Official Title of Study:

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

NCT Number: NCT01566695

Document Date (Date in which document was last revised): 24 May 2022

# 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

| | |
|---|---|
| **INVESTIGATIONAL PRODUCT (IP):** | Oral Azacitidine |
| **PROTOCOL NUMBER:** | AZA-MDS-003 |
| **ORIGINAL DATE FINAL:** | 01 May 2012 |
| **AMENDMENT No. 1.0 DATE FINAL:** | 11 Apr 2014 |
| **AMENDMENT No. 2.0 DATE FINAL:** | 08 Oct 2015 |
| **AMENDMENT No. 3.0 DATE FINAL:** | 21 Feb 2018 |
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| **AMENDMENT No. 5.0 DATE FINAL** | 28 Nov 2018 |
| **AMENDMENT No. 6.0 DATE FINAL** | 24 May 2022 |
| **EudraCT NUMBER:** | 2012-002471-34 |
| **IND NUMBER:** | 074618 |
| **SPONSOR NAME / ADDRESS:** | Celgene Corporation<br>86 Morris Avenue<br>Summit, NJ 07901 |

## MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

| Contact Information: | |
|---|---|
| **Name:** | [redacted] |
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| **Phone:** | [redacted] |
| **E-mail:** | [redacted] |

**Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.**

| **Back-up 24 Hour Global Emergency Contact Call Center:** [redacted] |
|---|

## CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

*{See appended electronic signature page}*

**Signature of Celgene Therapeutic Area Head** **dd mmm yyyy**

[redacted]

**Printed Name of Celgene Therapeutic Area Head and Title**

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

## CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted]

**Signature of Celgene Therapeutic Area Head** **dd mmm yyyy**

[redacted]

**Printed Name of Celgene Therapeutic Area Head and Title**

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

## SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Signature of Site Principal Investigator** | **dd mmm yyyy** |
| **Printed Name of Site Principal Investigator**<br>**Institution Name:**_____<br>By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonization (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies. | |

## COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Signature of Coordinating Principal Investigator** | **dd mmm yyyy** |
| **Printed Name of Coordinating Principal Investigator**<br>**Institution Name:**_____<br>By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed. | |

## OVERALL RATIONALE FOR PROTOCOL AMENDMENT 6.0:

This protocol was amended to reduce the duration of survival follow-up for the patients in the Extension Phase (EP) from following up on regular basis until death, withdrawal of consent, lost to follow-up, or study termination, whichever is earlier, to 35 days ± 7 days after treatment discontinuation or until death, withdrawal of consent for further data collection, lost to follow-up, or study termination, whichever is earlier. This 35-day follow-up period includes a 28-day safety follow-up plus a 7-day window.

As of 04-Feb-2020, the primary analysis Clinical Study Report (CSR) for this study, with data cut-off date of 25-Jan-2019, was finalized. At data cut-off, 216 analyzed patients had completed 12 months of double-blind treatment or discontinued the study treatment, and after study unblinding by the Sponsor (Celgene), eligible patients had entered the Extension Phase.

This Protocol Amendment 6.0 is to reduce data collection and the protocol burden for the patients in the Extension Phase.

The revision of this Protocol Amendment applies to all participants currently enrolled.

| SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Medical Monitor / Emergency Contact Information | Updated contact details for the Medical Monitor of the study. | Administrative change. |
| Celgene Therapeutic Area Head Signature Page | Therapeutic Area Head and their title were updated. | Administrative change. |
| Section 1.4: Risk/Benefit Assessment | New section added. | To incorporate the stand-alone risk benefit assessment information into the protocol. |
| Appendix J: Extension Phase | Survival follow-up (FU) was updated by reducing the duration of survival FU to 35 days (± 7 days) after treatment discontinuation. | To reduce data collection and protocol burden for the patients in the Extension Phase. |

## PROTOCOL SUMMARY

### Study Title

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.

