DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

AZA-MDS-003

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO PLUS BEST SUPPORTIVE CARE IN SUBJECTS WITH RED BLOOD CELL TRANSFUSION-DEPENDENT ANEMIA AND THROMBOCYTOPENIA DUE TO IPSS LOWER-RISK MYELODYSPLASTIC SYNDROMES

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STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO PLUS BEST SUPPORTIVE CARE IN SUBJECTS WITH RED BLOOD CELL TRANSFUSION-DEPENDENT ANEMIA AND THROMBOCYTOPENIA DUE TO IPSS LOWER-RISK MYELODYSPLASTIC SYNDROMES

STUDY DRUG: Oral Azacitidine (CC-486)

PROTOCOL NUMBER: AZA-MDS-003

DATE FINAL: 27MAR2019

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SAP AUTHOR		*{See appended electronic signature page}*
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PROTOCOL NUMBER	AZA-MDS-003	
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SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.	

Statistical Therapeutic Area Head

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Printed Name _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature *{See appended electronic signature page}*

Printed Name _____ Date _____

Lead Product Safety Physician

Signature *{See appended electronic signature page}*

Printed Name _____ Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ATC	Anatomical therapeutic chemical
BMI	body mass index
AZA	Azacitidine
CI	Confidence interval
CR	Complete remission
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data management committee
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EP	Extension phase
ESA	Erythropoiesis-stimulating agents
FCBP	Female of child-bearing potential
HI	Hematologic improvement
HI-E	Hematologic improvement erythroid
HI-N	Hematologic improvement neutrophil
HI-P	Hematologic improvement platelet
HLT	Higher level term
HRQoL	Health-related quality-of-life
IC	Informed consent
INT-1	Intermediate-1
IP	Investigational Product
IPSS	International Prognostic Scoring System
IRT	Interactive Response Technology
ITT	Intent to treat

IVRS	Interactive Voice Response System
IWG	International Working Group
KM	Kaplan-Meier
mCR	Marrow CR
MDS	Myelodysplastic syndromes
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NCI	National Cancer Institute
OS	Overall survival
PFS	Progression-free survival
PR	Partial remission
pRBC	Packed red blood cell
PT	Preferred term
QD	Once daily
RBC	Red blood cell
RDI	Relative dose intensity
ROW	Rest of world
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneously/subcutaneous
SD	Stable disease
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
WBC	White blood cell
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol [AZA-MDS-003] "A Phase 3, Multicenter, Randomized, Double-blind Study to Compare the Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care versus Placebo Plus Best Supportive Care in Subjects with Red Blood Cell (RBC) Transfusion-dependent Anemia and Thrombocytopenia due to International Prognostic Scoring System (IPSS) Lower-risk Myelodysplastic Syndromes (MDS)" Amendment 5, which was issued on 28 November 2018. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include the final analysis for the primary study efficacy endpoint of RBC transfusion independence and the interim analysis for the key secondary endpoint of overall survival (OS). Throughout this SAP, the treatment arms will be referred to as oral azacitidine (CC-486) or placebo. The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of study data prior to database lock for the primary analysis (and the interim analysis for OS) when all randomized subjects have completed 12 months of double-blind treatment or have discontinued the double-blind treatment. This SAP will be finalized and signed off prior to the clinical database lock for the primary analysis including the final analysis for the primary efficacy endpoint and all secondary efficacy endpoints. The final analysis for OS and progression to acute myelogenous leukemia (AML) will be conducted separately in the future. The interim analysis for OS and progression to AML is included. The analysis plan for Health-related quality of life will be provided separately and not included in this SAP. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis Software (SAS)® Version 9.2 or higher.

3. OBJECTIVES

The primary objective is to evaluate RBC transfusion independence in the 2 treatment arms (oral azacitidine plus best supportive care versus placebo plus best supportive care) in subjects with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS.

The secondary objectives of the study are:

- To evaluate in both treatment arms
  - Overall survival (OS);
  - Hematologic improvement-platelet response (HI-P);
  - Duration of RBC transfusion independence and time to RBC transfusion independence;
  - Progression to acute myeloid leukemia (AML), and time to AML progression;
  - Hematologic improvement-erythroid response (HI-E);
  - Platelet-transfusion independence, duration of platelet transfusion independence, and time to platelet transfusion independence;
  - Hematologic response;
  - Clinically significant bleeding events;
  - Safety;
  - Health-related quality-of-life (HRQoL); and
  - Healthcare resource utilization.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study that compares the efficacy and safety of oral azacitidine plus best supportive care therapy to that of placebo plus best supportive care in subjects with RBC transfusion-dependent anemia and thrombocytopenia (platelet count ≤ 75 x 10^9/L) due to IPSS lower-risk MDS. The study enrolled 216 subjects at approximately 150 sites globally.

The study consists of 4 phases: Screening, Double-blind treatment, Follow-up, and Extension.

4.1.1. Screening Phase

Subjects will provide informed consent prior to undergoing any study-related procedures. Screening assessments for protocol eligibility will be performed within 56 days prior to randomization as outlined in Table 1 of the protocol.

Confirmation of MDS disease, WHO classification (Appendix B), and IPSS risk classification (Appendix C) is based on independent central pathology review, independent central cytogenetic review, and central laboratory hematology result. Thus bone marrow aspirate and bone marrow biopsy must be collected at screening. The bone marrow aspirate and biopsy slides together with a peripheral blood smear slide are sent to the central pathology reviewer for morphologic assessment. Samples of the bone marrow aspirate or biopsy are sent to the central cytogenetic reviewer for processing and analysis. The independent central cytogenetic review will provide standardized analysis and reporting for all subjects. The results from independent central cytogenetic review will be used for the statistical analyses.

RBC transfusion history must be available for the 56 days immediately preceding and including the date of randomization. Transfusion data should include the type, number of units, reason and date of transfusion. Transfusion data must include the hemoglobin (Hgb) value for which the transfusion was administered. Hgb levels at the time of or within 7 days prior to administration of a RBC transfusion must have been ≤ 10.0 g/dL for the transfusion to be counted towards RBC transfusion-dependent status. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL will not qualify as a required transfusion for the purpose of providing evidence of RBC transfusion-dependent status. In addition, any RBC transfusion administered for elective surgery will not qualify towards determination of RBC transfusion dependent status at baseline. All RBC transfusion records for the 56 days immediately preceding the date of randomization should be collected, regardless of Hgb levels. RBC transfusion-dependent anemia at baseline is defined for this protocol as documentation of an average transfusion requirement of at least 2 units of RBCs per 28 days during the 56 days immediately preceding the date of randomization. There must also not be any consecutive 28 days within the 56-day period in which no RBC transfusions were administered. Platelet transfusion history, if applicable, must be available for the 56 days immediately preceding and including the date of randomization. Transfusion data must include the platelet value for which the transfusion was administered.

Platelet transfusion-dependence at baseline is defined for this protocol as at least 2 separate transfusion episodes during the 56 days immediately preceding the date of randomization. There must also not be any consecutive 28 days within the 56-day period in which no platelet

transfusion was administered. In addition, any platelet transfusions administered for elective surgery will not qualify towards determination of platelet transfusion dependent status at baseline.

Thrombocytopenia at baseline must be confirmed by two platelet counts that are ≤ 75 x 10^9/L and ≥ 21 days apart. The second confirmatory platelet count must be obtained ≤ 14 days prior to randomization.

Other screening assessments will be also collected according to the protocol.

4.1.2. Randomization and Double-blind Treatment Phase

Following confirmation of eligibility, subjects will be randomized in a 1:1 ratio to receive oral azacitidine or placebo 300 mg once daily (QD) for 21 days. Randomization will occur by a central randomization procedure using an Interactive Voice Response System (IVRS) with stratification as described in Section 4.3.

The first dose of IP should be administered within 3 days of Randomization and can be on the same day of randomization. After randomization, no crossover between the treatment groups will be permitted during any point of the study.

During the double-blind treatment phase, subjects will ingest IP (oral azacitidine or placebo) once a day on the first 21 days of each 28-day cycle (see Section 8.2.2 of the protocol for details). Dose modifications may occur for managing toxicity if necessary during treatment (Section 8.2.4 of the protocol).

Best supportive care may be used in combination with study treatment as deemed necessary. Best supportive care includes, but is not limited to, treatment with RBC transfusions (packed red blood cell [pRBC] or whole blood), single donor or pooled donor platelet transfusions, antibiotic, antiviral and/or antifungal therapy, nutritional support as needed, and granulocyte colony stimulating factors for subjects experiencing neutropenic infections (Section 9.1 of the protocol). Best supportive care for this study excludes the use of erythropoiesis-stimulating agents (ESAs) and other hematopoietic growth factors (granulocyte colony stimulating factors are allowed in subjects experiencing neutropenic fever/infections as well as for secondary prophylaxis under certain conditions as described in Section 9.1 of the protocol).

Visits during the double-blind treatment phase are scheduled weekly for the first 2 cycles, every other week for the next 10 cycles and then monthly once a subject has completed 12 cycles.

During the double-blind treatment, subjects will be assessed continuously for safety and efficacy. Assessments include adverse events (AEs), monitoring for progression to AML and second primary malignancy, physical examination, vital signs and weight measurement, Eastern Cooperative Oncology Group (ECOG) performance status, hematology and serum chemistry, serum ferritin level, pregnancy testing (females of child-bearing potential [FCBP] only), concomitant medications, therapies and procedures, transfusions administered, clinically significant bleeding events, central review of bone marrow aspirate (or biopsy if an adequate aspirate is not attainable) and peripheral blood smear, central review of cytogenetics, hematologic response/improvement assessment (International Working Group [IWG] 2006 criteria; Cheson, 2006; Appendix E), disease status assessment,

IP administration and accountability, HRQoL, and healthcare resource utilization.

