STATISTICAL ANALYSIS PLAN

Study Title:	ENHANCE: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome
Name of Test Drug:	Magrolimab (Hu5F9-G4) (GS-4721)
Study Number:	5F9009
Protocol Version (Date):	Amendment 7 (27 July 2022)
Analysis Type:	Interim Analysis
Analysis Plan Version:	1.0
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantitation
BMI	body mass index
BSA	body surface area
CI	confidence interval
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	duration of complete remission
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EQ-5D-5L	5-Level EuroQol 5 Dimensions
EQ VAS	EQ visual analogue scale
EOT	end of treatment
ET	early termination
FACT-Anemia	Functional Assessment of Cancer Therapy – Anemia
HLT	high-level term
HLGT	high-level group term
HRQoL	health-related quality of life
IA	Interim analysis
ICH	International Conference on Harmonization
ID	identification
ITT	Intent-to-Treat
IPSS-R	Revised International Prognostic Scoring System
IWG	International Working Group
IXRS	interactive voice/web/mobile response system (IXRS)

LLT	lower-level term
LOQ	limit of quantitation
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MST	MedDRA Search Term
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PR	partial remission
PRO	patient-reported outcome
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PT	preferred term
Q1, Q3	first quartile, third quartile
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
StD	standard deviation
SE	standard error
SI (units)	international system of units
SMQ	Standardised MedDRA Queries
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the first interim efficacy analysis for Study 5F9009, which is to be performed 8 months after 348 patients are randomized. The purpose of this interim analysis is to evaluate the efficacy of magrolimab in combination with azacitidine versus azacitidine plus placebo, based on the analyses of primary endpoints complete remission (CR) rate as well as overall survival (OS). The stopping criteria for the interim analysis may be found in Section 2 of this SAP.

This SAP is based on the study protocol amendment 7 dated 27 July 2022 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the interim analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The 2 primary objectives of this study are as follows:

- To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated patients with intermediate/high/very high risk myelodysplastic syndrome (MDS) by Revised International Prognostic Scoring System (IPSS-R) as measured by CR rate

- To evaluate the survival benefit of magrolimab + azacitidine compared with that of azacitidine + placebo

The secondary objectives of this study are as follows:

- To evaluate the duration of CR (DCR) of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate the objective response rate (ORR) and duration of response (DOR) of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate red blood cell (RBC) transfusion independence rate of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo as measured by event-free survival (EFS)

- To evaluate the CR of magrolimab + azacitidine compared with that of azacitidine + placebo in TP53 mutant population

- To assess the level of minimal residual disease (MRD) negativity of magrolimab + azacitidine compared with that of azacitidine + placebo

- To assess time to transformation to acute myeloid leukemia (AML) of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo, as measured by progression free survival (PFS)

- To assess the safety and tolerability of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate pharmacokinetics (PK) of magrolimab

- To evaluate the immunogenicity of magrolimab

- To evaluate the health-related quality of life (HRQoL) of magrolimab + azacitidine compared with that of azacitidine + placebo, as measured by Functional Assessment of Cancer Therapy – Anemia (FACT-Anemia) response rate

The exploratory objectives of this study are as follows:

- To evaluate transplantation rate of magrolimab + azacitidine compared with that of azacitidine + placebo

- To assess time to first transplant of magrolimab + azacitidine compared with that of azacitidine + placebo

- To evaluate the duration of RBC transfusion independence of magrolimab + azacitidine compared with that of azacitidine + placebo

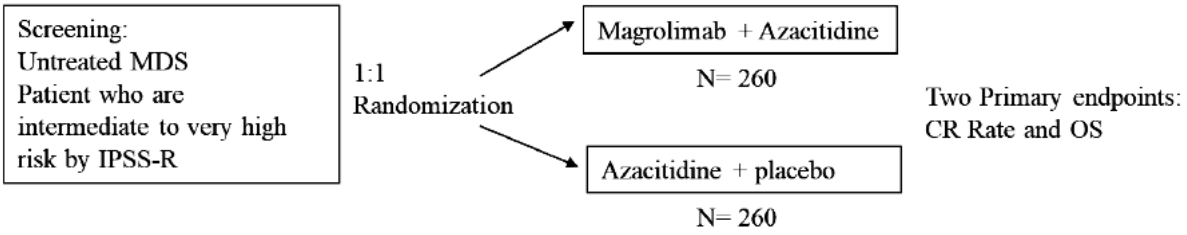
- To evaluate RBC transfusion independence of magrolimab + azacitidine compared with that of azacitidine + placebo among all patients irrespective of RBC transfusion-dependence at baseline

- To evaluate the HRQoL of magrolimab + azacitidine compared with that of azacitidine + placebo, as measured by score change from baseline in FACT-Anemia, Patient Global Impression of Severity/Patient Global Impression of Change (PGIS/PGIC), and 5-level EuroQol 5 dimensions (EQ-5D-5L) questionnaires

- To assess biomarkers including but not limited to, immune cell recruitment, immune cell signaling, and bone marrow penetration of magrolimab

1.2. Study Design

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



The primary analysis of CR rate will be conducted 8 months after 348 patients are randomized. Patient participation will include screening, treatment, and follow-up. Screening will last up to 30 days before the first dose of study treatment, during which time the patient's eligibility and baseline characteristics will be determined. Patients will receive study treatment per the dose schedule in Table 1-1. No cross-over between arms is allowed. Study treatment may be continued until disease progression (including treatment failure by International Working Group [IWG] 2006 criteria or relapse after partial/complete remission [PR/CR]), loss of clinical benefit, or unacceptable toxicities occur. In case patients discontinue the study treatment due to reasons other than disease progression, patients will be followed up for response assessments until documented disease progression occurs. For patients who come off the study treatment to receive a stem cell transplant (SCT), follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs or start of new anticancer therapy, whichever occurs first. Then patients will be observed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

The study treatments within each arm are described in Table 1-1:

Table 1-1. Dose Level and Schedule

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

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

Treatment with azacitidine as standard of care is recommended for a minimum of 6 cycles. Therefore, in this study, patients without evidence of disease progression (including treatment failure by IWG 2006 criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicity should continue azacitidine for at least 6 cycles. 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 Protocol Section 5.7.

The schedules of assessments are provided in Protocol Section 4.3.