### Indication

Treatment of lower-risk (Low or Intermediate-1 [INT-1] risk) Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS) with red blood cell (RBC) transfusion-dependent anemia and thrombocytopenia.

### Objectives

#### Primary Objective

- 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 (platelet count $\leq 75 \times 10^9$/L) due to IPSS lower-risk MDS.

#### Secondary Objectives

- 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.

[redacted]

**Study Rationale**

This clinical study will evaluate the efficacy and safety of oral azacitidine plus best supportive care versus 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. [redacted]

The study population represents a subset of IPSS lower-risk MDS patients who have both RBC transfusion-dependent anemia and thrombocytopenia. Lower-risk MDS patients often become dependent on frequent RBC transfusions, which leads to decreased HRQoL and increased morbidity and mortality (Hellstrom-Lindberg, 2003; Malcovati, 2005). In addition, recent studies have shown that lower-risk MDS patients who are thrombocytopenic have a significantly worse prognosis compared to lower-risk MDS patients who are not thrombocytopenic. Lower-risk MDS patients with significant thrombocytopenia have a median OS of approximately 14 to 16 months (Garcia-Manero, 2008a; Cruz, 2010; Yong, 2010; Gonzalez-Porras, 2011).

In the United States (US), azacitidine (Vidaza®) is approved for the treatment of all 5 French-American-British (FAB) classification subtypes of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML), but it is not routinely utilized in the lower-risk disease setting. Azacitidine is approved in the European Union (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with IPSS Intermediate-2 (INT-2) or High risk MDS, CMML with 10% to 29% marrow blasts without myeloproliferative disorder, and AML with 20% to 30% blasts and multi-lineage dysplasia, according to World Health Organization (WHO) classification. In addition to the US and EU, azacitidine is currently approved in 30 other countries, including Canada, Switzerland, Australia and Japan, for the treatment of MDS (approvals for specific subtypes vary by country). Azacitidine is approved for subcutaneous (SC) and intravenous (IV) routes of administration (approvals vary by country). Similarly, decitabine (Dacogen®), another hypomethylating agent, is approved in the US for treatment of all FAB classification subtypes and IPSS INT-1, INT-2 and High risk MDS.

While parenteral azacitidine and decitabine are approved for treatment of lower-risk MDS in some countries, these agents are not routinely administered and the mainstay therapy remains supportive treatment with erythropoiesis stimulating agents (ESAs) and RBC and/or platelet transfusions. While administration of ESAs may be beneficial for some RBC transfusion-dependent subjects, this therapy has no effect on thrombocytopenia. Bone marrow transplantation is an option for only a subset of MDS patients that are good candidates for such an intensive procedure. In addition, the outcomes of patients with lower-risk MDS are not improved by early introduction of allogeneic

stem cell transplantation (Cutler, 2004). As a result, this treatment modality is recommended at the time of disease progression for lower-risk MDS patients. No currently approved therapies have been shown to improve OS in lower-risk MDS patients with both RBC transfusion-dependent anemia and thrombocytopenia.

In addition to the absence of a demonstrated survival benefit in lower-risk MDS for currently approved therapies, other limitations include the association of clinically significant neutropenia and worsening thrombocytopenia in a high proportion of patients receiving parenteral azacitidine or decitabine, and the need for injections involving inconvenient drug product preparation and administration schedules for patients and health care providers. The association of neutropenia with azacitidine is well established and dose-related, with the highest proportion of patients experiencing neutropenia in the first few cycles of treatment (Silverman, 2006; Lyons, 2009). The requirement to receive SC or IV azacitidine for 7 consecutive days in a clinic or hospital setting often presents a challenge and may be a deterrent to patients who might otherwise benefit from treatment intervention before they develop higher-risk disease. Even in higher-risk MDS or AML studies, clinical sites sometimes decline study participation due to the inconvenience of the preparation, administration, and treatment schedule requirements of azacitidine. Injection and catheter site reactions for both azacitidine and decitabine can cause patient discomfort and morbidity. In addition, SC administration of either agent can be problematic in subjects with thrombocytopenia.