4.1.3. Follow-up Phase

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for a period of 28 days following the last dose of IP or until the date of the last study visit, whichever period is longer, for the collection of AEs, concomitant medications and procedures, transfusions administered and healthcare resource utilization. Females of childbearing potential should avoid becoming pregnant for 3 months after the last dose of IP and male subjects should avoid fathering a child for 3 months after the last dose of IP.

All subjects discontinued from protocol-prescribed therapy for any reason will also be followed for survival, subsequent MDS therapies, progression to AML and second primary malignancy every month for the first year following Treatment Discontinuation and every three months thereafter until death, lost to follow-up, withdrawal of consent for further data collection.

4.1.4. Extension Phase

The Extension Phase (EP) allows subjects who are receiving oral azacitidine, at time of study unblinding, and who are demonstrating clinical benefit as assessed by the Investigator, to continue to receive oral azacitidine after unblinding by Sponsor (Celgene Corporation) until they meet the criteria for study discontinuation. In addition, all subjects in the placebo arm and subjects who have been discontinued from the treatment phase (irrespective of randomization arm) and continuing in the Follow-up Phase will be followed for survival in the EP upon their approval and eligibility of entering the EP.

4.1.5. Study Closure

The study will conclude once all subjects have completed or discontinued from the extension phase.

4.2. Study Endpoints

The primary endpoint is the proportion of subjects in the overall population achieving RBC transfusion independence with duration ≥ 56 days (8 weeks).

The secondary endpoints are:

- OS;
- HI-P（IWG 2006 criteria；Cheson, 2006; Appendix E）;
- Proportion of subjects achieving RBC transfusion independence with duration ≥ 84 days (12 weeks);
- Duration of RBC transfusion independence of ≥ 56 days (8 weeks);
- Duration of RBC transfusion independence of ≥ 84 days (12 weeks);
- Time to RBC transfusion independence of ≥ 56 days (8 weeks);
- Time to RBC transfusion independence of ≥ 84 days (12 weeks);
- Proportion of subjects progressing to AML and time to AML progression;
- HI-E（IWG 2006 criteria；Cheson, 2006; Appendix E）;

- Duration of RBC transfusion reduction;
- Proportion of platelet transfusion-dependent subjects at baseline achieving platelet transfusion independence with duration ≥ 56 days (8 weeks);
- Duration of platelet transfusion-independence;
- Time to platelet transfusion independence;
- Hematologic response (IWG 2006 criteria; Cheson, 2006; Appendix E);
- Proportion of subjects experiencing clinically significant bleeding events;
- Safety (type, frequency, severity of AEs and relationship of AEs to oral azacitidine/placebo; monitoring for progression to AML and second primary malignancy);
- HRQoL utilizing the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and EuroQoL Group EQ-5D (EQ-5D-3L) instruments; and
- Measures of healthcare resource utilization.

4.3. Stratification, Randomization and Blinding

Following confirmation of eligibility at screening, subjects will be randomized to receive oral azacitidine or matching placebo in a 1:1 ratio. Randomization will be accomplished by Interactive Response Technology (IRT) to ensure timely registration and randomization. Subjects will be randomized according to the following stratification factors: average baseline RBC transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent or independent), country of enrollment (ie, Japan versus Rest of World [ROW]) and ECOG performance status (0 to 1 versus 2).

4.4. Sample Size

The basis for the power and sample size determination will be a test of the equality of the overall survival curves between the oral azacitidine and placebo treatment groups using a stratified log-rank test. Assuming a median OS of 18 months in the placebo treated group (Garcia-Manero, 2008a), which takes into account possible cross-over outside of the protocol of placebo treated

subjects to active treatment during the observation period, and a median OS of 25.7 months (43% improvement) in the oral azacitidine treated group, 216 subjects (108 in each group) would have approximately 72% power to detect a constant hazard rate ratio of 0.70 using a two-sided log rank test with overall significance level of 0.05. It is assumed that the OS distribution is exponential with a constant failure (hazard) rate and that accrual is uniform during the accrual period (56 months) with an overall drop-out rate of 5% from both treatment groups. Full information necessary for a log rank test to have 72% power will be achieved when approximately 205 deaths have occurred in both treatment groups, which is expected approximately 134 months after randomization of the first subject into the study.

An interim analysis of the OS endpoint will be performed and reported when all subjects have completed 12 months [52 weeks (364 days)] of double-blind treatment or have been discontinued from treatment (see Section 15).

While 56 days (8 weeks) is the standard response criteria for hematologic improvement (IWG 2006 criteria; Cheson, 2006; Appendix E), limited information is available on the target population for estimating the response rate for the primary endpoint of RBC transfusion independence maintained for ≥ 84 days (12 weeks).

A total sample size of 216 subjects (108 in the active treatment group and 108 in the placebo group) will have approximately 99% power to detect the difference between a response rate of 0.30 in the active treatment group and a response rate of 0.05 in the placebo group, and approximately 70% power to detect the difference between a response rate of 0.15 in the active treatment group and a response rate of 0.05 in the placebo group. The power calculations for response rate are based on a two-sided alpha of 0.05 and test statistics on the difference of proportions using an un-pooled estimate of variance.

Sample size and power were calculated using the East® Version 5.3 software system (Cytel Inc., 675 Massachusetts Avenue, Cambridge, MA 02139, http://www.cytel.com).

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

- Program source (e.g., SAS program name, including the path, that generates the output) and
- Data extraction date (e.g., the database lock date, run date)

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table and figure.

Descriptive summaries for continuous data will include the following statistics: N, mean, standard deviation, minimum, median, and maximum, unless specified otherwise. Categorical summaries for discrete data will include the frequency (count) and percentage at each discrete value (category), unless specified otherwise.

5.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which a given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as "NOT DONE" in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in case report form (CRF) data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix A. However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine

progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur but are not otherwise subject to imputation.

- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules (see Section 5.1.2).

Dates recorded in comment fields will not be imputed or reported in any specific format.

5.1.2. Calculation Using dates

Calculations using dates (*e.g.*, relative day after the date of randomization) will adhere to the following conventions:

- If not otherwise specified, study day will be calculated with respect to randomization date for efficacy measures and will be calculated with respect to first dose date for all other measures. Study days will be calculated as the difference between the date of interest and the date of randomization or first dose date plus 1 day. The generalized calculation algorithm for relative day: STUDY DAY = [(TARGET DATE – (RAND or FDOSE)) + 1 where RAND = the date of randomization and FDOSE= the date of first dose] if the target data is on or after the randomization/ first dose date and STUDY DAY = [(TARGET DATE – (RAND or FDOSE)) if the target date is before the randomization/first dose date. Note that Study Day 1 is the date of randomization/first dose date. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the date of randomization/first dose date are not imputed in general. All effort should be tried to avoid incomplete randomization/first dose date.
- Intervals that are presented in weeks, months, or years will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7;

  MONTHS = DAYS /30.4375;

  YEARS = DAYS/365.25.

5.1.3. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records (with non-zero dosing) for each patient. The start date of the first cycle (S_1) will be the date when the subject receives the first dose of study drug.

Once the start dates, e.g., S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, i.e., $E_i = S_{i+1} - 1$, i=1, 2, …. For the last cycle, the end date will be calculated as the cycle start date plus prescribed cycle length (28 days), or the death date, whichever is earlier. The cycle number for each date of interest, e.g., AE or lab, will be calculated based on the cycle window set by their start and end dates. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i. For AEs or lab results which meet the treatment-emergent criterion or reporting criterion, the events or results after the end date of the last cycle will be included in the summary of the last cycle.

5.2. Analysis Populations

5.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population includes all subjects who are randomized, regardless of whether they received treatment or not. All efficacy analyses will be conducted for the ITT population and the subjects will be analyzed based on randomized treatment group.

5.2.2. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all ITT subjects who have at least one post-baseline efficacy assessment performed, met all inclusion/exclusion criteria, and received a minimum of one cycle of treatment.

Key efficacy analysis will be performed for the mITT population as supportive evidence and/or sensitivity analysis only and the subjects will be analyzed based on randomized treatment group.

5.2.3. Safety Population

The safety population includes all randomized subjects who received at least one dose of IP. The safety population will be used for all safety analysis and the subjects will be analyzed according to the treatment actually received.

6. SUBJECT DISPOSITION

All subjects screened/randomized will be included in these analyses.

The disposition of subjects will be summarized with counts and percentages. Summaries will include the number of subjects screened and randomized. For subjects randomized, subject disposition will be summarized for analysis population by treatment group and overall for:

- ITT Population
- mITT Population
- Safety Population

Reasons for excluding subjects from mITT population will be summarized and listed for each subject in the ITT population. A separate listing will be provided for subjects who were not randomized. A frequency table of enrollment by site and treatment will be provided.

The reasons for excluding subjects from mITT population are:

1. Did not have at least one post-baseline efficacy assessment;
2. Did not meet all inclusion/exclusion criteria;
3. Did not receive a minimum of one cycle of treatment.

The post-baseline efficacy assessments include any type of transfusions, local or central lab of Hgb and/or platelets count, disease status assessment (by investigator), IWG MDS Response assessment (by investigator), and assessment of bleeding events.

Subjects who have been dosed in Cycle 2 will be considered as receiving a minimum of one cycle of treatment. For subjects who did not have Cycle 2 treatment, they will be considered as receiving a minimum of one cycle of treatment if: 1) they have been dosed (actual dose) for at least 21 days if they were assigned to “21 days” dose; or 2) they have been dosed (actual dose) for at least 14 days if they were assigned to “14 days” dose. Days with missing (or zero) dose due to any reason will not be included in the “21 days” or “14 days”.