1.3. Sample Size and Power

The study will randomize approximately 520 patients in total into 2 treatment arms at a 1:1 ratio, determined by formal hypothesis testing performed on 2 primary efficacy endpoints: CR rate and OS, with family-wise Type I error controlled at a 2-sided significance level of 0.05. The primary analysis of the CR rate will be conducted at 8 months after 348 patients are randomized. Based on the first 348 randomized patients, the study has 95% power to reject the null hypothesis that the CR rates in the 2 treatment arms are the same at the 2-sided 0.03 significance level, assuming the true CR rate is 20% in the control arm and 39% in the experimental arm (i.e., a 19% improvement).

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

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

2. TYPE OF PLANNED ANALYSIS

2.1. DMC Interim Analyses

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study, perform interim reviews of safety data at regular intervals, and provide recommendation to Gilead on whether the nature, frequency, and severity of AEs associated with study treatment warrant the early termination (ET) of the study in the best interests of the patient, whether the study should continue as planned, or whether the study should continue with modifications.

In addition, the DMC will review the results from the 2 planned interim efficacy analyses. Based on the pre-specified superiority and futility rules, the DMC may make recommendations to Gilead on whether the study should be stopped early due to overwhelming efficacy, be terminated for futility, or continue as planned. Efficacy superiority boundaries are specified below.

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

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, the ultimate decision on whether to implement or act based upon the recommendations of the DMC will be made by Gilead.

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

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

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

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

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

In addition to the 2 planned interim efficacy analyses, the DMC will convene to review interim safety analysis results periodically, or convene for any ad hoc data review meeting, if deemed necessary.

The Lan-DeMets approach with O'Brien-Fleming type alpha spending function will be used for the first and second interim analyses, and final analysis for OS. The stopping boundaries at each analysis time are provided in Table 2-1.

Table 2-1. Stopping Boundaries for Efficacy Superiority Analyses

Planned Analyses		Efficacy Analysis	Events (%)	Stopping Boundary	
				HR[a]	Two-sided p-value
First IA		CR	-	-	0.03
If the test of CR is rejected in 1st IA	First IA	OS	158 (43%)	0.600	0.0013*
	Second IA	OS	257 (71%)	0.738	0.0148*
	Final Analysis	OS	364 (100%)	0.811	0.0453*
If the test of CR fails to be rejected in first IA	First IA	OS	158 (43%)	0.552	0.0002*
	Second IA	OS	257 (71%)	0.700	0.0043*
	Final Analysis	OS	364 (100%)	0.781	0.0186*

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

The primary efficacy endpoint of OS will be tested for superiority first at the significance level specified in Table 2-1. If the superiority of OS is established, key secondary efficacy endpoints listed in Table 2-2 will be tested for superiority. To strongly control the overall type I error across the testing of the key secondary efficacy endpoints, a hierarchical testing strategy will be performed with a predefined order as listed below. For each key secondary endpoint, an O'Brien-Fleming boundary will be derived based on the information fraction at each interim analysis and the remaining type I error respectively per Table 2-2.

Table 2-2. Definition of Information Fraction

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

AML = acute myeloid leukemia; EFS = event-free survival; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; MRD = minimal residual disease; ORR = objective response rate; OS = overall survival, PFS = progressionfree survival
*The information fraction at each analysis timepoint will be based on the actual observed OS events

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

- ORR
- RBC transfusion independence rate
- EFS
- CR in TP53 mutant population

- MRD-negative response
- Time to transformation to AML
- PFS
- FACT-Anemia response rate

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

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

2.2. Optional Interim Analysis Performed by Sponsor

At the time of the first DMC interim efficacy analysis, if the null hypothesis on CR rate is rejected at a 2-sided significance level of 0.03, or if the null hypothesis on CR rate is not rejected at a 2-sided significance level of 0.03 but the null hypothesis on OS is rejected at the allocated significance level at the interim analysis, the Sponsor study team may be unblinded for all randomized patients by the data cutoff date and conduct additional interim analyses. Gilead Oversight Committee will make the decision on whether study team will be unblinded. Duration of CR will be estimated for each arm using Kaplan-Meier (KM) estimates, including median duration with 2-sided 95% CIs. Safety analysis will be conducted. Other secondary endpoints may be included in the analysis scope. However, no formal hypothesis testing will be conducted for any key secondary endpoint at the first interim analysis, unless the testing on OS is rejected.

2.3. Final Analysis

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

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of patients in each category will be presented; for continuous variables, the number of patients (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all patients in the Intent-to-Treat (ITT) Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the patients to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of patients eligible for inclusion will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set includes all patients who were randomized in the study, with treatment assignment designated according to the treatment to which the subject is randomized. This is the primary analysis set for efficacy analyses.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all randomized patients who took at least 1 dose of any study treatment, with treatment assignment designated according to the actual treatment received. This is the primary analysis set for safety analyses.

3.1.3. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all patients who took at least 1 dose of Magrolimab, and have at least 1 measurable post-treatment serum concentration of magrolimab. This is the primary analysis set for all PK analyses.

3.1.4. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all patients who took at least 1 dose of Magrolimab, and have at least 1 reported anti-drug antibody (ADA) result.

3.2. Subject Grouping

For analyses based on the ITT Analysis Set, patients will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, patients will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set and the Immunogenicity Analysis Set, patients will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Patients will be randomized in a 1:1 ratio to treatment arms using an interactive voice/web/mobile response system (IXRS) with a stratified randomization schedule. Stratification will be based on the following variables:

- geographic region (US versus ex-US sites)
- cytogenetic risk status (very good/good/intermediate versus poor/very poor versus unknown) according to IPSS-R
- percentage of bone marrow blasts (≥ 10% versus < 10% blasts)

If bone marrow blasts stratification factor value is not recorded in the clinical database, the value recorded in the IXRS will be used for analyses. If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses. Additionally, stratification discrepancies will be reviewed and assessed. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses when applicable, as specified in Section 6. If there is an imbalance in presumed prognostic baseline characteristics between treatment groups, efficacy evaluations may be performed that include these baseline values in efficacy analysis models as covariates; these evaluations will be considered as sensitivity analyses.

In the situation where there is insufficient information in a stratum, pooling of the stratum with the smallest adjacent stratum for stratified analyses will be considered.

