1	2	3	4	8	11	15	18	22	25	1	8	15	22
Informed consent	X[b]																									
Demographics	X																									
Medical and cancer history	X																									
Entry criteria	X																									
Enrollment cohort assignment	X[b]																									
Pregnancy test	X	X[c]											X										X			
Donor chimerism[d]	X																									
CBC with differential, platelets, reticulocytes[e,f]	X	X	X	X	X	X	X			X	X	X	X				X		X		X		X		X	
Peripheral blood smear[e,g]	X	X	X		X		X				X		X										X			
Serum or plasma chemistry[e]	X	X	X		X		X				X		X				X		X		X		X		X	
Serum uric acid, phosphorus[e]	X	X	X		X		X																			
Haptoglobin, D-dimer, thrombin, fibrinogen[e]	X	X	X		X		X						X										X			
PT/INR, aPTT[e]	X				X								X										X			
Type and screen (ABO/Rh), DAT	X																									

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohorts (Safety)																								
Cycle (28-day Cycles)	1												2									3+			
Visit Window (Days)	-30	None		± 3[a]									± 3[a]									± 3			
Cycle Day	SC	1	2	4	8	11	15	16	17	18	22	25	1	2	3	4	8	11	15	18	22	25	1	8	15	22
Urinalysis[e]	X						X																			
Correlative studies[h]		X			X		X						X										X			
PK (Safety Cohort)[i]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X Q2C[y]			
Anti-drug antibodies[k]		X			X								X										X			
CD47 RO blood[l]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X Q2C-Q3C[y]			
Bone marrow aspirate/ biopsy for CD47 RO/[redacted] studies[x]	X						X						X										X Q2C-Q3C[s,t]			
Bone marrow biopsy and cytogenetics[r,s]	X												X										X Q2C-Q3C[s,t]			
MRD monitoring[u]	X												X										X Q2C-Q3C[s,t]			
Response assessment													X										X Q2C-Q3C[s,t]			
ECOG[e]	X	X			X		X				X		X										X			
Vital signs[n]	X	X	X		X		X				X		X				X		X		X		X	X	X	X
Physical examination[e,o]	X	X			X		X						X						X				X		X	
Visual acuity[e]	X	X			X		X				X		X										X			

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – R/R Cohorts (Safety)																								
Cycle (28-day Cycles)	1												2									3+			
Visit Window (Days)	-30	None		± 3[a]									± 3[a]									± 3			
Cycle Day	SC	1	2	4	8	11	15	16	17	18	22	25	1	2	3	4	8	11	15	18	22	25	1	8	15	22
ECG[q]	X	X			X								X													
Adverse events	→																									→
Concomitant medications	→																									→
Study Drug Administration																										
Hu5F9-G4 premedication[z]																										
Hu5F9-G4: Safety Cohort[v]		X		X	X	X	X				X		X			X	X	X	X		X		X	X	X	X

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CR = complete remission; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; RO = receptor occupancy; R/R = Relapsed/Refractory; SC = Screening; W = week(s); WBC = white blood cell.

a. Note that ± 3 day visit window does not apply to specimen collection for correlative, PK, or RO assessments in Cycles 1 and 2 – refer to Table 7-6, Table 7-8, and Table 7-13 for details.
b. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Donor chimerism only applicable to patients with prior allogeneic hematopoietic stem cell transplant.
e. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before study drug administration; thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
f. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.