Number of subjects who are ongoing in treatment and number of subjects who are ongoing in follow-up will be tabulated. Reasons for study drug discontinuation as collected on the CRF will be summarized for all ITT subjects with the following categories:

- Adverse events
- Lack of efficacy
- Withdrew consent
- Death
- Lost to follow-up
- Protocol violation
- Progressive disease
- Sponsor Decision
- Other

Reasons for study discontinuation as collected on the CRF will be summarized for all randomized subjects with the following categories:

- Death
- Adverse Event
- Pregnancy
- Progressive Disease
- Lack of Efficacy
- Recovery
- Withdrew Consent
- Non-compliance with study drug
- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Protocol Violation
- Other

A by-subject listing of subject's reason for discontinuation will be presented.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by clinical research physician or designee following company standard operational procedure. The protocol deviations/violations will be summarized by treatment group for the ITT population.

A by-subject listing of subjects with protocol deviations/violations in the ITT population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline clinical characteristics will be summarized by treatment group for ITT, mITT and the Safety population. Baseline clinical characteristics are defined as the latest data collected on or before date of randomization, if not otherwise specified. When there are retested values, the retest values will be used for the analysis. Individual subject listings will be provided to support the tables.

Summary statistics (mean, standard deviation, median, minimum, and maximum) will be provided for variables measured on a continuous scale. The frequency distribution (n, %) will be provided for those categorical variables measured on a nominal scale.

8.1. Demographics

Demographic characteristics consist of age, gender, race, ethnicity, reproductive status, weight (kg), height (cm), and body mass index (BMI).

Age, collected from Demographic CRF page, will be summarized both descriptively and categorically using the following age categories: (≤ 64, 65-74, and ≥75 years).

Baseline BMI will be summarized both descriptively and categorically using the following categories (<20, 20-<25, 25-<30, ≥30 kg/m^2) and calculated, using the formula:

BMI (kg/m^2) = baseline weight (kg) / (height(m)²).

Gender, race, ethnicity and reproductive status will be summarized categorically with respect to the categories as specified in the CRF. A by-subject listing of demographic characteristics will be presented.

8.2. Baseline Disease Characteristics

Baseline disease characteristics includes following variables:

- MDS World Health Organization (WHO) 2008 classification,
- Eastern Cooperative Oncology Group (ECOG) performance status (0 – 1, 2),
- Time since initial diagnosis (defined as the number of months from the date of initial diagnosis to the date of randomization),
- IPSS score classification (Greenberg, 1997, Appendix C),
- Baseline platelet transfusion status (Dependent, Independent),
- Average baseline RBC transfusion requirements (units per 28 days) and category (≤ 4 units per 28 days, > 4 units per 28 days),
- Bone marrow blasts baseline values and category (< 5%, ≥ 5%),
- Hgb (g/dL) values,
- Platelet count (10^9/L) values,
- Absolute neutrophil count (10^9/L) values,
- White blood cell count (10^9/L) values,

- Transferrin saturation baseline values (%) values.

Subjects will be considered platelet transfusion dependent at baseline if they have received ≥ 2 platelet transfusions during the 56 days immediately preceding randomization and had no consecutive 28-day period during which no platelet transfusions were administered.

The average number of units (in 28 days) of baseline RBC of transfusions is determined by the following rules:

If the subject was randomized under the original protocol and protocol amendment 1, the average number of units per 28 days = sum of RBC transfusion units during the 84-day interval prior to the randomization date / 84 days * 28 days.

- If the subject was randomized under protocol amendment 2, the average number of units per 28 days = sum of RBC transfusion units during the 56-day interval prior to the randomization date / 56 days * 28 days.
- RBC transfusion and whole blood transfusion during the above specified period will be included. For whole blood transfusion, the number of units collected in the CRF will be used to calculate the RBC transfusions required units.

To eliminate the impact of transfusion, the baseline values for Hgb will be determined by following steps:

Step 1: Apply the "7-day rule" on all Hgb values from the Central lab which are collected on or prior to Cycle 1 Day 1. Use the lowest value among the Hgb values which are collected after >7 days of a RBC/whole blood transfusion or collected on the same of the transfusion as the baseline value.

Step 2: For subjects who don't have baseline value from Step 1, apply the "7/3-day rule". Use the lowest value among the Hgb values from the Central lab which are collected within 7 days after a RBC/whole blood transfusion and within 3 days before another transfusion as the baseline value. The rationale is that the Hgb value within 7 days from the first transfusion was only somewhat influenced by that transfusion.

Step 3: For subjects who don't have baseline values from Steps 1 and 2, use the lowest value among all Hgb values from the Central lab which are collected on or prior to Cycle 1 Day 1.

The baseline values for platelet count will be determined similarly to eliminate the impact of platelet transfusion.

For absolute neutrophil count, white blood cell count and bone marrow blasts, the baseline values will be determined by selecting the last non-missing value from the Central lab on or prior to Cycle 1 Day 1. In case that a randomized subject was not treated (no Cycle 1 Day 1 date), the date of randomization will be used.

Baseline transferrin saturation will be derived using the serum samples collected at screening. The transferrin saturation result is derived as: iron (umol/L) / total iron binding capacity (umol/L). In case the result of total iron binding capacity is reported as "<xxx", xxx-1 will be used as the total iron binding capacity to derive the transferrin saturation.

By-subject listings of the baseline disease characteristics will be provided.

In addition to the above baseline disease characteristics, the revised international prognostic scoring system for MDS (IPSS-R, Greenberg, 2012, Appendix G) will be summarized for exploratory purpose.

IPSS-R score will be classified and summarized as: very low, low, intermediate, high, very high. The derivation for the IPSS-R score is provided in Appendix G. The revised IPSS cytogenetic classification (from central lab) will also by summarized (very good, good, intermediate, poor, very poor).

By-subject listings of IPSS-R will be provided.

8.3. Medical History

A summary of medical and surgical history will be presented by treatment group and system organ class (SOC) Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. A by-subject listing of medical and surgical history will also be presented.

8.4. Prior MDS Treatment

A frequency table by Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) (March 2018 version, or higher) and preferred name will be provided. A by-subject listing of all prior MDS treatments given will also be presented.

8.5. Prior Cancer, Systemic Anti-cancer Therapy (Not for MDS) and Prior Radiation Therapy

A frequency tabulation of the number of subjects with prior cancer and prior systemic anti-cancer therapy will be provided. A listing of types of prior cancer and all prior systemic anti-cancer therapies documented on the CRF will also be presented.

A frequency tabulation of the number of subjects with prior radiation therapy, the types of radiation therapy used as well as descriptive statistics on the dose received will be given. A listing of all prior radiation therapies documented on the CRF will also be presented.

8.6. Prior Thrombocytopenia Therapy

A frequency tabulation of the number of subjects with prior thrombocytopenia therapy and the types of therapy given. A listing of all prior thrombocytopenia therapies as well as the date the thrombocytopenia was first reported as documented on the CRF will also be presented.

8.7. Prior Medications

Prior medications are defined as medications that were started before the date of first dose (whether or not ended before the date of first dose). Prior medications that continue into study treatment period will be also reported as concomitant medication.

Prior medications will be coded using WHO March 2018 version, or higher. Medication not in the WHO drug dictionary will be classified as "Not Coded" in the analysis.

A frequency table by ATC class and preferred name will be provided. A listing of prior medications documented on the CRF will also be provided.

8.8. Coombs Test Results

A by-subject listing of baseline Coombs test results and reticulocyte count based on the data collected on the CRF page will be provided.

8.9. Subsequent MDS Therapies

Subsequent MDS therapies will be summarized by ATC level 1 term and preferred name for the safety population, respectively. Details of subsequent MDS therapies will be presented in subject data listings.

8.10. Concomitant Medications

Concomitant mediations are defined as non-study medications that are started after the initiation but before the end of the study treatment (last dose of study drug + 28 days, death, whichever earlier), or started before the initiation of the study treatment and ended or remain ongoing after the study treatment initiation. Concomitant medications will be coded in WHO drug dictionary (March 2018 version, or higher). Medication not in the WHO drug dictionary will be classified as "Not Coded" in the analysis.

The ATC coding scheme of the WHO will be used to group medications into relevant categories. A frequency table by ATC class and preferred name will be provided. All concomitant medications documented on the CRF will be listed for the ITT population.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

See Section 5.1 for cycle start and end date as well as cycle number calculation.

The treatment duration (months) is defined as:

[(The treatment duration end date) – (the first study drug start date) + 1]/ 30.4375,

where treatment duration end data is defined as the last dose date + 7 days (the prescribed rest period of each cycle), or the death date, whichever is earlier.

Summary statistics will be provided for treatment duration by treatment group.

By-subject listings of all exposure information collected on the CRF will be provided.

9.2. Number of Treatment Cycles

Number of cycles for each treatment group will be summarized both descriptively and categorically for the safety population by treatment group.

9.3. Duration of Exposure

Duration of exposure will be calculated for each treatment group. Duration of exposure (days) of a study drug is defined as the total number of days on the study drug during the treatment period (excluding the periods of dose break per protocol or dose interruptions). Duration of exposure will be summarized descriptively for the safety population.

9.4. Average Length of Cycle

The average length of cycle (days) is defined as the treatment duration (in days) divided by the number of cycles. The average length of cycle (days) will be summarized descriptively for the safety population by treatment group.

9.5. Average Number of Days Dosed per Cycle

The average number of days dosed per cycle is defined as the number of days a subject is dosed divided by the number of cycles the subject had. The average number of days dosed per cycle will be summarized descriptively for the safety population by treatment group.

9.6. Cumulative Dose

The cumulative dose (mg) for a study drug is defined as the sum of all doses taken during the treatment period (in mg). Cumulative dose will be summarized for the safety population by treatment group.

9.7. Average Daily Dose

Average daily dose (mg/day) of a study drug is defined as the cumulative dose of the study drug divided by the number of days dosed (received a non-zero dose). Average daily dose will be summarized for the safety population by treatment group.

9.8. Dose Intensity

Actual dose intensity (mg/day) during the treatment is defined as the cumulative dose divided by treatment duration, which is defined as in Section 9.1.