3.4. Examination of Subject Subgroups

The primary efficacy endpoints will be examined using the following subgroups:

- geographic region (US versus ex-US sites)

- cytogenetic risk status (very good/good/intermediate versus poor/very poor versus unknown) according to IPSS-R

- percentage of bone marrow blasts (≥ 10% versus < 10% blasts)

The analysis may also be conducted in the subgroups by TP53 mutational status (mutant and wild type), age (< 65 years and ⩾ 65 years; < 75 years and ⩾ 75 years), sex at birth (male and female), race (White, Asian, Black, Other), IPSS-R (Intermediate, High, Very high), baseline ECOG (0, 1, and 2), disease type (non therapy related vs therapy related), peripheral blood, hemoglobin, and platelet count.

If the number of subjects in one or more subgroups is too small to conduct the analysis, some subgroups will be pooled for the analysis.

3.5. Multiple Comparisons

The Multiple Comparisons are provided in Section 2.1.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for disease diagnosis is described in Section 5.3, for the start date of new MDS therapy in Section 6.1.1, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4. Imputation rules adopted in the efficacy analyses are specified in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then “15” will be imputed as the day of birth

- If only year of birth is collected, then “01 July” will be imputed as the day and month of birth

- If year of birth is missing, then date of birth will not be imputed

In general, age collected at the randomization (in years) will be used for analyses and presented in listings. If age at randomization is not available for a subject, then age derived based on date of birth and the randomization visit date will be used instead. For screen failures or unrandomized patients, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of any study drug, which is the date of the first dose of magrolimab/placebo, or azacitidine, whichever occurs first and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration. If the subject is randomized but not dosed, the randomization date will be study day 1.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis windows for lab are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Lab By-visit Summaries

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1[a]
Week 1	7	1[b]	10
Week 2	14	11	17
Week 3	21	18	24
Week 4	28	25	31
Week 5	35	32	38
Week 6	42	39	45
Week 7	49	46	52
Week 8	56	53	62
Week 10	70	63	76
Week xx	xx*7	(xx-1)*7	xx*7+6

a Prior to first dose date time.
b Post first dose date time.

The analysis windows for PRO are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for By-visit Summaries of PRO assessments

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week xx	xx*7	xx*7-13	xx*7+14

Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of any study drug will be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of any study drug will be included in determining the maximum postbaseline toxicity grade and anti-magrolimab antibody status.
- Response assessments and PRO assessments performed at unscheduled visits after the date of randomization will be included in the analyses of the efficacy endpoints and the PRO related endpoints, respectively.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug (and prior to first dosing time) will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the arithmetic average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.

- For postbaseline values:

  — The record closest to the nominal day for that visit will be selected.

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — If there is more than 1 record on the selected day, the arithmetic average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator and overall. The summary will present the number and percentage of patients enrolled. For each column, the denominator for the percentage calculation will be the total number of patients analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of patients in the stratum will be the total number of enrolled patients. If there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of patients with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group. This summary will present the number of patients screened and the number of patients who met all eligibility criteria but were not randomized with reasons patients not randomized in total; and the number of patients in each of the categories listed below by treatment group:

- ITT Analysis Set
- Safety Analysis Set
- Continuing study treatment (magrolimab/placebo, azacitidine)
- Discontinued study treatment (magrolimab/placebo, azacitidine) with reasons for discontinuation
- On-going in study (including long-term follow-up and survival follow-up)
- Discontinued study with reasons for discontinuation

For the status of study drug and study completion and reasons for discontinuation, the number and percentage of patients in each category will be provided. The denominator for the percentage calculation will be the total number of patients in the ITT Analysis Set corresponding to that column. In addition, a CONSORT flow diagram will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for study drug discontinuation
- Reasons for study discontinuation

4.2. Extent of Study Drug Exposure

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and relative dose intensity. Each variable will be calculated for magrolimab/placebo, and azacitidine separately. No formal statistical testing between treatment group is planned.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to each study drug (magrolimab/placebo, and azacitidine) will be defined for a subject as last dosing date minus first dosing date plus 1 day, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

The total duration of exposure to each study drug will be summarized using descriptive statistics for continuous variables, as well as using the number (i.e., cumulative counts) and percentage of patients exposed for at least the following time periods: 1 day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks, etc.

For azacitidine, the number of cycles patients are exposed will be summarized using descriptive statistics, and the number and percentage of patients who received at least 1, 2 …, 6 cycles will be presented.

The number and percentage of patients who have dose reduction for azacitidine or delay for each drug and the reasons will be summarized.

4.2.2. Relative Dose Intensity

Relative dose intensity is the percentage of the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

For magrolimab/placebo:

The relative dose intensity is the percentage of the total amount of study drug administered relative to the total amount of study drug expected to be administered. For doses administered from Day 11 (at 30 mg/kg IV) and onward will be expressed as a percentage using the following formula:

$$\text{Relative dose intensity } (\%) = \left(\frac{\text{Cumulative dosage received (in mg/kg)}}{\text{Total assigned Magrolimab/Placebo dosage (in mg/kg)}}\right) \text{x } 100$$

Cumulative dosage (mg/kg) received for each subject is defined as the sum of all delivered dosages (mg/kg) of all infusions the subject received from Day 11 and onward.

Total assigned dosage (mg/kg) for each subject is defined as the product of the assigned dose of magrolimab/placebo (30 mg/kg) and number of doses the subject was scheduled to receive during the subject's treatment period (number of infusions administered plus the number of infusions not administered).

A separate summary for the relative dose intensity of magrolimab/placebo administered for Day 1/Day 4 (at 1 mg/kg IV) and re-priming visits of Day 1/Day 4, Day 8 (at 15 mg/kg IV) and re-priming visits of Day 8 will be provided, respectively. The calculation will be similar to that of from Day 11 and onward (at 30 mg/kg IV).

For azacitidine:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Total Amount of Azacitidine Administered}}{\text{Azacitidine Expected to be Administered on Treatment}}\right) \text{x } 100$$

For each study drug, descriptive statistics for the relative dose intensity with the number and percentage of patients belonging to relative dose intensity categories (eg, < 75%, ≥ 75 to < 90%, ≥ 90%) will be provided by treatment group for the Safety Analysis Set.

A by-subject listing of each study drug administration will be provided by treatment group, subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Patients who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized. The summary will present the number and percentage of patients who did not meet at least 1 eligibility criterion and the number of patients who did not meet specific criteria by treatment group based on the ITT Analysis Set. A by-subject listing will be provided for those patients who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that patients did not meet and related comments, if collected.