h. Time point details for correlative studies are provided in Table 7-6.
i. Time point details for PK studies (Safety Cohort) are provided in Table 7-8.
j. Not applicable to this cohort.
k. Samples to be collected before dose administration (within 72 hours for initial dose and within 24 hours for subsequent doses).
l. Time point details for RO studies (Safety Cohort – US only) are provided in Table 7-13. For visits that include bone marrow assessments (e.g., Cycle 2 Day 1), RO blood specimen should be collected on same day as RO bone marrow specimen is collected.
m. Not applicable to this cohort.
n. Vital signs prior to infusion and within 30 minutes after the end of each infusion. Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
o. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
p. Not applicable to this cohort.
q. Single ECG at screening for all patients. Triplicate ECGs within 2 hours prior to dosing and within 30 minutes of the end of Hu5F9-G4 infusion. Details are provided in Section 7.3.7.
r. If a patient is in CR, a bone marrow biopsy for response assessment is not needed unless there are clinical signs of relapse. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
s. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
t. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
u. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
v. Hu5F9-G4 should not be given on consecutive days. During Cycle 1, infuse Hu5F9-G4 over 3 hours (± 30 min); thereafter, infuse over 2 hours (± 30 min). Ongoing patients who continue in this cohort after Amendment 3 approval will go from twice weekly dosing to once weekly dosing, which is reflected in Cycle 3+ in this schedule of assessments.
w. Not applicable to this cohort.
x. Bone marrow aspirate and biopsy required for RO/CCI [redacted] studies (not a response assessment) on Day 15 for US patients only; however, bone marrow aspirate only is required in the UK at this time point. Bone marrow study must be done prior to Hu5F9-G4 infusion. The CTSC may remove this assessment during the R/R Expansion Cohort based on emerging data.
y. RO blood samples collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13 for US patients only. Beginning at Cycle 3 Day 1, pretreatment PK samples to be collected every other cycle through Cycle 13.
z. Premedication was not required for R/R Cohort (Safety) prior to Amendment 3 approval. For ongoing patients who continue in this cohort, premedication for subsequent Hu5F9-G4 treatments may be started or continued based on the treating physician's clinical judgement and the presence/severity of prior infusion-related reactions.

Table 14-7. Schedule of Assessments, R/R MDS Magrolimab Monotherapy Cohort

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R MDS Magrolimab Monotherapy Cohort																												
Cycle (28-day Cycles)	**1**												**2**										**3+**							
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3[a]**							
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**15**
Informed consent	X[b]																													
Demographics	X																													
Medical and cancer history	X																													
Entry criteria	X																													
Enrollment cohort assignment	X[b]																													
Pregnancy test	X	X[c]											X										X							
Donor chimerism[d]	X																													
CBC with differential, platelets, reticulocytes[e,f]	X	X	X		X				X	X	X	X	X							X	X	X	X							X
Peripheral blood smear[e,g]	X	X	X						X		X	X	X										X							
Serum or plasma chemistry[e]	X	X	X						X		X	X	X							X	X	X	X							X
Serum uric acid, phosphorus[e]	X	X	X						X		X																			
Haptoglobin, D-dimer, thrombin, fibrinogen[e]	X	X	X						X		X		X										X							
PT/INR, aPTT[e]	X								X				X										X							
Type and screen (ABO/Rh), DAT	X																													
Urinalysis[e]	X										X																			
Correlative studies[h]		X							X		X		X										X							
PK (Expansion Cohort)[i]		X						X	X		X	X	X							X			X Q2C[v]							
Anti-drug antibodies[j]		X							X				X										X Q2C[v]							

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R MDS Magrolimab Monotherapy Cohort																											
Cycle (28-day Cycles)	1												2									3+							
Visit Window (Days)	-30	None		± 3[a]									± 3[a]									± 3[a]							
Cycle Day	SC	1	2	3	4	5	6	7	8	11	15	22	1	2	3	4	5	6	7	8	15	22	1	2	3	4	5	6	7	15
CD47 RO blood[k]		X							X	X	X		X										X Q2C-Q3C[v]							
Bone marrow aspirate/biopsy for CD47 RO/CCI studies[l]	X																						X Q2C-Q3C[n,s]							
Bone marrow biopsy and cytogenetics[m,n]	X																						X Q2C-Q3C[n,s]							
MRD monitoring[o]	X																						X Q2C-Q3C[n,s]							
Response assessment																							X Q2C-Q3C[n,s]							
ECOG[e]	X	X							X		X	X	X										X							
Vital signs[p]	X	X	X						X		X	X	X							X	X	X	X							X
Physical examination[e,q]	X	X							X		X		X								X		X							X
ECG[r]	X	X							X				X																	
Adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Study Drug Administration																														
Magrolimab premedication		X			X				X	X																				
Magrolimab[t,u]		X			X				X	X	X	X	X							X	X	X	X							X
Azacitidine (may be given if no response at first response																							X	X	X	X	X	X	X	