An oral formulation of azacitidine provides an opportunity to deliver the drug at lower doses over a more prolonged schedule than can be practically achieved with parenteral therapy. In addition, an oral formulation that can be taken at home rather than in the hospital/clinic setting represents an opportunity for subjects with lower-risk MDS disease to have a more convenient route of administration, thus alleviating the morbidity of injection and catheter-site reactions, and avoiding the inconvenience and resource utilization costs associated with frequent hospital/clinic visits. In addition, intervention with azacitidine in lower-risk MDS subjects with both RBC transfusion-dependent anemia and thrombocytopenia may offer better quality of life and possibly a survival advantage.

This study is randomized, double-blind, placebo-controlled, and parallel-group in order to eliminate bias in assignment of investigational product (IP) and data interpretation. This will allow for a more accurate assessment of study endpoints and especially allow an improved assessment of OS according to blinded treatment assignment. Placebo is the appropriate comparator, since the approved therapies available in some countries are not routinely used for treatment of lower-risk disease. Best supportive care in both treatment arms will include, but is not limited to RBC (packed red blood cell [pRBC] and whole blood) and platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support as needed, and granulocyte colony stimulating factors for subjects experiencing neutropenic fever/infections. Best supportive care in this study excludes the use of ESAs and other hematopoietic growth factors (granulocyte colony stimulating factors are allowed only for subjects experiencing neutropenic fever/infections as well as for secondary prophylaxis under certain conditions as described in Section 9.1) as these therapies are not approved for the treatment of MDS and do not increase

platelet counts in subjects with concomitant thrombocytopenia associated with their MDS. ESAs are less effective for RBC transfusion-dependent anemia than for RBC transfusion-independent anemia (Hellstrom-Lindberg, 2003). Thus the best supportive care for this study should minimize the risk of not providing subjects with appropriate care, while providing the potential benefit of achieving RBC transfusion independence and/or having improvement in platelet counts.

**Study Design**

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study consists of 3 phases: Screening, Double-blind treatment, and Follow-up.

*Screening Phase*

Subject screening procedures are to take place within 56 days prior to randomization.

Independent central review of bone marrow aspirate, biopsy and peripheral blood smear slides, central analysis of cytogenetics, central laboratory hematology result is used to confirm MDS disease and WHO classification (Appendix A) and to determine the IPSS risk classification (Appendix B).

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. Hemoglobin (Hgb) levels at the time of or within 7 days prior to administration of an RBC transfusion must have been ≤ 10.0 g/dL in order 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 56 days immediately preceding and including 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 and including the date of randomization. There must not be any consecutive 28 days within the 56-day period during 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 should include the type, number of units, reason and date of transfusion. 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 and including the date of randomization. There must not be any consecutive 28 days within the 56-day period during which

* As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

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 $\leq 75 \times 10^9$/L and $\geq 21$ days apart. The second confirmatory platelet count must be obtained $\leq 14$ days prior to randomization.

- At least one platelet count must be centrally analyzed within the 56 day screening period with results of $\leq 75 \times 10^9$/L; the second platelet count may be centrally or locally analyzed, with results that are also $\leq 75 \times 10^9$/L.
- Prior documented medical history of thrombocytopenia may be used to demonstrate eligibility for the study if at least one historical platelet count of $\leq 75 \times 10^9$/L was obtained within 56 days of randomization and $\geq 21$ days apart from the centrally analyzed platelet count.
- If additional platelet counts were obtained during the interim period, these must also have been $\leq 75 \times 10^9$/L. If platelet counts within the interim period are $> 75 \times 10^9$/L, this would be acceptable only if directly associated with a platelet transfusion administered within 7 days prior to the date of the platelet count.