Protocol deviations occurring after patients entered the study are documented during routine monitoring. The number and percentage of patients with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the ITT Analysis Set. A by-subject listing will be provided for those patients with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A summary of reasons for discontinuing study drug or study due to COVID-19 will be provided by treatment group and overall, similar to the summary described in the subject enrollment and disposition section (see Section 4.1).

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A summary of important protocol deviations due to COVID-19 will be provided, similar to the summary described in the protocol deviations section (Section 4.3).

The number and percentage of subjects with non-important protocol deviations related to COVID-19 will be summarized by treatment group.

A by-subject listing will be provided for subjects with important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

An overall summary of the number and percentage of subjects with at least 1 missed scheduled or virtual visits due to COVID-19 will be provided by treatment group and overall. The denominator for the percentage calculation will be the total number of subjects in the safety population for that column.

4.4.4. Adverse Events Due to COVID-19

A by-subject listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex at birth, race, ethnicity, geographic region) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], Body Surface Area [BSA; in m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The summary of demographic data will be provided for the ITT Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by treatment group and subject ID number.

5.2. Other Baseline Characteristics

Other baseline characteristics include but are not limited to: ECOG, BM blast, Cytogenetic Risk Status, and TP53 mutational status. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The summary of these baseline characteristics will be provided for the ITT Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

MDS Diagnosis history will be summarized by treatment group and overall by the number and percentage of patients with each prepopulated categories including but not limited to: IPSS-R, WHO Classification of MDS, Therapy-related MDS, RBC Transfusion Independence. The summary will be provided for the ITT Analysis Set. Time since diagnosis (months) will be calculated by (date of randomization – date of diagnosis) / 30.4375. Time since diagnosis will be summarized using summary statistics for a continuous variable. No formal statistical testing is planned. A by-subject listing of disease-specific medical history will be provided. In deriving the time since disease diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoints

6.1.1. Definition of Primary Efficacy Endpoints

The two primary efficacy endpoints of this study are CR rate and OS.

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

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

The date of the last known alive will be determined by selecting the last available visit date across all datasets.

When the date of initiation of a new anticancer therapy other than the study treatment or the date of SCT is incomplete or missing, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month.
- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the month for the last adequate disease assessment if the year of new anticancer therapy and the year of last adequate disease assessment are the same.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoints

The first primary efficacy hypothesis to be tested is that there is no difference between magrolimab + azacitidine (experimental arm) and placebo + azacitidine (control arm) in CR rate for the first 348 randomized patients. Using CR rate_{exp} and CR rate_{ctrl} to denote the CR rates for the experimental arm and control arm, respectively, the statistical hypotheses to be tested in this study will be:

H_0: CR rate_{exp} = CR rate_{ctrl}

H_1: CR $\text{rate}_{exp} \neq$ CR rate_{ctrl} (experimental arm is not equal to control arm in terms of CR rate)

The second primary efficacy hypothesis to be tested is that there is no difference between magrolimab + azacitidine (experimental arm) and placebo + azacitidine (control arm) in OS for patients. Using $S_{exp}(t)$ and $S_{ctrl}(t)$ to denote the OS distribution functions of the experimental arm and control arm, respectively, the statistical hypotheses to be tested in this study will be:

H_0: $S_{exp}(t) = S_{ctrl}(t)$ at all time points t

H_1: $S_{exp}(t) \neq S_{ctrl}(t)$ (experimental arm is not equal to control arm in terms of OS for some $t > 0$)

6.1.3. Analysis of the Primary Efficacy Endpoints

The primary analysis of CR rates will compare the CR rates of two treatment groups in the first 348 randomized patients in the ITT Analysis Set using the Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors at randomization. The odds ratio comparing the 2 arms adjusted for the stratification factors will be presented along with 95% confidence interval (CI).

The point estimate of the CR rate and the corresponding 2-sided exact 95% CI based on the Clopper-Pearson method will be provided for each arm. Patients, who are randomized but have no on-study response assessment or receive any new anticancer therapy including SCT prior to achieving CR, will be considered as non-responders.

If the CR rate of experimental arm is higher than that of control arm and 2-sided p-value from the stratified CMH test using SAS procedure freq is less than 0.03, the null hypothesis of CR rate in Section 6.1.2 will be rejected and the superiority of experimental arm to control arm in terms of CR rate is established.

The primary analysis of OS will compare the OS distributions of two treatment groups using the stratified log-rank test, stratified by the stratification factors at randomization for the ITT Analysis Set. Medians, Q1, Q3 of the OS distributions, and the proportion of patients who are alive at 6, 12, 18 and 24 months from randomization will be estimated along with corresponding 95% CIs using the Kaplan-Meier method. Kaplan-Meier curves will be provided by treatment group.

If the median survival time of experimental arm is longer than that of control arm and two-sided p-value from the stratified log-rank test using SAS procedure Lifetest is less than the cutoff p-values based on observed number of OS events by the data cutoff date as mentioned in Section 2.1, the null hypothesis of OS in Section 6.1.2 will be rejected and the superiority of experimental arm to control arm in terms of OS is established.

In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model stratified by the stratification factors. For pre-specified non-binding futility analysis boundary of HR=0.99 at the first interim analysis if CR is not statistically significant, the HR from the Cox model will be used to check whether the futility boundary has been crossed or not.

6.1.4. Follow-up Time

The follow-up time for OS is defined as the interval from date of randomization to the death date for patients who died on or prior to the data cutoff, or from the date of randomization to the last known alive date for patients who are alive up to the data cutoff. The follow-up time will be summarized by treatment groups using descriptive statistics including median and range

(minimum and maximum). It will also be summarized by treatment groups using statistics such as median, Q1, Q3 with corresponding 95% CIs estimated with the reverse Kaplan-Meier (K-M) method. The reverse K-M model switches the event/censoring indicators of patients in the original OS analysis with Kaplan-Meier method. It considers patients lost to follow-up or administratively censored due to analysis data cut as achieving the full follow up, and the full follow up time of those patients who died could not be observed as it is 'censored' by death.

6.1.5. Sensitivity Analysis of the Primary Efficacy Endpoint

To assess the robustness of the primary CR results, the following sensitivity analysis will be performed:

- CR will be analyzed using stratification factors in IXRS for the Cochran-Mantel-Haenszel (CMH) test.