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – R/R MDS Magrolimab Monotherapy Cohort																												
Cycle (28-day Cycles)	1												2										3+							
Visit Window (Days)	-30	None		± 3[a]									± 3[a]										± 3[a]							
Cycle Day	SC	1	2	3	4	5	6	7	8	11	15	22	1	2	3	4	5	6	7	8	15	22	1	2	3	4	5	6	7	15
assessment to magrolimab monotherapy)[x]																														

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MIN = minute; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2 = every 2; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; RO = receptor occupancy; R/R = relapsed/refractory; SC = screening; US = United States; W = week(s); WBC = white blood cell.

a. Note that ± 3-day visit window does not apply to specimen collection for correlative, PK, or RO assessments in Cycles 1 and 2 – refer to Table 7-6, Table 7-7, and Table 7-11 for details.
b. First dose of magrolimab must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Donor chimerism only applicable to patients with prior allogeneic hematopoietic stem cell transplant.
e. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of either study drug (magrolimab or azacitidine); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
f. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
h. Time point details for correlative studies are provided in Table 7-6.
i. Time point details for PK studies (Expansion Cohort and MDS Magrolimab Monotherapy Cohort) are provided in Table 7-7.
j. Samples to be collected before administration of either study drug (magrolimab or azacitidine), within 72 hours for initial dose and within 24 hours for subsequent doses.
k. Time point details for RO studies (US only) are provided in Table 7-11. For visits that include bone marrow assessments, RO blood specimen (US only) should be collected on same day as RO bone marrow specimen is collected.
l. Bone marrow aspirate and biopsy required for RO/CCI studies (not a response assessment) on Day 15 in US patients only; however, bone marrow aspirate only is required in the UK at this time point. Bone marrow study must be done prior to magrolimab infusion. The CTSC may remove this assessment during the R/R Expansion Cohort based on emerging data.

m. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
n. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
o. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
p. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of each study drug (magrolimab or azacitidine). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
q. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
r. Single ECG at all visits for all patients within 2 hours prior to dosing and within 30 minutes of the end of magrolimab infusion. Details are provided in Section 7.3.7.
s. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
t. Magrolimab should not be given on consecutive days. On Cycle 1 Day 1 and Day 4, infuse magrolimab over 3 hours (± 30 min); starting on Cycle 1 Day 8 and thereafter, infuse over 2 hours (± 30 min).
u. Patients will have their magrolimab dosing schedule changed from weekly to Q2 weeks beginning at Cycle 3.
v. RO blood samples (US only) collected on Day 1 of every other cycle during Cycles 3-7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13. Beginning at C3 Day 1, pretreatment PK and ADA samples to be collected every other cycle through Cycle 13.
x. R/R MDS patients who do not achieve an objective response with magrolimab monotherapy at the first protocol response assessment may have azacitidine added to magrolimab for subsequent cycles. For patients who respond to magrolimab monotherapy and then progress, azacitidine may be added to magrolimab and patients can still be continued to be treated with the combination.