Relative dose intensity (RDI) is defined as the ratio of actual dose intensity to the planned dose intensity, which is 300mg/day × 21 days/28days = 225 mg/day for all subjects.

The overall relative dose intensity will be categorized into < 75%, 75% to 85%, 85% to 100%, and > 100%, and frequency counts will be provided by treatment group.

9.9. Dose Adjustment

Dose adjustment (reduction/interruption), as reported in the Study Drug Record CRF page, will be summarized by treatment group and include the following:

- Subjects with at least one dose adjustment
- Reason for dose adjustment
- Time to the first dose adjustment
- Time to the first dose adjustment due to AE
- Duration of the first dose adjustment due to AE

Subjects who have been assigned to 300 mg x 14 days dose during Cycle 1 or Cycle 2 and subjects who have not been assigned to 300 mg x 14 days dose during Cycle 1 or Cycle 2 will be identified and the number of subjects will be presented by treatment group.

For subjects who have not been assigned to 300 mg x 14 days dose during Cycle 1 or Cycle 2, the number of dose reductions will be identified and summarized by treatment group:

- Subjects with only one dose reduction (from 300 mg x 21 days to 200 mg x 21 days);
- Subjects with only two dose reductions (from 300 mg x 21 days to 200 mg x 21 days, then from 200 mg x 21 days to 200 mg x 14 days);
- Subjects with three dose reductions (from 300 mg x 21 days to 200 mg x 21 days, then from 200 mg x 21 days to 200 mg x 14 days, then from 200 mg x 14 days to 200 mg x 7 days).

9.10. Treatment Compliance

The compliance rate (%) for each subject will be computed as 100 times the cumulative dose (in mg) taken over the period divided by the intended cumulative dose (in mg) that should have been taken over the same period. It will be calculated for each subject for each treatment cycle and overall.

Treatment compliance will be summarized using descriptive statistics by cycle and overall. Additionally, for overall treatment compliance, the number and percentage of subjects will be summarized by category < 75%, ≥75 to ≤ 120%, and > 120%.

10. EFFICACY ANALYSIS

All efficacy analysis will be performed on the ITT population. Key efficacy analysis will be performed on the mITT population as supportive evidence and to assess the robustness of the efficacy findings. Subjects will be analyzed according to randomized treatment group.

A sequential gate-keeping approach will be used to control the overall type I error rate and to perform hypothesis testing on multiple endpoints. Two endpoints, the primary efficacy endpoint of RBC transfusion independence and the key secondary endpoint of OS, will be tested sequentially in the pre-specified order. The primary efficacy endpoint will be tested first at the two-sided 0.05 significance level. In order to preserve the overall alpha level at 0.05 across the RBC transfusion independence and OS endpoints, formal statistical inference for the OS analyses can only be made if superiority of oral azacitidine is demonstrated for the primary efficacy endpoint, RBC transfusion independence, at the two-sided 0.05 significance level.

The primary efficacy endpoint, RBC transfusion independence, will be analyzed and reported only once after all 100% of the information is available for RBC transfusion independence rates (ie, after all 216 subjects have completed 12 months (52 weeks [364 days]) of double-blind treatment or have been discontinued from treatment). An interim analysis of the OS endpoint will also be conducted at the time of the analysis of the primary efficacy endpoint as the number of required 205 death events will not be reached by the time of the final analysis for the RBC transfusion independence endpoint. An O'Brien-Fleming group sequential type boundary will be used to preserve the overall alpha level of 0.05 for the analysis of OS.

The remaining secondary efficacy variables, with the exception of the proportion of subjects progressing to AML and time to AML progression, will be analyzed and reported once at the time of the analysis of RBC transfusion independence. Subjects will continue to be followed for progression to AML and survival until 205 deaths have been observed. Other than the pre-specified sequential testing of RBC transfusion independence and OS, no additional alpha adjustments for multiplicity will be made.

As there were no subjects enrolled from Japanese sites, the randomization stratification factor "country of enrollment (ie, Japan versus ROW)" will not be used when the analysis is performed.

10.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of RBC transfusion independence is defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days within the treatment period. A subject who did not receive any RBC transfusion during a consecutive rolling 56 days (i.e., day 1 to day 56, day 2 to day 57) will be considered as a 56-day RBC transfusion independent responder. Subjects without achieving the response as defined above, subjects with less than 56 days of assessment during the double-blind treatment period, and subjects who had average baseline RBC transfusion units less than 2 units per 28 days (as defined in Section 8.2) will be counted as non-responders.

All RBC transfusion records on or after randomization within the evaluation period will be used to assess the response for each subject. In other words, the days after the end of the evaluation period will not contribute to a rolling period. The end date of the evaluation period is defined as:

- For a subject who discontinues the treatment,

  - If the subject doesn't receive a subsequent MDS treatment, use the date of end of treatment visit;
  - If the subject receives a subsequent MDS treatment, use the start date of the subsequent MDS treatment – 1 day, or the date of end of treatment visit, whichever is earlier;
- For a subject who is still on-treatment at the time of the database lock for the primary analysis, the subject's latest available assessment date in the database (from AE, vital sign, local and central lab, study drug records, efficacy assessments) will be used.

The 56-day rolling period for the RBS transfusion independent assessment starts on the date of randomization.

Note if the interval between the last RBC transfusion in the evaluation period (if there is at least one RBC transfusion during the evaluation period) and the end date of the evaluation period is less than 56 days, this rolling period, which is less than 56 days, won't be considered as meeting the transfusion independence criteria even though there is no RBC transfusion in it. The day on which the transfusion is received will not contribute to the 56-day without receiving RBC transfusion rolling period.

The primary efficacy analysis will be performed on the ITT population and will compare the RBC transfusion independence rates in the two treatment groups. The number and percentage of subjects achieving RBC transfusion independence and corresponding 95% confidence intervals (CI) will be tabulated and presented by treatment group. A stratified Mantel-Haenszel (MH) chi-squared test, stratifying for average baseline RBC transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent or independent) and ECOG performance status (0 to 1 versus 2), at a two-sided alpha level of 0.05, will be used to compare the RBC transfusion independence rate between the two treatment groups. The p-value from the stratified MH chi-square test will be the confirmatory p-value for the test of the null hypothesis that the proportion of subjects achieving RBC transfusion independence is equal between the two treatment groups. Summaries will include the unadjusted difference in proportions between the two treatment groups with corresponding 95% CI and the common odds ratio with corresponding 95% CI. Subject listings with supporting data will be provided.

The stratification variables, average baseline RBC transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent or independent) and ECOG performance status (0 to 1 versus 2), will be derived from the corresponding CRF pages (see Section 8.2) and used in the stratified MH test.

The analysis of the primary endpoint will be repeated for the mITT population as the supportive analysis. Additionally, the following sensitivity analyses will be conducted after re-define the transfusion dependent subjects at baseline. Only the re-defined baseline RBC transfusion dependent subjects will be included in the sensitivity analyses:

- Re-define baseline RBC transfusion dependent subjects using the RBC transfusion data during the 56 days immediately preceding randomization, and only including RBC transfusion units that were given for a hemoglobin value ≤ 9.0 g/dL;
- Re-define baseline RBC transfusion dependent subjects using the RBC transfusion data during the 84 days immediately preceding randomization, and only including

RBC transfusion units that were given for a hemoglobin value ≤ 9.0 g/dL for 84 days, only subjects who were randomized under the original protocol and protocol amendment 1 are included;

For the sensitivity analyses, the pre-transfusion hemoglobin value collected on the Transfusion CRF will be used to assess the baseline transfusion dependency.

10.2. Analyses of Secondary Efficacy Endpoints

To control alpha, the Key Secondary Endpoint of Overall Survival (OS) will only be analyzed if the primary endpoint is statistically significant. The primary and key secondary endpoints are the only endpoints that will be controlled for alpha.

10.2.1. Key Secondary Endpoint

Overall survival (OS), defined as the time from randomization to death from any cause, will be calculated using randomization date and date of death, or date of last follow-up for censored subjects. Time to death is defined as the time between randomization and death from any cause. All subjects will be followed until drop-out, death, or study closure. Drop-out may be due to withdrawal of consent from further data collection or lost to follow-up. Subjects who drop-out or are alive at study closure (or at the time of the interim analysis [Section 15.2]) will have their OS times censored at the date of last known alive, as appropriate.

The analysis of OS will be performed using the ITT population for the interim and final analysis. The null hypothesis for testing the key secondary efficacy endpoint, time to death from any cause, is that the overall survival distributions for the two treatment groups are equivalent. Overall survival curves will be estimated using Kaplan-Meier (KM) methods and will be compared using a stratified log-rank test, stratifying by average baseline RBC transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent or independent) and ECOG performance status (0 to 1 versus 2). The p-value from the stratified log-rank test will be the confirmatory p-value. The p-value from the final analysis of the OS endpoint will be adjusted for the interim analysis to preserve the overall alpha level at 0.05 (see Section 15.2 for further details regarding the interim analysis and methods for controlling the overall alpha level). Kaplan-Meier estimates for median OS as well as the 25th and 75th percentiles and associated two-sided 95% CIs will be summarized for each treatment group, unadjusted for the stratification variables. In addition, both the numerical difference and the 95% CI of the difference, in the median, 25th, and 75th percentiles between the two treatment groups will be presented for the unstratified analysis. Plots of the KM survival curves will be presented for the two treatment groups, without adjustment for the stratification variables. At the time of the final OS analysis, a stratified Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI for oral azacitidine relative to placebo. The stratification variables average baseline RBC transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent or independent) and ECOG performance status (0 to 1 versus 2), will be derived from the corresponding CRF pages and used in the stratified log-rank test and the stratified Cox proportional hazards model.

Additionally, KM methods will be used to estimate the 1-year and 2-year survival probabilities for time to death from any cause. Estimates of the 1-year (365 days) and 2-year (730 days) survival probabilities and corresponding 95% confidence intervals will be presented by treatment

group. Median follow-up time by treatment will be estimated using KM methods. The analysis of the OS endpoint will be repeated for the mITT population as a supportive analysis.