Additional screening assessments include demographics and medical history, prior treatments for MDS (and other malignancy, if applicable), prior medications, physical examination, vital signs, weight and height measurements, Eastern Cooperative Oncology Group (ECOG) performance status (Appendix C), electrocardiogram (ECG), urinalysis, coagulation, Coombs' test, reticulocyte count, serum erythropoietin (EPO) level, serum ferritin level, hematology, serum chemistry, pregnancy testing (females of childbearing potential [FCBP] only), [redacted] Adverse events (AEs) will be collected beginning on the date the informed consent is signed.

*Randomization and Double-blind Treatment Phase*

Following confirmation of eligibility at screening, subjects will be randomized 1:1 to receive oral azacitidine or placebo 300 mg once a day (QD) for 21 days. Randomization will occur by a central randomization procedure using Interactive Response Technology (IRT). Subjects will be stratified based on average baseline RBC transfusion requirement ($\leq 4$ 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). The stratification on country of enrollment is due to the different transfusion treatment practices in Japan versus those in other countries.

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 arms will be permitted at any point during 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

† As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

Section 8.2.2 for details). Dose modifications may occur for managing toxicity if necessary during treatment (see Section 8.2.4 for details).

During the double-blind treatment phase, subjects will be assessed continuously for safety and efficacy. Assessments during the double-blind treatment phase will include AEs, monitoring for progression to AML and second primary malignancy, physical examination, vital signs and weight measurement, ECOG performance status, hematology and serum chemistry, serum ferritin level, pregnancy testing (FCBP only), concomitant medications, therapies and procedures, transfusions administered, clinically significant bleeding events, central review of bone marrow aspirate (or biopsy if adequate aspirate is not attainable) and peripheral blood smear slides, cytogenetic analysis, assessing hematologic response/improvement (International Working Group [IWG] 2006 criteria; Cheson, 2006; Appendix D), disease status assessment, [redacted] IP administration and accountability, HRQoL, and healthcare resource utilization.

Disease Status Assessment

Because a hematologic response to treatment with azacitidine may frequently be delayed, it is recommended that subjects receive at least 6 cycles of treatment with IP; however, subjects may be discontinued from treatment at the investigator's discretion prior to reaching the recommended minimum number of cycles for any of the reasons detailed in Section 12. Subjects will be assessed for disease status at the end of Cycle 6, prior to starting Cycle 7.

- If subjects have met any of the following criteria, subjects can continue on to Cycle 7 and beyond, and will be assessed for disease status at the end of every cycle:
  - RBC transfusion independence, or
  - platelet transfusion-independence for those subjects who were platelet transfusion dependent at baseline, or
  - Hematologic Improvement (HI; Cheson, 2006; Appendix D), or
  - ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
  - any other clinical benefit, including no evidence of progressive disease (see Section 12 for definitions of progressive disease).

  Thereafter, subjects may be discontinued from protocol-prescribed therapy for any of the reasons detailed in Section 12.
- If subjects have failed to meet any of the above criteria at the end of Cycle 6, subjects will be discontinued from protocol-prescribed therapy.

The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects who have received at least one dose of IP should undergo Treatment Discontinuation procedures (Section 6.13) when treatment is discontinued.

The reason for discontinuation will be recorded in the case report form (CRF) and in the source document for all randomized subjects, regardless of whether they are dosed or not.

*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, therapies 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, or withdrawal of consent for further data collection.

**Extension Phase**

At the Investigator's discretion and following confirmation of eligibility criteria below, subjects can enter the Extension Phase (EP):

Eligible Criteria:

- Subjects who have signed the informed consent for the EP of the study;
- Subjects randomized to the oral azacitidine treatment arm and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral azacitidine in the EP;
- Subjects randomized into the placebo arm of the study will not receive oral azacitidine in the EP, but will be followed for survival in the EP;
- Subjects currently in the Follow-up Phase, after permanent study treatment discontinuation, will continue to be followed for survival in the EP;
- Subjects who do not meet any of the criteria for study discontinuation (see Section 12).

Details for the EP are provided in Appendix J.