Table 14-8. Schedule of Assessments, TN/U Dose Evaluation Cohort

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Dose Evaluation Cohort																														
Cycle (28-day Cycles)	1												2										3+								
Visit Window (Days)	-30	None		± 3[a]									± 3[a]										± 3								
Cycle Day	SC	1	2	3	4	5	6	7	8	11	15	22	1	2	3	4	5	6	7	8	15	22	1	2	3	4	5	6	7	8	15	22
Informed consent	X[b]																															
Demographics	X																															
Medical and cancer history	X																															
Entry criteria	X																															
Enrollment cohort assignment	X[b]																															
Pregnancy test	X	X[c]											X										X									
CBC with differential, platelets, reticulocytes[e,f]	X	X	X		X				X	X	X	X	X							X	X	X	X								X	
Peripheral blood smear[e,g]	X	X	X						X		X	X	X										X									
Serum or plasma chemistry[e]	X	X	X						X		X	X	X							X	X	X	X								X	
Serum uric acid, phosphorus[e]	X	X	X						X		X																					
Haptoglobin, D-dimer, thrombin, fibrinogen[e]	X	X	X						X		X		X										X									
PT/INR, aPTT[e]	X								X				X										X									
Type and screen (ABO/Rh), DAT	X																															
Urinalysis[e]	X										X																					

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Dose Evaluation Cohort																														
Cycle (28-day Cycles)	**1**												**2**										**3+**									
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3**									
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**
Correlative studies[h]		X							X		X		X										X									
PK (Evaluation Cohort)[i]		X						X	X		X	X	X							X			X Q2C[y]									
PK (Expansion Cohort)[j]		X						X	X		X	X	X							X			X Q2C[y]									
Anti-drug antibodies[k]		X							X				X										X Q2C[y]									
CD47 RO blood (Evaluation Cohort)[l]		X							X	X	X		X										X Q2C[y]									
CD47 RO blood (Expansion Cohort)[m]		X							X	X	X		X										X Q2C-Q3C[y]									
Bone marrow aspirate/biopsy for CD47 RO/CCI studies	X																						X Q2C-Q3C[s,t]									
Bone marrow biopsy + cytogenetics[r,s]	X																						X Q2C-Q3C[s,t]									
MRD monitoring[u]	X																						Q2C-Q3C[s,t]									
Response assessment																							Q2C-Q3C[s,t]									
ECOG[e]	X	X							X		X	X	X										X									
Vital signs[n]	X	X	X						X		X	X	X							X	X	X	X							X	X	X
Physical examination[e,o]	X	X							X		X		X								X		X								X	
DLT assessment[p]													X																			

Assessment	Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies – TN/U Dose Evaluation Cohort																														
Cycle (28-day Cycles)	**1**												**2**										**3+**									
Visit Window (Days)	**-30**	**None**		**± 3[a]**									**± 3[a]**										**± 3**									
Cycle Day	**SC**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**11**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**
Visual acuity[e]	X	X							X		X	X	X										X									
ECG[q]	X	X							X				X																			
Adverse events	→																															→
Concomitant medications	→																															→
Study Drug Administration																																
Hu5F9-G4 premedication		X			X				X	X																						
Hu5F9-G4[v,z]		X			X				X	X	X	X	X							X	X	X	X							X	X	X
Azacitidine[w]		X	X	X	X	X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X	X			

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CR = complete remission; CTSC = Clinical Trial Steering Committee; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2 = every 2; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; RO = receptor occupancy; SC = Screening; TN/U = Treatment-naïve/Unfit; US = United States; W = week(s); WBC = white blood cell.

a. Note that ± 3 day visit window does not apply to specimen collection for correlative, PK, and RO assessments in Cycles 1 and 2. Refer to Table 7-7, Table 7-10, Table 7-11, Table 7-15, and Table 7-16 for details.
b. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
c. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 7.3.1.
d. Not applicable to this cohort.
e. Pretreatment assessments for the initial dose (Cycle 1 Day 1) may be collected up to 72 hours before administration of either study drug (Hu5F9-G4 or azacitidine); thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.

f. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.
h. Time point details for correlative studies are provided in Table 7-7.
i. Time point details for PK studies (Dose Evaluation Group) are provided in Table 7-10.
j. Time point details for PK studies (Expansion Group) are provided in Table 7-11.
k. Samples to be collected before administration of either study drug (Hu5F9-G4 or azacitidine), within 72 hours for initial dose and within 24 hours for subsequent doses.
l. Time point details for RO studies (Dose Evaluation Group, US only) are provided in Table 7-15. For visits that include bone marrow assessments (e.g., Cycle 3 Day 1), RO blood specimen (US only) should be collected on same day as RO bone marrow specimen is collected.
m. Time point details for RO studies (Expansion Group, US only) are provided in Table 7-16.
n. Vital signs prior to infusion/injection and within 30 minutes after the end of each infusion/injection, before and after administration of each study drug (Hu5F9-G4 or azacitidine). Weight at screening and Day 1 of each cycle. Details are provided in Section 7.3.5.
o. Full PE at screening, symptom-directed PE thereafter. For Cycles 4 and beyond, PEs may be done only on Day 1 of each cycle, at the discretion of the Investigator.
p. DLT will be assessed throughout the first 4 weeks of study treatment for the Dose Evaluation Cohort only.
q. Single ECG at screening for all patients. For TN/U Dose Evaluation Cohort only, triplicate ECGs within 2 hours prior to infusion study drug and within 30 minutes of the end of Hu5F9-G4 infusion. Details are provided in Section 7.3.7.
r. If a patient is in CR, a bone marrow biopsy for response assessment is not required unless there are clinical signs of relapse. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment as well as CD47 receptor occupancy (US only), MRD assessment, correlative studies, and biobanking. Conventional cytogenetics to be tested per institutional standards.
s. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, the window is ± 14 days.
t. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
u. MRD monitoring to be performed on bone marrow aspirate samples obtained at the bone marrow biopsy time points.
v. Hu5F9-G4 should not be given on consecutive days. During Cycle 1, infuse Hu5F9-G4 over 3 hours (± 30 min); thereafter, infuse over 2 hours (± 30 min).
w. Azacitidine administration should be completed at least 1 hour before Hu5F9-G4 administration, on days when both drugs are administered.
x. Not applicable to this cohort.
y. RO blood samples (US only) collected on Day 1 of every other cycle during Cycle 3-7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13. Beginning at Cycle 3 Day 1, pretreatment PK and ADA samples to be collected every other cycle through Cycle 13.
z. Patients will have their Hu5F9-G4 dosing schedule changed from weekly to Q2 weeks beginning at Cycle 3.

Table 14-9. Schedule of Assessments, Rollover Cohort

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – Rollover Cohort												
Cycle (28-day Cycles)	**1**					**2**				**3+**			
Visit Window (Days)	**-30**	**± 3[a]**				**± 3[a]**				**± 3**			
Cycle Day	**SC**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Informed consent	X[b]												
Entry criteria	X												
Enrollment	X[b]												
Pregnancy test[c]		X				X				X			
CBC with differential, platelets, reticulocytes[e,f]		X		X		X		X		X		X	
Peripheral blood smear[e,g]		X				X				X			
Serum or plasma chemistry[e]		X				X				X			
Haptoglobin, D-dimer, thrombin, fibrinogen[e]		X				X				X			
PT/INR, aPTT[e]		X				X				X			
PK[i]		X				X				X Q2C[i]			
Anti-drug antibodies[k]		X				X				X			
Bone marrow biopsy and cytogenetics[r,s]										Q2C[s,t]			
Response assessment										Q2C-Q3C[s,t]			
ECOG [e]		X				X				X			
Vital signs[n]		X				X				X			
Physical examination[e,o]		X				X				X			
Adverse events	→												→