To assess the potentially confounding effects of other cancer therapy received subsequent to the protocol therapy on the survival estimates, a sensitivity analysis based on the ITT population, will be performed using modified censored criteria. For this analysis, subjects who received subsequent therapy for MDS following discontinuation from their protocol therapy will be censored on the date that the subsequent therapy was started regardless of their survival status at the time of the final analysis. This modified time-to-death endpoint will be analyzed using the same methods as described above for the key secondary efficacy analysis.

The supportive and sensitivity analyses for the OS endpoint will be performed only at the time of the final analysis of OS.

10.2.2. Platelet response (HI-P)

HI-P is defined according to IWG 2006 criteria (Appendix E). HI-P rates will be summarized and compared between the two treatment groups using the same methods as the primary endpoint (see Section 10.1). The response collected in the IWG MDS Response Criteria CRF, and the response derived using central labs per IWG criteria will be summarized and analyzed separately. The detailed derivation is provided in Appendix F.

10.2.3. RBC transfusion independence for 84 days

RBC transfusion independence for 84 days is defined as the absence of any RBC transfusion during any consecutive "rolling" 84 days during the treatment period, i.e., Day 1 to 84, Day 2 to 85, Days 3 to 86, etc. The response is derived similarly as the derivation of the primary efficacy endpoint, except the rolling period is 84-day. The response of RBC transfusion independence for 84 days will be analyzed similarly as the RBC transfusion independence for 56 days (Section 10.1).

10.2.4. Duration of RBC transfusion independence of ≥ 56 days (8 weeks)

Duration of RBC transfusion independence will be analyzed only for subjects who achieve RBC transfusion independence of ≥ 56 days on treatment. Duration of RBC transfusion independence is defined as the time from the date transfusion independence is first observed (day 1 of a ≥ 56 days period without a transfusion) until the date the subject has a subsequently documented RBC transfusion. In case a subject has more than one ≥56 days rolling periods which meet the RBC independence criteria, the duration with the longest rolling period will be used in the analysis. Subjects who maintain RBC transfusion independence through the end of the treatment period or who are still on-going with the treatment will be censored at the end date of evaluation period which is defined in Section 10.1. Duration of RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using an unstratified log-rank test.

10.2.5. Time to RBC transfusion independence of ≥ 56 days (8 weeks)

Time to RBC transfusion independence of ≥ 56 days is defined as the time between randomization and the date onset of transfusion independence is first observed (ie, Day 1 of 56 without any RBC transfusions). Subjects who do not achieve RBC transfusion independence

during the treatment period will be censored at the end date of evaluation period which is defined in Section 10.1. In case a subject has more than one rolling periods which meet the independence criteria, the time to the first rolling period will be used in the analysis. Time to RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using a stratified log-rank test. A stratified Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI. Time to RBC transfusion independence (in month) for at least 56 days will also be summarized using descriptive statistics based on subjects who achieve the response.

10.2.6. Duration of RBC transfusion independence of ≥ 84 days (12 weeks)

Duration of RBC transfusion independence will be analyzed only for subjects who achieve RBC transfusion independence of ≥ 84 days on treatment. The calculation and analysis are similar as for the duration of RBC transfusion independence of ≥ 56 days (Section 10.2.4).

10.2.7. Time to RBC transfusion independence of ≥ 84 days (12 weeks)

Time to RBC transfusion independence of ≥ 84 days is defined as the time between randomization and the date onset of transfusion independence is first observed (ie, Day 1 of 84 without any RBC transfusions). The derivation and analysis are similar as for the time to RBC transfusion independence of ≥ 56 days (Section 10.2.5). Time to RBC transfusion independence (in month) for at least 84 days will also be summarized using descriptive statistics based on subjects who achieve the response.

10.2.8. Progression to AML

Progression to AML will be documented in central lab report or Follow-up Status CRF. Subjects who have a diagnosis of "s-AML arising from previous MDS" documented in central lab report (in case multiple records are available for the bone marrow and/or peripheral blood samples collected on the same day, the records with the latest report date will be used), or subjects with progression to AML documented in the Follow-up Status CRF will be identified. Number and percentage of subjects progressing to AML will be presented by treatment group.

10.2.9. Time to AML Progression

Time to AML Progression is defined as the time from the date of randomization until the date the subject has documented progression to AML. For subjects who have progression to AML documented in central lab report, the earliest sample collection date with the diagnosis of "s-AML arising from previous MDS" will be used as the date to AML progression (in case multiple records are available for the samples collected on the same day, the records with the latest report date will be used). For subjects who only have progression to AML documented in the Follow-up Status CRF, the date of progression from the CRF page will be used. Subjects who do not progress to AML will be censored at the date of last follow-up or at date of death. Time to AML progression curves will be estimated using KM methods and treatment groups will be compared using a log-rank test. KM estimates for median time to AML progression and the 1-year and 2-year AML progression rate will be summarized for each treatment group. A Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI. A competing risk analysis, treating death as a competing risk for AML progression, will be conducted for exploratory purposes.

10.2.10. Erythroid response (HI-E)

HI-E is defined according to IWG 2006 criteria (Appendix E). HI-E response will be analyzed similarly as HI-P (Section 10.2.2). The response collected in the IWG MDS Response Criteria CRF, and the response derived using central labs per IWG criteria will be summarized separately. The detailed derivation is provided in Appendix F.

10.2.11. Duration of RBC transfusion reduction

A subject will be considered as a RBC transfusion reduction responder if the subject has at least 4 units reduction in transfusion units over any consecutive 56 days period compared to the baseline transfusion units in 56 days. Subjects with less than 4 units RBC transfusions during the 56 days immediately preceding randomization will not be considered as a RBC transfusion reduction responder. The duration of response will only be determined for RBC transfusion reduction responders. Subjects who maintain the response through the end of the treatment period or who are still on-going with the treatment will be censored at the end date of evaluation period which is defined in Section 10.1. The derivation for responder and the calculation of the duration are similar as for the RBC transfusion independence described in Section 10.1 and Section 10.2.4. Duration of RBC transfusion reduction response will be analyzed descriptively using KM methods for the RBC transfusion reduction responders.

10.2.12. Platelet transfusion independence

Platelet transfusion independence is defined as the absence of any platelet transfusion during any consecutive "rolling" 56 days during the treatment period, (ie, Day 1 to 56, Day 2 to 57, Days 3 to 58, etc.). Subjects will be considered platelet transfusion dependent at baseline if they have received ≥ 2 platelet transfusions during the 56 days immediately preceding randomization and had no consecutive 28-day period during which no platelet transfusions were administered. The response is derived similarly as the derivation of the primary efficacy endpoint, except using platelet transfusion. Frequency cross-tabulations of platelet transfusion status (dependent or independent) at baseline versus on treatment will be presented by treatment group.

10.2.13. Duration of platelet transfusion independence

Duration of platelet transfusion independence will be analyzed only for subjects who are platelet transfusion dependent at baseline and achieve platelet transfusion independence on treatment. The calculation of the duration is similar as for the duration of RBC transfusion independence of ≥ 56 days (Section 10.2.4), except using platelet transfusion. Duration of platelet transfusion independence will be analyzed descriptively using KM methods.

10.2.14. Time to platelet transfusion independence

Time to platelet transfusion independence is defined as the time between randomization and the first documented date of onset of transfusion independence (ie, Day 1 of 56 without any platelet transfusions). The derivation is similar as for the time to RBC transfusion independence of ≥ 56 days (Section 10.2.5), except using platelet transfusion. Subjects who are platelet transfusion independent at baseline will be excluded from the analysis. Time to platelet transfusion independence will be analyzed descriptively using KM methods. Time to platelet transfusion

independence (in month) for at least 56 days will also be summarized using descriptive statistics based on subjects who achieve the response.

10.2.15. Hematologic response

Hematologic response (Complete Remission [CR], Partial Remission [PR], Marrow CR [mCR], Stable Disease [SD], Disease Progression [PD], Failure, Relapse after CR or PR, and Cytogenetic Response) is defined according to IWG 2006 criteria (Appendix E). Subjects will be classified according to their best response achieved during treatment for the response categories of CR, PR, mCR, SD, PD, and failure. Only subjects who achieve CR or PR will be included in the Relapse after CR or PR category. Subjects will be evaluated for cytogenetic response regardless of their response status in other categories. For cytogenetic response, subjects will be classified as having a complete or partial response based on the best response achieved during treatment. Hematologic response will be presented descriptively, by treatment group, using counts and percent. All above responses collected in the IWG MDS Response Criteria CRF will be summarized. In addition, hematologic response CR, PR, SD, mCR, relapse after CR or PR, cytogenetic response, and hematologic improvement will be derived using central labs per IWG criteria and will be summarized separately. The detailed derivation is provided in Appendix F.

10.2.16. Clinically significant bleeding event

Clinically significant bleeding event is defined as: any intracranial or retroperitoneal bleed; bleeding requiring transfusions of > 2 units of blood/blood products; bleeding associated with a decrease in hemoglobin of > 2 g/dL; or bleeding from any site requiring transfusions of > 2 units of blood. Number and percentage of subjects experiencing a clinically significant bleeding event will be presented by treatment group. Additionally, the number and percentage of subjects by the number of clinically significant bleeding events experienced during the treatment period will be summarized by treatment group.

10.2.17. ECOG Performance Status

ECOG performance will be summarized categorically with a shift from baseline to the worst post-baseline by cycle and for all cycles. Individual subject data will be listed. The ECOG performance score collected as Cycle 1 Day 1 will be used as the baseline value.