**Study Population**

The study is closed to further enrollment, and at the time of this amendment, 216 subjects with IPSS lower-risk MDS and associated RBC transfusion-dependent anemia and thrombocytopenia (platelet count $\leq 75 \times 10^9$/L) have been enrolled. Prior treatment with a hypomethylating agent or stem cell transplant is prohibited. Subjects must have had ECOG performance status of 0, 1 or 2, and adequate renal and liver function (Section 7).

**Length of Study**

The expected duration of the study is 134 months, including a 56-month enrollment followed by 78 months of subject treatment and/or observation, including EP. The study is planned to conclude 78 months after the last subject is randomized.

**Study Treatments**

*Oral Azacitidine/Placebo*

Subjects will be randomized 1:1 to receive 300 mg oral azacitidine or placebo QD for the first 21 days of each 28-day treatment cycle. Subjects can continue to receive additional cycles of protocol-prescribed therapy provided that all protocol-specified treatment criteria are met (see Section 8.2.5). As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle.

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 (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 fever/infections (Section 9.1). Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors (granulocyte colony stimulating factors are allowed only for subjects experiencing neutropenic fever/infections as well as for secondary prophylaxis under certain conditions as described in Section 9.1).

**Overview of Efficacy Assessments**

The primary efficacy endpoint is the proportion of subjects in the overall population achieving RBC transfusion independence with a duration of ≥ 56 days (8 weeks). Red blood cell transfusions administered during the 56 days immediately preceding and including the date of randomization will be used to establish baseline requirements. Red blood cell transfusions administered during the treatment period will be used in the efficacy analysis. Red blood cell transfusions administered for elective surgery will not be counted towards baseline requirements, efficacy analysis, or progressive disease status.

Secondary efficacy endpoints include OS, HI-P, proportion of subjects in the overall population achieving RBC transfusion independence with duration of ≥ 84 days (12 weeks), duration of RBC transfusion independence, [≥ 84 days (12 weeks) and ≥ 56 days (8 weeks)], time to RBC transfusion independence [≥ 84 days (12 weeks) and ≥ 56 days (8 weeks)], the proportion of subject progressing to AML, time to AML progression, HI-E (IWG 2006 criteria; Cheson, 2006; Appendix D), duration of RBC transfusion reduction, the 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 D), and the proportion of subjects experiencing clinically significant bleeding events.

Platelet transfusions administered during the 56 days immediately preceding and including the date of randomization will be used to establish baseline requirements. Platelet transfusions administered during the treatment period will be used in the efficacy analysis. Platelet transfusions

administered for elective surgery will not be counted towards baseline requirements, efficacy analysis or progressive disease status.

**Overview of Safety Assessments**

Safety assessments include AEs, monitoring for progression to AML and second primary malignancy, physical examination, vital signs and body weight measurement, ECOG performance status, hematology (complete blood count [CBC] with white blood cell [WBC] differential and platelets) and serum chemistry, serum ferritin level, and concomitant medications, therapies and procedures, and pregnancy testing (for FCBP subjects only). Electrocardiogram, urinalysis and coagulation testing will be repeated as clinically indicated during the double-blind treatment phase.

Progression to AML and development of second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report progression to AML and any second primary malignancies as serious adverse events (SAEs) regardless of causal relationship to IP (oral azacitidine or placebo), occurring at any time for the duration of the study, from the time of signing the Informed Consent Document (ICD) until death, lost to follow-up, or withdrawal of consent for further data collection.

**Overview of Health-Related Quality of Life and Healthcare Resource Utilization Assessments**

Health-related quality of life assessment will be based on the Functional Assessment of Cancer Therapy-Anemia (FACT-An; Cella, 1997; Appendix E) and EuroQoL Group EQ-5D (EQ-5D-3L) instruments (Rabin, 2001; Appendix F). Healthcare resource utilization data, including, but not limited to hospitalization information, diagnostic procedures and treatment intervention not requiring hospitalization, or for treatment-related adverse events, and resource use associated with treatment administration for MDS will be collected through specially designed case report forms and/or through routine study activities.