To assess the robustness of the primary OS results, the following sensitivity analysis will be performed:

- OS will be analyzed on the same population as CR analysis (ie, the first randomized 348 patients in the ITT Analysis Set).

- OS will be analyzed using the stratified log-rank test, stratified by the stratification factors in IXRS. In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model stratified by the stratification factors in IXRS.

6.1.6. Exploratory Analysis of the Primary Efficacy Endpoint

An exploratory analysis may be performed to investigate the potential prognostic factors influencing the primary efficacy endpoint OS using the Cox regression model approach. The variables with prognostic potential will be included in the model as covariates to identify plausible significant factors on OS, such as age, gender, percentage of bone marrow blast, ECOG, etc.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Duration of CR: The DCR is measured from the time measurement criteria are first met for CR to the first date of relapse or death, whichever occurs earlier. Those who are not observed to relapse or die will be censored at their last response assessment date with evidence of no relapse. Patients who achieve a CR and then proceed to SCT will continue to be followed for the response assessment posttransplant, will be included in the analysis of DCR, and will not be censored at the time of transplant. If patients start taking new anticancer therapies (excluding SCT) before relapse or death, DCR will be censored at the last response assessment before the initiation of the new anticancer therapies.

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

Duration of Response (DOR): The DOR is measured from the time measurement criteria are first met for objective response to the first date of relapse, disease progression after the initial objective response or death, whichever occurs earlier. Those who are not observed to relapse, disease progress after the initial objective response or die will be censored at their last response assessment date with evidence of no relapse/no disease progression. Patients who achieve a response and then proceed to SCT will continue to be followed for the DOR posttransplant, will be included in the analysis of DOR, and will not be censored at the time of transplant. If patients start taking new anticancer therapies (excluding SCT) before relapse, disease progression or death, DOR will be censored at the last response assessment before the initiation of the new anticancer therapies.

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

Event-free Survival: The EFS is defined as the time from randomization to transformation to AML or death from any cause, whichever occurs first. Response assessments and deaths post SCT will be included in the analysis. Patients who are not observed to have one of these events during the study will be censored at their last response assessment date with evidence of no transformation to AML. If patients start taking new anticancer therapies (excluding SCT) before transformation to AML or death, EFS will be censored at the last response assessment before the initiation of the new anticancer therapies. Patients will be censored at the date of randomization if no response assessment performed after randomization and the patients didn't die.

CR in TP53 Mutant Population: CR in TP53 Mutant Population is defined as the proportion of patients who achieve a morphologic CR based on Investigator-assessed IWG criteria {Cheson 2006} prior to initiation of any new anticancer therapy, including SCT in TP53 mutant population.

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

Time to Transformation to AML: Time to transformation to AML is defined as the time from randomization to transformation to AML. Patients who are not observed to have transformation to AML will be censored at their last response assessment date with evidence of no AML diagnosis. Response assessments post SCT will be included in the analysis. If patients start taking new anticancer therapies (excluding SCT) before documented AML diagnosis, Time to Transformation to AML will be censored at the last response assessment before the initiation of the new anticancer therapies. Patients will be censored at the date of randomization if no response assessment performed after randomization.

Progression-free Survival: PFS is defined as the time from randomization to the date of documented disease progression (including treatment failure by IWG criteria or relapse after PR/CR), or death from any cause, whichever occurs first. Response assessments and deaths post SCT will be included in the analysis. Those who are not observed to have one of these events will be censored at their last response assessment date with evidence of no disease progression/relapse. If patients start taking new anticancer therapies (excluding SCT) before disease progression (including treatment failure by IWG criteria or relapse after PR/CR) or death, PFS will be censored at the last response assessment before the initiation of the new anticancer therapies. Patients will be censored at the date of randomization if no response assessment performed after randomization and the patients didn't die.

FACT-Anemia Response Rate: The FACT-Anemia response rate is defined as the proportion of patients who showed clinically meaningful improvement in health-related quality of life (HRQoL) based on the score from the FACT-Anemia instrument prior to initiation of any new anticancer therapy, including SCT {Cella 2002}. The minimal clinically meaningful difference of 7.0 as suggested in the referenced literature will be used as cutoff for clinically meaningful improvement. Patients, who are randomized but have no baseline or no postbaseline FACT-Anemia questionnaire assessment or receive any new anticancer therapy including SCT prior to achieving the FACT-Anemia response, will be considered as non-responders.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

Key secondary efficacy endpoints will be tested according to the order specified in Section 2.1, after the superiority for the primary efficacy endpoint OS is established.

6.2.2.1. Objective Response Rate, CR in TP53 Mutant Population, MRD-negative Response Rate, and FACT-Anemia Response Rate

The ORR, CR in TP53 mutant population, MRD-negative response rate, and FACT-Anemia response rate will be evaluated in a similar manner as the CR rate.

6.2.2.2. Duration of CR, and Durations of Response

For the time-to-event endpoints of DCR and DOR, analyses will be conducted based on the subsets on which the outcome measures are defined. Specifically, DCR will be based on patients who achieve CR, and DOR will be based on patients who achieve objective response. The Kaplan-Meier method will be used to estimate median duration with its 95% CI, and Kaplan-Meier plots will be provided. The censoring rules for DCR and DOR are summarized in Table 6-1.

6.2.2.3. Event-Free Survival, Time to Transformation to AML, and Progression-Free Survival

The distribution of EFS, time to transformation to AML, and PFS will be estimated for each treatment arm using Kaplan-Meier method and compared between treatment arms using the stratified log-rank test, stratified by the stratification factors at randomization for the ITT Analysis Set. Medians, Q1, Q3 of the distributions, and the proportion of patients who are event-

free at 6, 12, 18 and 24 months from randomization will be estimated along with corresponding 95% CIs using the Kaplan-Meier method. Kaplan-Meier curves will be provided by treatment group. The hazard ratio between treatment arms will be estimated using the Cox proportional hazards regression model stratified by the stratification factors. The censoring rules for EFS, Transformation to AML, and PFS are summarized in Table 6-2.

6.2.2.4. RBC Transfusion Independence Rate

The point estimates of RBC transfusion independence rate as well as the corresponding 2-sided exact 95% CIs based on Clopper-Pearson method will be provided by treatment arm respectively. Estimation will be based on a subset of all randomized patients who are RBC transfusion dependent at baseline. Difference in transfusion independence rate between treatment group will be tested using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors.