10.3. Subgroup Analysis

In addition to analyses that include all ITT subjects, additional exploratory subgroup analyses will be performed where an adequate number of subjects are available in each subgroup to allow for meaningful interpretation of results. Analyses will be performed within the following subgroups for the RBC transfusion independence for at least 56 days and OS endpoints:

- Age group (< 65, ≥ 65 years)
- Sex (Male, Female)
- Race (White, Asian, Others)
- WHO MDS diagnosis classification (RCMD, RAEB-1, Others)
- Baseline bone marrow blasts (< 5%, ≥ 5%)

- Geographic region (North America, Europe, ROW)
- Average baseline RBC transfusion requirements prior to randomization (≤ 4 units of RBC per 28 days, > 4 units of RBC per 28 days)
- Baseline platelet transfusion status (Dependent, Independent)
- ECOG performance status (0 or 1, 2)
- Baseline Platelet Count (≤ 50 x 10^9/L, >50 x 10^9/L- ≤ 75 x 10^9/L)
- Prior lenalidomide use (Yes, No)
- Subject enrolled under Amendment 2 (Yes, No)
- IPSS-R risk category (Very low or low, Intermediate, High or very high)

RBC transfusion independence for 56 days and OS will be analyzed separately within each subgroup using the appropriate analysis methods as described in Section 10.1 and Section 10.2.1. The odds ratios (ORs) for RBC transfusion independence and the hazard ratios (HRs) for OS will be presented graphically in forest plots.

The OS will also be explored by whether a subject achieves RBC transfusion independence for at least 56 days or not. Kaplan-Meier estimates for median OS as well as the 25th and 75th percentiles and associated two-sided 95% CIs will be summarized for each subgroup group (Responders and Non-responders), unadjusted for the stratification variables. This will be explored for all subjects in ITT population as well as for subjects within oral azacitidine arm and within Placebo arm.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the safety population.

Besides the safety analysis described in this section, additional safety analysis may be performed, displayed and summarized, when deemed necessary.

11.1. Adverse Events

Adverse events (AEs) will be coded according to the MedDRA version 21.0 or higher. The severity of AEs will be assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For any AE not listed in the CTCAE grading system, the severity of these events will be assessed by the Investigator using a 5-point scale as described in Section 11.2.2. of the protocol.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening with an onset date on or after the date of the first dose of the study medication and within 28 days after the date of the last dose. AEs will be summarized by SOC, preferred term (PT) and treatment group. The AE summarizes will include incidence tables of:

- Summary of TEAEs.
- TEAEs.
- Treatment-related TEAEs.
- Serious TEAEs.
- Treatment-related serious TEAEs.
- TEAEs with CTCAE toxicity grade of 3 or 4.
- Treatment-related TEAEs with CTCAE toxicity grade of 3 or 4.
- Serious TEAEs with severity of grade 3 or 4.
- Treatment-related Serious TEAEs with severity of grade 3 or 4.
- TEAE leading to death.
- TEAEs leading to dose reduction.
- TEAEs leading to dose interruption.
- TEAEs leading to dose interruption and reduction.
- TEAEs leading to treatment discontinuation.
- Treatment-related TEAEs leading to death.
- TEAEs by maximum severity.
- TEAEs by age group (<65, 65 to 74, ≥75 years).
- TEAEs by sex.
- TEAEs by decreasing order of frequency of preferred term.

- TEAEs by decreasing order of frequency of system organ class.
- Serious TEAEs by decreasing order of frequency of preferred term.
- Serious TEAEs by decreasing order of frequency of system organ class
- Pre-treatment AEs.
- Non-serious TEAEs

Subjects with multiple events reported for the same preferred term will be counted only once per SOC and PT level. For summaries by severity (CTCAE grade), if a subject experience the same PT multiple events, then the subject will be counted only once and for the greatest severity.

In summaries of treatment-related TEAEs, if a subject reports multiple occurrences of the same AE, only the treatment-related occurrence will be summarized. Adverse events with missing relationship to study medication will be imputed as related to study medication.

Additionally, the exposure-adjusted incidence rate (EAIR) per 100 person-years will be summarized for all TEAEs and Grade 3 or 4 TEAEs by system organ class, preferred term, and treatment group. The EAIR per 100 person-years is defined as 100*(n/T), where n is the number of subjects with the specific AE at the SOC or PT level, and T is total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event will be counted only once in the numerator. The exposure time for a subject without the specific event is the treatment duration (calculated as Min [death date, last dose date + 28] – first dose date + 1 day), whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event. The total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25. The EAIR per 100 person-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 person-years of exposure to the study drug.

Listings for the corresponding summary tables for TEAE, Serious TEAE, TEAEs leading to study drug discontinuation and TEAEs leading to death will be presented separately.

11.1.1. Adverse Events by Cycle

The following TEAEs will be summarized by incidence tables, for the safety population by treatment group and cycle group:

- All TEAEs
- Serious TEAEs
- TEAEs with severity of grade 3 or 4;
- TEAEs leading to death
- Treatment-related TEAE leading to death
- TEAEs leading to study medication discontinuation

The following cycle group will be used:

- Cycles 1-2

- Cycles 3-4
- Cycles 5-6
- Cycles 7-12
- Cycles 13-24
- Cycles > 24

The analysis of TEAE by cycle of onset for any occurrence will be based on the onset date of AE to determine the cycle. AEs with a duration that overlaps multiple cycles will only be counted in the first overlapped cycle. Subjects with multiple occurrences reported with the onset date within the same cycle for the same SOC / PT will be counted once per SOC level / PT level within the cycle.

TEAEs by cycle day of onset for any occurrence will also be summarized. The cycle day will be grouped as: cycle days 1-7, cycle days 8-14, cycle days 15-21, and cycle days >21.

The first occurrence of TEAEs by cycle of onset, and by cycle day of onset will be summarized by SOC and PT. Subjects with multiple occurrences reported for the same SOC / PT will be counted only once based on the earliest onset date (the first occurrence) per SOC level / PT level.

11.1.2. Adverse Events of Special Interest

The AEs described in this section have been identified as treatment-emergent AEs of special interest (AESI) based on the known safety profile of azacitidine. These treatment-emergent AESI include those adverse events which Celgene is actively monitoring.

AESIs refer to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. The AESI category or term refers to the group of PTs, rather than the individual PT. Standardized MedDRA queries (SMQs) or company MedDRA queries based on specific SOC, higher level terms (HLT) or PTs were used to define the categories of AEs of special interest.

TEAEs will be summarized for the following categories of AESIs, by PT and treatment group:

- Myelosuppression,
  - Neutropenia
  - Thrombocytopenia
  - Anemia
  - General myelosuppression
- Hemorrhagic events
- Infection
- Hepatic failure
- Renal failure
- Ischemic colitis

- Gastrointestinal events
- Interstitial lung disease
- Tumour lysis syndrome
- Cardiac events:
  - Cardiac arrhythmias
  - Myocardial infarction
  - Cardiac failure
- Anxiety, Confusional State, Insomnia
- Psychiatric Disorders

Separate frequency tables will be provided for the AESIs identified above by AESI category, PT and treatment group:

- Summary of AESIs;
- All AESIs;
- Treatment-related AESIs;
- Serious AESIs;
- Treatment-related serious AESIs;
- AESIs with severity of grade 3 or 4;
- AESIs leading to death;
- AESIs leading to death by cycle of onset;
- Treatment-related AESIs leading to death;
- AESIs leading to dose reduction;
- AESI leading to dose interruption;
- AESI leading to dose interruption and dose reduction;
- AESIs leading to study medication discontinuation;
- Treatment-related AESI leading to study drug discontinuation;
- AESI with EAIR.

The summaries of all AESIs, serious AESIs, AESIs with severity of grade 3 or 4, AESIs leading to death, and AESIs leading to study medication discontinuation will also be presented by cycle group as defined in Section 11.1.1.

Additional safety analyses may be displayed by specific parameters, (e.g. time to occurrence, demographics, exposure/duration) if warranted. Similarly, other selected listings may be necessary to assist with analysis of the safety data.

11.1.2.1. Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as adverse events of interest and reported in the CRF serious adverse event for SPM page throughout a subject's duration in the study (signing of informed consent form through the follow-up period of study). By-subject listings will be provided for SPMs and related procedures/surgeries, radiation therapies and regimen therapies.

SPM identified as treatment-emergent AESI will be summarized by treatment group.

11.1.2.2. Progression to AML

Progression to AML will be identified as treatment-emergent AESI and will be summarized by treatment group.

11.2. Death

Frequency tables of primary cause of death category (as selected by the investigator), and the primary diagnosis (by SOC and PT) per the death CRF page will be provided by treatment period (on-treatment, or post-treatment) by treatment group for subjects in the safety population, as well as for subjects who are screen failures (pre-treatment period). A listing of deaths from the death CRF page, will be provided for all subjects who died after signing informed consent.

11.3. Clinical Laboratory Evaluations

Clinical laboratory values will be presented using the reported units. Change in clinical laboratory results from baseline (last non-missing value on or prior to the date of first dose of the study drug) to each scheduled time point will be provided for the safety population. Clinical laboratory values will be graded according to CTCAE version 4.0 for applicable tests. Shift tables for change in maximum CTCAE grades of high and low lab values, separately, will be provided for the safety population by treatment for those labs that have CTCAE grades. Separate shifts tables will be provided for lowest value by cycle and highest value by cycle. Clinically significant laboratory abnormalities that meet Grade of 3 or Grade 4 criteria according to the CTCAE will be listed and summarized (counts and percentages) by cycle. Laboratory data collected after the date of the end of treatment visit, last dose date + 28 days, whichever the latest, will not be used for summary. Nadirs, the minimum values, of selected hematology parameters, ie. Hgb, platelets, absolute neutrophil count (ANC), white blood cell counts, and RBC, across all cycles and within each cycle will be summarized. The day of nadir will be summarized categorically by frequency of the day of the cycle that the nadir observation occurs, by cycle and treatment. The categories for the days within a cycle are day 1-7, Day 8-14, Day 15-21 and Day >21. The average onset day of nadir across all cycles, the analyte value at nadir by cycle, and the change from baseline to analyte value at nadir will be summarized descriptively by treatment for each selected hematology test.