[redacted]

**Analysis and Reporting**

All efficacy analyses will be performed on the intent-to-treat (ITT) population. All safety analyses will be performed on the safety population.

A sequential gate-keeping approach will be used to control the overall type I error rate in order 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 given, 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 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 analysis of the OS endpoint will also be conducted at the time of the analysis of the primary efficacy endpoint. This analysis of the OS endpoint may be an interim analysis or it may be the final analysis, depending on the maturity of the survival data (e.g. the required 205 deaths have occurred) at 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 in the event that OS is analyzed twice.

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.

**Study Closure**

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

### Pathology Review

An independent central pathology reviewer will review slides of bone marrow aspirate, bone marrow biopsy and peripheral blood smear, and applicable central laboratory results prior to randomization to confirm MDS diagnosis and WHO classification. If the central pathology reviewer and local pathologist disagree on the diagnosis of a subject, a third party reviewer will adjudicate and make the final assessment. For these cases the third party reviewer's assessment will be used for the statistical analyses.

The independent central pathology reviewer will also assess bone marrow aspirates, biopsies (if adequate aspirate is not attainable), peripheral blood smears and applicable central laboratory results during the study.

### Cytogenetics Review

An independent cytogeneticist will conduct cytogenetic analysis throughout the study. The independent central cytogenetic review will provide standardized analysis and reporting for all subjects. The independent central cytogenetic review results will be used for the statistical analyses.

### Data Monitoring Committee

An independent Data Monitoring Committee (DMC) with multidisciplinary representation will evaluate safety during the course of the study in compliance with a prospective charter. The DMC will be comprised of medical oncologists/hematologists with experience treating MDS and a statistician, all of whom are not otherwise involved in the study as investigators. An independent statistician will generate critical safety reports for the DMC to review periodically. The DMC chairperson may convene formal DMC meetings if there are safety concerns. The sponsor can also request a DMC review of safety data. The sponsor will not have access to the unblinded data. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter which will be endorsed and signed by DMC members before the first data review meeting.

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# 1 INTRODUCTION

## 1.1 Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) is an umbrella term that encompasses a heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. MDS is typically characterized by bone marrow hyperplasia and peripheral cytopenias that manifest clinically as anemia, neutropenia and/or thrombocytopenia of variable frequency and severity, with symptoms of anemia being the most frequent presenting manifestation. Anemia is the most frequent laboratory finding and it often progresses to red blood cell (RBC) transfusion dependence. Other less common presenting clinical features related to the cytopenias are an increased risk of infection and/or hemorrhage, and a potential to progress to acute myeloid leukemia (AML) (Catenacci, 2005). The latter clinical features will often evolve over the ensuing follow up of these patients.

MDS is classified according to World Health Organization (WHO) criteria by pathologic features on bone marrow examination (Brunning, 2008; Vardiman, 2009; Appendix A). MDS is also categorized into one of 4 prognostic groups (Low, Intermediate-1 [INT-1], Intermediate-2 [INT-2], and High risk) according to the International Prognostic Scoring System (IPSS) based on cytogenetic features, number of cytopenias and bone marrow blast percentages (Greenberg, 1997; Appendix B). Overall survival and risk of progression to AML is significantly different in the 4 risk groups (Greenberg, 1997). The low and INT-1 groups tend to have a better prognosis than do subjects with INT-2 or High risk disease, with the median survival for patients in these risk groups being 5.7 years (low), 3.5 years (INT-1), 1.2 years (INT-2) and 0.4 years (High) (Greenberg, 1997). The median time for 25% of patients to progress to AML is 9.4, 3.3, 1.1, and 0.2 years, respectively, in the Low, INT-1, INT-2 and High risk groups (Greenberg, 1997).