Table 6-1. Censoring Rules for DCR, DOR, and Duration of RBC Transfusion Independence

Situation	Date of Censoring
No subsequent response assessments and no death after the first date CR/OR/RBC transfusion independence met	Date of first time meet CR/OR/RBC transfusion independence
No corresponding events or no subsequent response assessments prior to initiation of any new anticancer therapy (excluding SCT)	Date of the last response assessment before the initiation of the new anticancer therapies (excluding SCT) or Date of first time meet CR/OR/RBC transfusion independence
No corresponding events and no any new anticancer therapy (excluding SCT)	Date of the last response assessment

Table 6-2. Censoring Rules for EFS, Time to Transformation to AML, and PFS

Situation	Date of Censoring
No postbaseline response assessment (for Time to Transformation to AML); No postbaseline response assessment and no death (for EFS and PFS)	Date of randomization
No corresponding events or no postbaseline response assessment prior to initiation of any new anticancer therapy (excluding SCT)	Date of the last response assessment before the initiation of the new anticancer therapies (excluding SCT) or date of randomization
No corresponding events and no any new anticancer therapy (excluding SCT)	Date of the last response assessment

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

Duration of RBC Transfusion Independence: The duration of RBC transfusion independence is measured from the time the assessment criteria are first met for RBC transfusion independence until RBC transfusion dependence again (including assessments post SCT) or death, whichever occurs first. Those who are not observed to have RBC transfusion dependence again or death will be censored at the date of their last response assessment. If patients start taking new anticancer therapies (excluding SCT) before becoming RBC transfusion dependent again or death, duration of RBC transfusion independence will be censored at the last response assessment before the initiation of the new anticancer therapies (excluding SCT).

Transplantation Rate: The transplantation rate is the proportion of patients who initiated transplant type subsequent anti-cancer therapy for MDS.

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

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

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

Time to first transplant will be analyzed in a similar manner as the analysis of EFS, as specified in Section 6.2.2.3. Patients who are not observed to initiate transplant type subsequent anti-cancer therapy will be censored at their last known alive date or death date if the patient died.

The duration of RBC transfusion independence will be analyzed in a similar manner as the analysis of DCR, as specified in Section 6.2.2.2. The censoring rule for duration of RBC transfusion independence is summarized in Table 6-1.

The transplantation rate will be analyzed in a similar manner as the analysis of ORR, as specified in Section 6.2.2.1.

A by-subject listing for RBC transfusions required throughout the study will be provided by treatment group and subject ID in chronological order. Date of transfusion, transfusion type, and the number of units transfused will be presented.

6.4. Patient-Reported Outcome

6.4.1. Definition of Patient-Reported Outcome Data

Four PRO instruments will be administered in this study: the Functional Assessment of Cancer Therapy-Anemia (FACT-Anemia), the 5-level EuroQol 5 dimensions (EQ-5D-5L), the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC).

Functional Assessment of Cancer Therapy-Anemia is described in Section 6.2.1.

6.4.2. Analysis of Patient-Reported Outcome Data

In addition to the analyses specified in Section 6.2 for the secondary PRO endpoint, exploratory analyses comparing the effects of magrolimab + azacitidine versus placebo + azacitidine on health-related quality of life will be performed on the 4 PRO measures: FACT-Anemia, EQ-5D-5L, PGIS, and the PGIC. Analyses will be based on the ITT Analysis Set.

FACT-Anemia

- FACT-G: Mean total score and subscale scores at baseline and all follow-up timepoints by treatment arm. The FACT-G consisits of the physical, social/family, emotional, functional subscales.
- FACT TOI-An: Mean total score at baseline and all follow-up timepoints by treatment arm. The FACT TOI-An consists of the physical, functional and anemia symptoms subscales.
- FACT TOI-F: Mean total score at baseline and all follow-up timepoints by treatment arm. The FACT TOI-F consists of the physical, functional and fatigue subscales.
- FACT-F: Mean total score at baseline and all follow-up timepoints by treatment arm. The FACT-F consisits of the physical, social/family, emotional, functional and fatigue subscales.

EQ-5D-5L

The EQ-5D-5L questionnaire data will be scored, processed, and standardized according to the user manual. Missing values will not be imputed and will be left as missing.

Descriptive statistics will be calculated for the EQ-5D-5L dimensional score, the EQ-5D VAS score, and PGIS/PGIC response score at scheduled assessments. The mean and change from baseline to each subsequent assessment will be summarized by treatment group.

PGIC/PGIS

The proportion of patients who report each response category on the PGIC and PGIS at scheduled time-point will be summarized by treatment group. The mean and change from baseline on the PGIS to each subsequent assessment may be summarized.

Additional exploratory analyses may be conducted and documented in a separate PRO SAP.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 5.0. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Severity of adverse events will be determined by the investigator as mild, moderate, or severe.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" for a drug on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and reported as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date on or after the study drug start date and no later than 70 days after the study drug last dose date or initiation of new anticancer therapy including SCT (whichever is earlier).

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff date of TEAE period, which is defined as the 70 days after the study drug last dose date or initiation of new anticancer therapy including SCT (whichever is earlier)

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first dosing date if they have the same month and year, or the first day of the month otherwise.
- If the day and month are missing but year is available, then the imputed day and month will be the first dosing date if they have the same year, or 01Jan otherwise.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number of percentage of patients who experienced at least 1 TEAE in the categories described below will be provided by treatment group.

The number and percentage of patients who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group.