A separate listing, including only values outside the normal range, if any, will also be provided. A listing of all clinical laboratory values will be provided. Separate listings will be provided for the hematology, blood chemistry, coagulation, urinalysis, erythropoietin, ferritin and serum tranferrin saturation laboratory values.

Graphical display of select laboratory parameters over the course of the study will be provided (if needed).

11.4. Vital Sign Measurements

Vital sign measurements (weight, systolic and diastolic blood pressure, pulse rate, respiration rate and temperature) as well as change from baseline will be summarized descriptively by scheduled time point. The last vital sign measurement on or prior to the date of first dose of study drug will be used as the baseline value. Frequency summaries (shift tables) of shifts from baseline to post-baseline by cycle and to the worst post-baseline value in terms of normal/abnormal will be provided for pulse, respiratory and blood pressure. The normal ranges are defined as: 60-100 beats/minute for pulse, 12 to 16 breaths/minutes for respiratory rate, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure). Vital sign data collected after the date of the end of treatment visit, last dose date + 28 days, whichever the latest, will not be used for summary. A listing of all vital signs will be provided.

11.5. Bone Marrow Aspirate Differential and Peripheral Blood Smear

Bone marrow aspirate differential and peripheral blood smear differential, including erythroid precursors, Monocytic lineage, bone marrow blasts (%), ringed sideroblast (%), myeloid lineage, and peripheral blood blasts, as well as their changes from baseline, will be summarized descriptively by cycle and treatment for the Safety population. For each variable, the last observed values on or prior to the date of the first dose date will be used as the baseline value. Bone marrow and peripheral blood data collected after the date of the end of treatment visit, last dose date + 28 days, whichever the latest, will not be used for summary. Individual subject information for bone marrow aspirate and bone marrow biopsy will be listed.

11.6. Electrocardiogram

A 12-lead electrocardiogram (ECG) is required for all subjects at Screening visit. ECG results will be provided in a by-subject listing.

11.7. Pregnancy

A by-subject listing of pregnancy tests and results will be provided for all female patients of childbearing potential.

12. HEALTH-RELATED QUALITY OF LIFE ANALYSIS

The primary objective of the HRQoL assessment is to evaluate the impact of oral azacitidine on HRQoL relative to placebo. Analyses will address mean differences by treatment group on HRQoL scale and subscale scores and treatment group differences in the proportion of subjects who achieve a minimal clinically important difference. Complete analysis plans, including methods to assess responsiveness and minimally important differences will be described in a separate HRQoL statistical plan.

13. HEALTHCARE RESOURCE UTILIZATION

Healthcare resource utilization collected on the CRF healthcare utilization form will be summarized by treatment group and listed for individual subject. Summaries will include number of events, reasons for hospitalization, total number of days hospitalized, the rate of events and days of hospitalized per person-year of exposure and associated relative risk of hospitalization with the corresponding 95% CI.

15. INTERIM ANALYSIS

15.1. General Information

An independent Data Monitoring Committee (DMC) with multi-disciplinary representation has evaluated safety during the course of the study in compliance with a prospective charter. The DMC comprised of medical oncologists/hematologists with experience treating MDS and a statistician, all of whom were not otherwise involved in the study as investigators. An independent statistician generated critical safety reports for the DMC to review periodically. The DMC chairperson might convene formal DMC meetings if there were safety concerns. The Sponsor can also request a DMC review of safety data. The DMC responsibilities, authorities, and procedures were documented in the DMC charter, which were endorsed and signed by the DMC prior to the first data review meeting.

15.2. Statistical Approaches for Control of Alpha

An interim analysis of the OS endpoint will be performed when all 216 subjects have completed 12 months of double-blind treatment or discontinued before reaching 12 months of double-blind treatment (100% information for the primary endpoint), whichever occurs first. It is projected that approximately 68% of the expected total deaths will have occurred at the time of the interim analysis. An O'Brien-Fleming group sequential boundary with a Lan-Demets alpha spending function will be used to preserve the overall alpha level at 0.05 for testing the OS endpoint. The required (two-sided) significance levels are estimated to be 0.013 at the interim and 0.037 at the final analysis for OS assuming 68% of the events have occurred, but the actual levels used will depend on the actual number of events at the time of the interim analysis.

In order to preserve the overall alpha level at 0.05 across the RBC transfusion independence and OS endpoints, formal statistical inference for the OS analyses can only be made if superiority of oral azacitidine is demonstrated for the primary efficacy endpoint, RBC transfusion independence, at the two-sided 0.05 significance level.

16. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

As there were no subjects enrolled from Japanese sites, the randomization stratification factor "country of enrollment (ie, Japan versus ROW)" will not be used when the analysis is performed.

Frequency cross-tabulations of RBC transfusion dependent status for 84 days at baseline versus on treatment will not be provided.

The end date of the evaluation period defined in Section 10.1 is used as the censoring date when calculating the duration of RBC transfusion independence ≥ 56 days and ≥ 84 days, duration of RBC transfusion reduction and duration of platelet transfusion independence. As defined in Section 10.1, the days after a subject started subsequent MDS treatment will not be included in the response duration. The end date of the evaluation period defined in Section 10.1 is also used as the censoring date for subjects who do not achieve the corresponding response during the treatment period in the analysis of time to RBC transfusion independence ≥ 56 days and ≥ 84 days, and time to platelet transfusion independence.

Progression to AML will be identified based on documentations in central lab report or Follow-up Status CRF, please see detail in Section 10.2.8.

No other changes to the statistical analyses section of the protocol are made in this SAP.

17. REFERENCES

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18. APPENDICES

18.1. Appendix A: Date Imputation Guideline

18.1.1. Impute Missing AE/ Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is **same** as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields
- If the year is **prior to** the year of first day on study medication, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.
- If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dose date of double-blind study medication, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

18.1.2. Impute Missing Start Dates of Subsequent MDS Treatment

If the start date of the subsequent MDS treatment is unknown, it will be imputed as the earliest possible date after the last dose date (1 day after) which is collected in the treatment discontinuation CRF.

Missing day and month

- If the year is **same** as the year of the last dose date, then the last dose date + 1 day will be assigned to the missing date.
- If the year is **after** the year of the last dose date, then January 1 will be assigned to the missing fields.
- The year should not be **prior to** the year of the last dose date. In case that happens, December 31 will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the year and month of the last dose date, then the last dose date + 1 day will be assigned to the missing date.
- If the month and year are **after** the year and month of the last dose date, then the first day of the month will be assigned to the missing day.
- If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.
- The month and year should not be **prior to** the year and month of the last dose date. In case that happens, the last day of the month will be assigned to the missing day.

Missing day, month, and year

- The start date of the post MDS treatment should not be completely missing. In case that happens, the last dose date + 1 day will be assigned to the missing date.

18.2. Appendix B: Myelodysplastic Syndromes World Health Organization Classification System

Myelodysplastic Syndromes WHO Classification System		
Category	**Definition**	
	Peripheral Blood Smear Evaluation	**Bone Marrow Evaluation**
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (< 1%)[b]	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ringed sideroblasts
Refractory Anemia With Ringed Sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ringed sideroblasts Erythroid dysplasia only < 5% blasts
Refractory Cytopenia With Multilineage Dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[b] No Auer rods < $1x10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ringed sideroblasts
Refractory Anemia With Excess Blasts-1 (RAEB-1)	Cytopenias < 5% blasts[b] No Auer rods < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[b] No Auer rods
Refractory Anemia With Excess Blasts-2 (RAEB-2)	Cytopenias 5%-19% blasts[c] Auer rods[c] < $1x10^9$/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[c] Auer rods ±[c]
Myelodysplastic Syndrome - Unclassified (MDS-U)	Cytopenias < 1% blasts[b]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS[d]
MDS Associated With Isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rods + and/or 5% to 19% blasts in the blood.

[d] Includes unbalanced abnormalities -7 or del(7q), -5 or del(5q), i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), balanced abnormalities t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.1), T2;11)(p21;q23), inv(3)(q21q26.2), and t(6;9)(p23;q34), and complex karyotype (3 or more

chromosomal abnormalities) involving one of more of the listed abnormalities.

Sources: Brunning RD, Bennett JM, Flandrin G, Matutes E, Head D, Vardiman JW, et al. Pathology and genetics of tumors of hematopoietic and lympoid tissues. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumors. Lyon (France). IARC Press, 2001:63-73.

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18.3. Appendix C: International Prognostic Scoring System Score

International Prognostic Scoring System for MDS					
	Score Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone Marrow Blasts (%)	< 5	5-10	-	11-20	21-30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0 or 1	2 or 3			

[a] Good: normal, -Y, del(5q), del(20q); Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate: other abnormalities.

[b] Defined as: Hemoglobin < 100 g/L, absolute neutrophil count < 1.5 x 10^9/L, and platelet count < 100 x 10^9/L.

Note: Scores for risk groups are as follows: Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5-2.0; and High: ≥ 2.5

Source: Greenberg, P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.

18.4. Appendix D: ECOG Performance Status

ECOG Performance Status	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 1982;5(6):649-55.

18.5. Appendix E: Hematologic Response According to the IWG Criteria for MDS

Modified Hematologic Response According to IWG Criteria for MDS	
Category	**Response criteria (responses must last at least 4 weeks)**
Complete Remission (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 X 10^9/L Neutrophils ≥ 1.0 X 10^9/L[b] Blasts 0%
Partial Remission (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 (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of 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
Cytogenetic Response	Complete - Disappearance of the chromosomal abnormality without appearance of new ones Partial - At least 50% reduction of the chromosomal abnormality
Disease Progression	For subjects with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase 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 Transfusion dependence

KEY: CR = complete remission; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PFS = progression free survival; PR = partial remission

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG response criteria.