Assessment	Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies – Rollover Cohort																							
Cycle (28-day Cycles)	**1**								**2**								**3+**							
Visit Window (Days)	**-30**	**± 3[a]**							**± 3[a]**								**± 3**							
Cycle Day	**SC**	**1**		**8**		**15**		**22**		**1**		**8**		**15**		**22**		**1**		**8**		**15**		**22**	
Concomitant medications	→																							
Study drug administration – once weekly or twice weekly[v]																								
Cycle Day	**SC**	**1**		**8**		**15**		**22**		**1**		**8**		**15**		**22**		**1**		**8**		**15**		**22**	
Magrolimab – once weekly[v]		X		X		X		X		X		X		X		X		X		X		X		X	
Cycle Day	**SC**	**1**	**4**	**8**	**11**	**15**	**18**	**22**	**25**	**1**	**4**	**8**	**11**	**15**	**18**	**22**	**25**	**1**	**4**	**8**	**11**	**15**	**18**	**22**	**25**
Magrolimab – twice weekly[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ABO = any of the four blood groups A, B, AB, and O comprising the ABO system; aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; CR = complete remission; DAT = direct antiglobulin test; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; PE = physical examination; PK = pharmacokinetics; PT/INR = prothrombin time/international normalized ratio; Q2C = every 2 cycles; Q3C = every 3 cycles; Rh = Rhesus factor; SC = Screening; W = week(s); WBC = white blood cell.

a. Note that ± 3 day visit window does not apply to specimen collection for PK assessments in Cycle 2 – refer to Table 14-13 and Table 14-9 for details.
b. First dose of magrolimab on this study must be given within 30 days of signing informed consent.
c. Patient must have a negative pregnancy test within 72 hours before study drug administration on Day 1 of each cycle.
d. Not applicable to this cohort.
e. Pretreatment assessments for the initial dose on this study may be collected up to 72 hours before study drug administration; thereafter, pretreatment assessments are to be collected within 24 hours prior to study drug administration.
f. Samples for CBC must be collected at least once per cycle. However, CBC sample collection to ensure a WBC level < 20×10^3/mcL may be deferred, based on Investigator assessment of the patient's WBC kinetics. Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level < 20×10^3/mcL.
g. Peripheral smears will be collected prior to selected study drug infusions/injections and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. Details are provided in Section 7.3.3.

h. Not applicable to this cohort.
i. Time point details for PK studies are provided in Table 7-14. Starting with Cycle 3 Day 1, samples will be collected every other cycle through Cycle 13 while patient is receiving magrolimab treatment.
j. Not applicable to this cohort.
k. Samples to be collected before dose administration (within 72 hours for initial dose and within 24 hours for subsequent doses).
l. Not applicable to this cohort.
m. Not applicable to this cohort.
n. Vital signs prior to infusion and within 30 minutes after the end of infusion. Weight at Day 1 of each cycle. Details are provided in Section 7.3.5.
o. Full PE at screening, symptom-directed PE thereafter.
p. Not applicable to this cohort.
q. Not applicable to this cohort.
r. At each bone marrow time point, both trephine (biopsy) and aspirate samples are to be collected for response assessment, MRD assessment, correlative studies, and biobanking. Cytogenetic assessments (per institutional standards) are required only for MDS patients or those who had prior cytogenetic assessments in the previous Phase 1 study (SCI-CD47-002).
s. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
t. After Cycle 7 Day 1, bone marrow biopsies will be collected every 3 cycles (i.e., Cycle 10 Day 1, Cycle 13 Day 1, etc.).
u. Not applicable to this cohort.
v. Magrolimab should not be given on consecutive days. For Rollover patients, magrolimab may be infused over 2 hours (± 30 min). Rollover patients may continue twice-weekly dosing from their previous study or transition to once-weekly dosing as described in Section 3.4.
w. Not applicable to this cohort.
x. Not applicable to this cohort.
y. Not applicable to this cohort.

Table 14-10. Correlative Studies Sample Time Points, R/R Safety Cohort

Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies R/R Safety Cohort							
Phase 1b	**Cycle 1**			**Cycle 2**	**C3+**	**EOT**	**LTFU**
Day	**1**	**8**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X[b]	X	X[c]	X	X[b,c]	X	X[d]
1 hour (± 15 min) after end of Hu5F9-G4 infusion	X	X					

Abbreviations: C = cycle; EOT = end-of-treatment; LTFU = long-term follow-up; min = minute(s); R/R = Relapsed/Refractory.

a. Pretreatment specimens may be collected up to 72 hours before administration of either study drug (Hu5F9-G4 or azacitidine).

b. Sample to be collected before azacitidine infusion.

c. When bone marrow biopsies are performed, collect blood samples ± 7 days from bone marrow collection date; otherwise, collect blood samples ± 7 days from Day 1 of each treatment cycle.

d. Obtained at the time of disease progression or relapse.