For patients with lower-risk disease (IPSS low or INT-1), refractory anemia remains the primary clinical issue. The development of RBC transfusion dependence significantly worsens the survival of patients with MDS and increases the propensity to develop AML (Malcovati, 2005). In addition, long-term RBC transfusion dependence has other clinical and economic consequences, including a potentially negative impact on health-related quality of life (HRQoL) (Hellstrom-Lindberg, 2003; Jansen, 2003; Thomas, 2007) and iron overload, as well as a number of immune related disorders and increased risks related to various infections.

Thrombocytopenia is an independent prognostic factor for survival in MDS and increased severity of thrombocytopenia correlates with shorter time to AML progression (Kantarjian, 2008; Kao, 2008). While thrombocytopenia is more prevalent in the INT-2 and High risk groups, at least one study has shown that as many as 50% of MDS patients classified as lower-risk are thrombocytopenic (Garcia-Manero, 2008a). In this study of 856 patients with lower-risk disease, thrombocytopenia significantly influenced survival. Median OS was [redacted] 22.4 months in those with platelet counts 50 to 99 x $10^9$/L, 27.1 months in those with platelet counts 100 to 199 x $10^9$/L, and 48.1 months in patients with platelet counts ≥ 200 x $10^9$/L. [redacted]

[redacted]

These findings were confirmed in 2 additional retrospective studies that reported median overall survival rates between 0.9 and [redacted] (Cruz, 2010; Yong, 2010). [redacted] Thus, the presence of thrombocytopenia (ie, platelets [redacted] in patients with lower-risk MDS has significant influence on survival. Furthermore, median survival would be further negatively influenced in this population, in that most patients have concurrent RBC transfusion dependence. Age also plays a significant role in the prognosis of this patient population. If age is ≥ 60 years and thrombocytopenia and anemia are both present, median survival would be expected to be 14 months, with only 9% surviving beyond 4 years (Garcia-Manero, 2008a).

The mainstay of therapy in lower-risk MDS has been supportive care, which includes the use of RBC and/or platelet transfusions, treatment of infections, and the use of erythropoiesis stimulating agents (ESAs) such as epoetin alfa or darbepoietin, plus hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) when needed (National Comprehensive Cancer Network [NCCN], 2011; Silverman, 2000; Lübbert, 2000). Neither ESAs nor myeloid growth factors are approved for the treatment of MDS. Furthermore, ESAs do not increase platelet counts in patients with concomitant thrombocytopenia associated with their MDS. Lenalidomide is the standard of care in those countries where it is approved for the proportion of lower-risk MDS patients with deletion (5q) in patients with RBC transfusion dependence. Therapy with lenalidomide is frequently associated with the development of thrombocytopenia, and it is thus not recommended for use in patients who have platelet counts below 50 x $10^9$/L (Revlimid® US Prescribing Information). There are limited available effective therapies for MDS patients with thrombocytopenia other than transfusion of platelets. Platelet transfusions may not be effective in a number of patients, especially when transfusions are required frequently, as patients can become refractory (Hod, 2008). Failure to respond to platelet transfusions may be related to immune and non-immune causes. Common immune causes are development of alloimmune reactions to platelets, and thus transfused platelets are rapidly removed and destroyed by preformed antibodies to various platelet associated antigens. A significant proportion of patients with thrombocytopenia do become refractory to platelet transfusions, often with development of more thrombocytopenia. Platelet transfusions are also associated with serious transfusion reactions, including Transfusion Related Lung Injury (TRALI) and transmission of a number of infectious agents that may lead to fatal outcomes (Silliman, 2009; Hillyer, 2003).

Allogeneic bone marrow transplantation has been effective, both in patients under the age of 50 years and in those older than 50 years who are in good health and who have suitable human leukocyte antigen (HLA) matched donors. However, this approach has limited value, since most patients with MDS are older than 65 years of age and have significant comorbidities that preclude the use of this modality as it is associated with a high morbidity and mortality rate (NCCN, 2011). In addition, the outcome of patients with lower-risk MDS is not improved by early introduction of

allogeneic stem cell transplantation (Cutler, 2004). As a result, this treatment modality is recommended at the time of disease progression for lower-risk MDS patients.