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs
- TEAEs with Grade 3 or higher
- TE treatment-related AEs for any study drug and for each study drug
- TE treatment-related AEs with Grade 3 or higher for any study drug and for each study drug
- TE SAEs
- TE treatment-related SAEs for any study drug and for each study drug
- TEAEs leading to dose reduction of azacitidine
- TEAEs leading to discontinuation of any study drug and for each study drug
- TEAEs leading to death

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of frequencies in magrolimab + azacitidine treatment arm within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition to the above summary tables, all TEAEs, TEAEs of Grade 3 or higher, TE SAEs and TEAEs leading to death will be summarized by PT only in descending order of frequencies in magrolimab + azacitidine treatment arm.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All SAEs leading to death
- All AEs with severity of Grade 3 or higher
- All AEs leading to discontinuation of study drug
- All AEs leading to dose reduction of azacitidine
- TEAEs leading to dose delay or interruption of study drug

A summary (number and percentage of patients) of deaths will be provided by treatment group. Summary will include the following categories:

- All deaths
- Deaths within 30 days of the first dosing of study drug
- Deaths within 30 days of the last dosing of study drug
- Deaths within 60 days of the first dosing of study drug
- Deaths within 70 days of the last dosing of study drug
- Deaths beyond 30 days of the last dosing of study drug
- Deaths beyond 70 days of the last dosing of study drug

7.1.7. Additional Analysis of Adverse Events

The incidence of infusion reaction AEs and Treatment-Emergent AEs will be examined.

7.1.7.1. Infusion Reaction Adverse Events (IRAE)

The incidence of infusion reaction AEs will be examined. Infusion reaction AEs 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". For the purpose of this study, they are defined as AEs described in Protocol Amendment 7 that occur within the 24-hour period beginning from the start of the infusion.

The number and percentage of subjects who experienced any of the infusion reaction AEs events will be summarized by PT.

7.1.7.2. Treatment-Emergent Adverse Events (TEAE) of Clinical Significance

Number and percentage of subjects with the following AEs of clinical significance will be summarized by PT:

- Anaemia/Hemolytic Anemia (MST Anemia Extravascular Transient Hemolysis)
- Infusion Related Reaction (IRR) (SMQ-Hypersensitivity Narrow Terms)
- Interference with blood cross match or packed RBC transfusion outcomes (Gilead's MST)
- Thromboembolic Events (SMQ- Embolic and Thrombotic Events Broad Terms)
- Pneumonitis (SMQ- Interstitial Lung Disease Broad Terms)

Number and percentage of subjects with the following AEs of clinical significance will also be summarized by AE onset time within 2 weeks, >2weeks to 2 months, >2 months to 6 months, >6 months to 12 months, and >12 months of first dosing of any study drug:

- Anaemia/Hemolytic Anemia
- IRR
- Interference with Blood Cross Match or Packed RBC Transfusion Outcomes
- Thromboembolic Events
- Pneumonitis

7.1.7.3. Other Important Safety Topics

Number and percentage of subjects with the following AEs of important safety topics will be summarized by PT:

- Infections and infestations (SOC)
- Immune-Mediated Events (SMQ-Immune-mediate and autoimmune disorder Narrow Terms)

Number and percentage of subjects with the following AEs of important safety topics will also be summarized by AE onset time within 2 weeks, >2weeks to 2 months, >2 months to 6 months, >6 months to 12 months, and >12 months of first dosing of any study drug:

- Immune-Mediated Events (SMQ-Immune-mediate and autoimmune disorder Narrow Terms)

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by treatment group, subject ID and visit in chronological order for hematology and serum chemistry separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

Plots of lab parameters will include (but not limit to) hemoglobin, platelet, and absolute neutrophil counts across time.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of any study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values will be plotted using a line plot by treatment group and visit for the laboratory tests including but not limited to hemoglobin, platelet, and absolute neutrophil counts.

In the case of multiple values associated with a visit, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days or initiation of new anticancer therapy including SCT (whichever is earlier). If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of patients in the study with the given response at baseline and each scheduled postbaseline time point.

The following summaries (number and percentage of patients) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; patients will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- TE laboratory abnormalities
- TE Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of patients with nonmissing postbaseline values up to 30 days after the last dosing date or initiation of new anticancer therapy including SCT (whichever is earlier).

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of patients who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): > 3 times of the upper limit of reference range (ULN)
- Alanine aminotransferase (ALT): > 3 x ULN
- AST or ALT: > 3 x ULN
- Total bilirubin: > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase (ALP) < 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, patients will be counted once based on the most severe postbaseline values. For the composite endpoints of AST or ALT and total bilirubin and ALP, patients will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of patients in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

A listing of patients who met at least 1 of the above criteria will be provided.

7.2.4. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to the worst grade postbaseline for hematology and chemistry laboratory tests.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI, and vital signs as follows:

- Baseline value
- Postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value.

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of any study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values for the same visit, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject takes the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 preferred name using the number and percentage of patients for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year

(if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by ATC drug class Level 2 preferred name using the number and percentage of patients for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to 70 days after last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or 70 days after the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug plus 70 days will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date plus 70 days will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Premedication

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

Premedications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 preferred name using the number and percentage of patients for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

7.6. Electrocardiogram Results

A by-subject listing of ECG results will be provided by subject ID number in ascending order.

7.7. Other Safety Measures

A by-subject listing of ECOG performance status will be provided by subject ID number in ascending order.

8. PHARMACOKINETIC (PK) AND IMMUNOGENECITY ANALYSES

8.1. PK Sample Collection

Blood samples for evaluating magrolimab serum concentrations will be collected at pre-dose at Day 1, Day 8, Day 29, Day 57, Day 113, Day 169, Day 253, Day 337, and EOT.

8.2. PK Analyses

Magrolimab concentration will be summarized for the PK Analysis Set. The individual subject's concentration data for magrolimab will be listed based on the sampling time point. Magrolimab PK data will be summarized per nominal time point using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for magrolimab serum concentration data at each time point.

The sample size (number of patients) at each time point will be based on the number of patients with nonmissing concentration data at that time point. Missing concentration values will be reported as is in data listings. The number of patients with concentration below the limit of quantitation (BLQ) will be presented for each time point.

Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes.

If more than one-third of the subjects have a concentration value of BLQ for a given time point, then only the number of samples and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."

Descriptive graphical plots of individual serum concentration versus time profiles and mean (StD) concentration versus nominal time profiles will be generated.

Due to the sparse nature of PK collection, PK parameters will not be calculated.

Data from this study may be combined with PK data from other magrolimab clinical studies and analyzed using a population PK model. Such an analysis will be reported separately.

8.3. Immunogenicity Analysis

The rate and magnitude of anti-magrolimab antibody prevalence, incidence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Neutralizing antibody occurrence rate will also be summarized.

Titer summaries may also be generated, if relevant. Exploratory evaluations may be conducted to determine the relationship between anti-magrolimab antibody positivity and safety, PK, or efficacy parameters (eg, drug concentrations, AEs, or disease response) using graphical, and/or tabular approaches.