Table 14-11. Pharmacokinetic Assessments, R/R Safety Cohort

Study 5F9005: A Phase 1b Trial of Magrolimab Monotherapy or Magrolimab in Combination with Azacitidine in Patients with Hematological Malignancies R/R Safety Cohort																			
	Cycle 1										**Cycle 2**							**C3+**	**EOT**	**SFU**
Day	**1**	**4**	**8**	**11**	**15**	**16**	**17**	**18**	**22**	**25**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Q2C[b]	X	X
1 hour (± 15 min) after end of magrolimab infusion	X	X	X	X	X				X	X	X			X						

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); R/R = Relapsed/Refractory; SFU = safety follow-up, Q2C = every 2 cycles.

Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. On days when study treatment is administered, collect pretreatment specimens within 12 hours prior to study drug administration; on days when no study drug is administered, collect specimens at the same time of day (± 8 hours) as the previous collection day.

b. Pretreatment samples to be collected every other cycle beginning with Cycle 3 through Cycle 13.

Table 14-12. Pharmacokinetic Assessments, TN/U Dose Evaluation Cohort

Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies **TN/U Dose Evaluation Cohort**										
Day	**Cycle 1**					**Cycle 2**		**C3+**	**EOT**	**SFU**
	1	**7**	**8**	**15**	**22**	**1**	**8**	**1**	**—**	**—**
Pretreatment [a]	X[b]		X	X	X	X[b]	X	X Q2C[d]	X	X
30 min (± 15 min) after end of azacitidine injection/ infusion[c]	X	X				X		X Q2C[d]		
1 hour (± 15 min) after end of Hu5F9-G4 infusion	X		X	X	X	X		X Q2C[d]		

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); Q2C = every 2 cycles; SFU = safety follow-up; TN/U = Treatment-naïve/Unfit.
Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or Hu5F9-G4) is started.
c. Azacitidine will be given at least 1 hour before Hu5F9-G4 on days on which both treatments are to be given.
d. Samples to be collected every other cycle beginning with Cycle 3 through Cycle 13.

Table 14-13. Pharmacokinetic Assessments, Rollover Cohort

Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies **Rollover Cohort**				
	Cycle 1	**Cycle 2+**	**EOT**	**SFU**
Day	**1**	**1**	**—**	**—**
Pretreatment[a]	X	X Q2C[b]	X	X

Abbreviations: EOT = end-of-treatment; PK = pharmacokinetic, Q2C = every 2 cycles; SFU = safety follow-up.
Note: PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site must be flushed with 10 mL of saline.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Starting with Cycle 3 Day 1, pretreatment PK samples are to be collected every other cycle while the patient is receiving Hu5F9-G4 treatment through Cycle 13.

Table 14-14. CD47 Receptor Occupancy Sample Time Points, R/R Safety Cohort

Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies
R/R Safety Cohort

Phase 1b	**Cycle 1**										**Cycle 2**							**C3+**	**EOT**	**SFU**
Day	**1**	**4**	**8**	**11**	**15**	**16**	**17**	**18**	**22**	**25**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**1**	**—**	**—**
Pre-treatment (or non-treatment day)[a]	X	X	X	X	X[b]	X	X	X	X	X	X[b]	X	X	X	X	X	X	X Q2C-Q3C[b,c]	X	X
1 hour (± 15 min) after end of Hu5F9-G4 infusion	X	X	X	X	X				X	X	X			X						

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); Q3C = every 3 cycles; RO = receptor occupancy; R/R = Relapsed/Refractory; SFU = safety follow-up; UK = United Kingdom; US = United States.
Note: RO is a US-only sub-study; RO specimens are not required for UK patients.

a. On days when study treatment is administered, collect pretreatment specimens within 12 hours prior to study drug administration; on days when no study drug is administered, collect specimens at the same time of day (± 8 hours) as the previous collection day.
b. For visits that include bone marrow assessments, RO blood specimen should be collected on same day as RO bone marrow specimen is collected.
c. RO blood samples collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13.