[d] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such subjects 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.

Notes: Subjects with CMML will be assessed for response using the IWG criteria for MDS. Deletions to IWG response criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: 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.

Modified Hematologic Improvement According to IWG Criteria

Hematologic improvement[a]	Response criteria (responses must last at least 8 week)[b]
Erythroid Response (HI-E) (pretreatment, <11 g/dL)	Hemoglobin increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation[b]
Platelet Response (HI-P) (pretreatment, <100 X 10^9/L)	Absolute increase of ≥ 30 X 10^9/L for subjects starting with > 20 X 10^9/L platelets Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%[b]
Neutrophil Response (HI-N) (pretreatment, <1.0 X 10^9/L)	At least 100% increase and an absolute increase > 0.5 X 10^9/L[b]
Progression or Relapse After HI[c]	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in hemoglobin by ≥ 1.5 g/dL Transfusion dependence

KEY: HI = hematologic improvement; HI-E = hematologic improvement erythroid response; HI-N = hematologic improvement neutrophil response; HI-P = hematologic improvement platelet response; IWG = International Working Group; MDS = myelodysplastic syndromes; RBC = red blood cell

a Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).

b Modification to IWG response criteria.

c In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Note: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Source: 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.

18.6. Appendix F: Derivation Rules for Hematologic Response and Hematologic Improvement According to the IWG Criteria for MDS

Following rules will be used to derive the hematologic response, cytogenic response, and hematologic improvement using central lab data, including central lab data for bone marrow. Lab data collected after the date of the end of treatment visit, or last dose date + 28 days, whichever occurs later, will not be used.

In the following derivations, if Hgb or platelet counts are used for evaluation, the Hgb values are only valid to use if there is no RBC/Whole blood transfusion within 7 days prior to the sample collection, the platelet count values are only valid to use if there is no platelet transfusion within 7 days prior to the sample collection.

18.6.1. Hematologic Response

- **Complete Remission (CR)**:

  1. At each time point, check if the following criteria are all met:

     a. Bone marrow blast ≤5%,
     b. Peripheral blood blast = 0%,
     c. Hgb ≥ 11 g/dL,
     d. Platelets ≥100 x 10^9 /L,
     e. Neutrophils ≥1.0 x 10^9/L;

  2. The criteria in item 1 must be met for at least 4 weeks, ie., within 4 weeks there is no lab result showing any of the criteria (a to e) can't be met. However, if the "4 weeks" assessment/confirmation is not available because the subject discontinued treatment within the 4 weeks following the previous assessment, these records will not contribute to CR.

  To derive the responses at each time point, if the bone marrow blast assessment, Hgb, platelet, and/or Neutrophils, are not available, the results obtained from the latest available assessment will be used. For peripheral blood blast, if it is assessed by both lab and lab at a time point, the higher value will be used; if it is assessed by either lab or (but not both) at a time point, then the result from the available lab lab or) will be used; if at a time point, both results are missing, the latest result from either lab or (but not both) will be used.

  CR (Yes) will only be available for subjects with baseline bone marrow blasts > 5%.

- **Partial Remission (PR)**:

  For PR, all criteria for CR must be met except for 1(a). Replace 1(a) by: Bone marrow blasts decreased by ≥ 50% over pretreatment (baseline value) but still > 5%.

  PR (Yes) will only be available for subjects with baseline bone marrow blasts > 5%.

- **Marrow CR** (mCR):

  1. At each time point, check if the following criteria are all met:

     a. Bone marrow <=5%;
     b. Bone marrow reduction from baseline ≥ 50%.

2. The criteria in item 1 must be met for at least 2 consecutive bone marrow assessments.

If a subject only has one post-baseline bone marrow result, the subject will not be considered as a responder for mCR.

mCR (Yes) will only be available for subjects with baseline bone marrow blasts > 5%.

- **Disease progression (modified from IWG)**:

A subject is considered having disease progress per the following rules:

For patients with:

- < 5% blasts: >= 50% increase in blasts and has blasts > 5%
- >= 5% - < 10% blasts: >= 50% increase and has blasts > 10%
- >= 10% - < 20% blasts: >= 50% increase and has blasts > 20%
- >= 20% - < 30% blasts: >= 50% increase and has blasts > 30%

Bone marrow blasts are used.

Or with any of the following:

a. At least 50% decrement from maximum remission / response levels in neutrophils and < 1.0 x 10^9 /L;
b. At least 50% decrement from maximum remission / response levels in platelets and <100 x 10^9 /L;
c. Reduction from maximum remission / response levels in Hgb by ≥ 2 g/dL and < 11 g/dL;

To confirm a "disease progression", any of the criteria (a, b and c) a subject met in a previous assessment must be kept for at least 4 weeks.

- **Stable disease**:

For at least 8 weeks, failure to achieve at least mCR, but no evidence of progression.

- **Failure due to death:**
  - Death during treatment; AND
  - No post-baseline efficacy assessments are available; i.e., no bone marrow or hematology available.
- **Not evaluable:**
  - Subject withdrew consent or was lost to follow-up, AND
  - Subject was alive at last contact, AND
  - No post-baseline efficacy assessments are available; i.e., no bone marrow or hematology available.
- **Relapse after CR or PR:**

A subject is considered having "Relapse after CR or PR" if any of the following is met:

- Return to pretreatment (baseline) bone marrow blast percentage;
- At least 50% decrement from maximum remission / response levels in neutrophils and < 1.0 x 10^9 /L;
- At least 50% decrement from maximum remission / response levels in platelets and <100 x 10^9 /L;
- Reduction in Hgb concentration from maximum remission / response levels by >= 1.5 g/dL and < 11 g/dL or transfusion dependence

To confirm a "relapse", the criterion a subject met in a previous assessment must be met for at least at least 4 weeks. Subjects will not be evaluable for relapse after CR or PR if no 4 weeks data available.

18.6.2. Cytogenetic response (Complete or Partial)

1. At each time point, Abnormality Rate = (abnormal_metaphases / metaphases_analyzed) * 100%;
2. The abnormality rate at the screening visit is considered as the baseline abnormality rate, in case there are multiple records, use the one with the larger "metaphases_analyzed";
3. Only the subjects with non-zero baseline abnormality rate will be included in the analysis;
4. **Cytogenetic Complete Response** (CR) is "Yes" if the post-baseline abnormal rate is decreased to 0; in case the number of baseline "abnormal_metaphases" is ≤ 4, the post-baseline responses from two consecutive time points will be needed to confirm a CR is "Yes" (this time point and the next time point both have 0 abnormality rate);
5. **Cytogenetic Partial Response** (PR) is "Yes" if the post-baseline abnormal rate is decreased by at least 50% from the baseline; in case the number of baseline "abnormal_metaphases" is ≤ 4, the post-baseline responses from two consecutive time points will be needed to confirm a PR is "Yes" (this time point and the next time point both have abnormality rate decrease by at least 50% from the baseline).

18.6.3. Hematologic Improvement

Following rules will be used to derive the hematologic improvement using the central lab data.

- Platelet Response (HI-P):
  - Absolute increase of ≥ 30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets, or
  - Increase from ≤ 20 x 10^9/L to > 20 x 10^9/L and by at least 100%.

  Platelet values within 7 days following a platelet transfusion will not be used.
- Erythroid Response (HI-E):
  - Hgb increase by ≥ 1.5 g/dL, or

  - Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 10.0 g/dL on treatment will count in the RBC transfusion response evaluation.

Hgb values within 7 days following a RBC/Whole blood transfusion will not be used.

- Neutrophil Response (HI-N) (only derived for subjects with baseline ANC < 1.0 x 10^9/L):
  - At least 100% increase and an absolute increase > 0.5 x 10^9/L.

For HI-E, the relevant reduction of units of RBC transfusions is confirmed by checking whether a subject is a RBC transfusion reduction responder as defined in Section 10.2.11, ie., if the subject has at least 4 units reduction in transfusion units over a consecutive 56 days period compared to the baseline transfusion units in 56 days.

For HI-P, HI-E and HI-N, the above criteria must be met for at least 8 weeks for a subject to be counted as a responder. If a subject doesn't have the subsequent data which meet the response criteria, the subject will not be considered as a responder.

18.7. Appendix G: Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes

The IPSS-R score will be derived per Greenberg, 2012.

Table 2. IPSS-R Prognostic Score Values

Prognostic Variable	0	0.5	1.0	1.5	2.0	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Bone Marrow Blast %	≤ 2		>2-<5%		5-10%	>10%	
Hemoglobin (g/dL)	≥10		8-<10	<8			
Platelets ($x10^9$/L)	≥100	50-<100	<50				
Absolute Neutrophil Count ($x10^9$/L)	≥0.8	<0.8					

Source: Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012; 120: 2454-2465.

Table 3. IPSS-R Prognostic Risk Categories/Scores

RISK CATEGORY	RISK SCORE
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Source: Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012; 120: 2454-2465.

The IPSS-R score will be the sum of the score values from the five prognostic variables. If at least one of the variables is missing, then the IPSS-R score is set to missing, unless the sum of the existing variables is >6 (in this case, the risk category is "Very High").

For baseline IPSS-R score, the central data collected during the screening phase and/or on Cycle 1 Day 1 (if available) will be used. The latest assessment for cytogenetics, bone marrow blast, and absolute neutrophil count, the worst values of hemoglobin, and platelets during the screening phase (including Cycle 1 Day 1) will be used. In case there are multiple results of cytogenetics and/or bone marrow blast from the same sample collection date, the record with the latest receiving date (XRDTC) will be used.

IPSS-R prognostic risk categories will be derived according to Table 3.

Celgene Signing Page

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UserName:
Title:
Date: Thursday, 28 March 2019, 08:36 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName:
Title:
Date: Friday, 29 March 2019, 01:01 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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UserName:
Title:
Date: Friday, 29 March 2019, 03:35 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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