9. PHARMACODYNAMIC ANALYSES

Exploratory analyses may be performed to evaluate the association of each biomarker or combination of biomarkers with clinical outcomes. Additional details will be provided separately by the biomarker sciences group.

10. Changes From Protocol-Specified Analyses

There are no deviations from the protocol-specified analyses.

11. REFERENCES

Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in Cancer Patients Compared with Fatigue in the General United States Population. Cancer 2002;94 (2):528-38.

Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21 (24):4642-9.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012;120 (12):2454-65.

12. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

13. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

14. APPENDICES

Appendix 1. Schedule of Assessments

Appendix Table 1. Schedule of Assessments – Screening

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

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

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

b Screening pregnancy test may be used as the Day 1 test if performed within 72 hours of first dose; additional guidance is provided in Protocol Section 5.1.1. FSH test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

c A trephine (biopsy) is to be collected for baseline. A bone marrow biopsy collected per SOC within 30 days of randomization can be considered the screening sample, and shipped to central laboratory. This procedure must be performed prior to the first dose of study treatment at the latest. An aspirate sample must be collected at the screening visit for blast evaluation, MRD assessment, biomarker studies, baseline for response assessment and biobanking. It is preferred that bone marrow aspirate samples are obtained at the time of bone marrow (trephine) biopsy. Conventional cytogenetics to be tested per institutional standards.

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

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

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

Appendix Table 2. Schedule of Assessments - Treatment Period-Azacitidine Dosing and Study Assessments

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

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

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

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

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

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

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

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

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

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

Appendix Table 3. Schedule of Assessments - Treatment Period-Magrolimab or Placebo Dosing and Study Assessments

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

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

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

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

c Pretreatment assessments for the initial dose may be collected up to 72 hours before administration of study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to study treatment administration.
d Additional samples for CBC may be collected outside of the protocol-specified time points to ensure a WBC level ≤ 20 × 103/μL prior to each magrolimab/placebo dose during the first 28 days of magrolimab priming dose. Peripheral blasts should be included in the CBC assessments.
e An additional hemoglobin check must be performed 3 to 6 hours after the initiation of the first and second doses of magrolimab/placebo during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or increased risk for complications of anemia.
f Peripheral smears will be collected predose and assessed locally.
g Samples for PK and biomarker studies will be collected predose within 12 hours prior to study treatment administration.
h Samples will be collected prior to first maintenance dose (Day 57), ninth (Day 169) maintenance dose, and EOT.
i Samples will be collected predose on Day 57, Day 113, Day 169, Day 253, Day 337, and EOT.
j When collected on the day of study treatment dosing, the blood sample for antidrug antibodies must be collected at the same time as the predose PK sample.
k Vital signs will be assessed prior to infusion/injection of each study treatment. Weight will be assessed every 4 weeks. Details are provided in Protocol Section 5.1.5.
l Premedication is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming. Premedication for subsequent treatment periods may be continued based on the treating physician's clinical judgment and the presence/severity of prior infusion-related reactions. In the case of a Grade 3 infusion-related reaction, a premedication regimen for subsequent treatment periods is required (Protocol Section 6.5).
m Magrolimab or saline placebo should not be given on consecutive days. The duration of each magrolimab/placebo infusion including flush will be 3 hours (± 30 minutes) for the first dose of treatment. After the first dose of treatment, the magrolimab/placebo infusion including flush will be 2 hours (± 30 minutes). All patients should be monitored for 1 hour after infusion for doses during the first 28 days and the repriming doses.
n Within 24 hours prior to each of the first 2 doses of magrolimab/placebo infusion during initial treatment, all subjects must have a documented hemoglobin ≥ 9.0 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9.0 g/dL prior to each of the first 2 doses of magrolimab.

Appendix Table 4. Schedule of Assessments – Post Treatment

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

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood count; CR = complete remission; eCRF = electronic case report form; EOT = end of treatment; EQ-5D-5L = 5-level EuroQol 5 dimensions; FACT-Anemia = Functional Assessment of Cancer Therapy-Anemia; IWG = International Working Group; MDS = myelodysplastic syndrome; MRD = minimal residual disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PR = partial remission; PRO = patient-reported outcome; QxM = every x months; QxW = every x weeks; SAE = serious adverse event.

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

Appendix Table 5. Schedule of Assessments – Repriming (Required After > 4 Weeks Have Lapsed Since the Last Dose of Magrolimab/Placebo Delays)

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

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

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

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

c Peripheral smears will be collected and assessed locally.

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

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

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

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

Appendix 2. Disease Response Assessment Based on International Working Group Criteria

Response will be assessed in myelodysplastic syndrome (MDS) patients using the 2006 International Working Group (IWG) criteria {Cheson 2006} with modifications as shown in Appendix Table 6. In addition, complete remission (CR) with partial hematologic recovery (CRh) will be assessed for MDS, defined as patients who achieve a CR per IWG 2006 MDS criteria {Cheson 2006}, with the exception of requiring partial hematologic recovery as defined by a platelet count of > 50 × 10^9/L and an absolute neutrophil count of > 500/µL.

In addition, HI will be assessed by 2006 IWG criteria {Cheson 2006}; Appendix Table 8) and cytogenetic/molecular response by 2003 IWG criteria {Cheson 2003}; Appendix Table 7).

Appendix Table 6. Response Criteria in MDS (IWG 2006 Criteria)

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

Category	Response Criteria
Disease Progression	For patients with: Less than 5% blasts: ≥ 50 increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL[d] Transfusion dependence[d]

Source: {Cheson 2006}
Abbreviations: CR = complete remission; FAB = French-American-British classification; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndrome; PR = partial remission.
a Dysplastic changes should consider the normal range of dysplastic changes.
b Modification to IWG response criteria
c In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. 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 Table 7. Additional Response Definitions Used in This Study (2003 IWG Criteria)

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

Appendix Table 8. Response Criteria for Hematologic Improvement

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

Source: {Cheson 2006}

a Pretreatment counts should be an average of at least 2 measurements (not influenced by transfusions) performed ≥ 1 week apart.

b In the absence of another explanation. For example, including, but not restricted to, acute infection, gastrointestinal bleeding and hemolysis.

5F9009 SAP – Primary CR and 1st OS Interim Analyses

ELECTRONIC SIGNATURES

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