Table 14-15. CD47 Receptor Occupancy Sample Time Points, TN/U Dose Evaluation Cohort

Study 5F9005: A Phase 1b Trial of Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination with Azacitidine in Patients with Hematological Malignancies
TN/U Dose Evaluation Cohort

Phase 1b	**Cycle 1**				**Cycle 2**	**C3+**	**EOT**	**SFU**
Day	**1**	**8**	**11**	**15**	**1**	**1**	**—**	**—**
Pretreatment (or non-treatment day)[a]	X[b]	X	X	X	X[b]	X Q2C-Q3C[b,c,d]	X	X
1 hour (± 15 min) after end of Hu5F9-G4 infusion	X							

Abbreviations: C = cycle; EOT = end-of-treatment; min = minute(s); RO = receptor occupancy; SFU = safety follow-up; TN/U = Treatment-naïve/Unfit.
Note: RO is a US-only sub-study; RO specimens are not required for UK patients.

a. Collect pretreatment specimens within 12 hours prior to study drug administration.
b. Pretreatment sample to be collected before either study drug (azacitidine or Hu5F9-G4) is started.
c. For visits that include bone marrow assessments, RO blood specimen should be collected on same day as RO bone marrow specimen is collected.
d. RO blood samples collected on Day 1 of every other cycle during Cycles 3 through 7, then every 3 cycles (same day as bone marrow RO samples) after Cycle 7 through Cycle 13.

Appendix G: Pandemic Risk Assessment And Mitigation Plan

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

These risks can be summarized as follows:

1. Study drug supplies to patients and sites:

    a. Patients may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to continue receiving the study drug as planned per protocol.
    Mitigation plan: Study drug supplies may be provided to the patient from the site without a clinic visit, once it is confirmed that the patient may safely continue on study drug as determined by the Principal Investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study patients if permitted by the local ethics committee/institutional review board/regulatory authority as applicable and with Sponsor's approval.
    b. Shipments of study drug could be delayed because of transportation issues. Without study drug, the patient would not be able to continue receiving the study drug as planned per protocol.
    Mitigation plan: The site's study drug inventory should be closely monitored. Site staff should notify the Sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The Sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2. Patient safety monitoring and follow-up:

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

        i. Confirm if patient has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow up on any unresolved AEs/SAEs.
        ii. Review the current list of concomitant medications and document any new concomitant medications.
        iii. If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.
        iv. If applicable, confirm the patient's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).
        v. If applicable, remind the patient to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

    b. Patients may be unable or unwilling to travel to the site for planned assessments (e.g., safety blood draws); hence samples may not be sent for central laboratory analyses.
    Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c. Patients may be unable or unwilling to attend the study visit to sign an updated informed consent form version.
   Mitigation plan: The site staff will follow their approved consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/institutional review board. 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 patient has a diagnosis of COVID-19 while on this clinical study, study drugs may be held until clinical improvement or resolution in accordance with the treating physician's judgement and general magrolimab/azacitidine dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Patients with a COVID-19 infection while participating in a clinical trial will have this event documented as an adverse event in the clinical database.

3. Protocol and monitoring compliance:

   a. Protocol deviations may occur in case scheduled visits cannot be conducted as planned per protocol.
      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol because of the pandemic must be reported in the eCRF and described in the clinical study report. Any remote study visits that are conducted in lieu

of clinic visits because of the pandemic will be documented as a protocol deviation related to the pandemic.

b. Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.
Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on site, must be tracked centrally and updated on a regular basis.

4. Missing data and data integrity:
There may be an increased amount of missing data because of patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.
Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (e.g., modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.
Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit risk assessment of magrolimab in study patients remains unchanged.

Protocol 5F9005-Amendment 9

ELECTRONIC SIGNATURES

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