## 1.2 Azacitidine

Azacitidine (Vidaza®) is an analog of the naturally occurring pyrimidine nucleoside cytidine and is classified as an antimetabolite. In the United States (US), azacitidine (Vidaza®) is approved for the treatment of all 5 French-American-British (FAB) classification subtypes of MDS: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML), but it is not routinely utilized in the lower-risk disease setting. Azacitidine is approved in the European Union (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with IPSS INT-2 or High risk MDS, CMML with 10% to 29% marrow blasts without myeloproliferative disorder and AML with 20% to 30% blasts and multi-lineage dysplasia, according to WHO classification. In addition to the US and EU, azacitidine is currently approved in 30 other countries, including Canada, Switzerland, Australia and Japan, for the treatment of MDS (approvals for specific subtypes vary by country). Current approved routes of administration include subcutaneous SC and intravenous IV (approvals vary by country). Similarly, decitabine (Dacogen®), another hypomethylating agent, is approved in the US for treatment of all FAB classification subtypes and IPSS INT-1, INT-2 and High risk MDS.

Azacitidine has strong in vitro and in vivo anti-leukemic activity and the ability to induce differentiation at lower concentrations in hematopoietic and non-hematopoietic cell lines. The effects of azacitidine may result from multiple mechanisms, including inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation can be attributed to its activity as a hypomethylating agent. The degree of methylation of cytosine residues in DNA has been demonstrated to play a role in gene expression. Indeed, hypermethylation of cytosine residues of genes critical to ensure orderly cell proliferation and maturation (differentiation) is frequently found in primary neoplasms and tumor cell lines (Zingg, 1997). Therefore, use of an inhibitor of DNA methylation, such as azacitidine, would be a rational approach to revert these epigenetic aberrations in the malignant clone and to re-establish the antiproliferative signals that were extinguished by hypermethylation. Preliminary data from the AZA-PH-GL-2003-CL-001 survival study with azacitidine in higher-risk MDS patients found, from analysis of pre-treatment bone marrow methylation density, that the overall survival benefit observed with azacitidine versus conventional care regimens (CCR) was independent of methylation status of the 5 genes analyzed (CDKN2B [p15], SOCS1, CDH1 [E-cadherin], TP73, and CTNNA1 [α-catenin]). However, increasing methylation was associated with worse overall survival. Patients with lower levels of methylation treated with azacitidine had the best overall survival, suggesting they may derive greater benefit from azacitidine.

Azacitidine has been extensively studied in MDS and has been shown in a large, randomized Phase 3 trial of higher-risk MDS patients to provide a survival advantage of 9.4 months over CCR. The

median overall survival of azacitidine-treated patients was 24.5 months compared with 15.0 months for the CCR group, which included best supportive care, low-dose cytarabine, or intensive chemotherapy (Fenaux, 2009). The clinical experience with azacitidine in AML is smaller, but positive efficacy results have been obtained. In a subset of 113 patients with WHO-defined AML (mean age 70 years, 24% with unfavorable karyotype, median bone marrow blasts 23%) from the larger MDS study discussed above, the median overall survival was 24.5 months (n=55) in the azacitidine arm compared with 16.0 months (n=58) in the CCR arm (Fenaux, 2008). Additionally, the outcome was not significantly different in patients with an unfavorable karyotype, although the sample size was small. Silverman et al, using WHO-defined AML criteria for diagnosis, reported a median overall survival of 19.3 months (n=27) in azacitidine treated patients compared with 12.9 months (n=25) in patients who received best supportive care (Silverman, 2006). Additionally, Goldberg et al, reported on 33 patients who received azacitidine (n=11, median age 74) or 7 +3 intensive chemotherapy (n=22, median age 67 years) (Goldberg, 2006). Median blast count at baseline was 42% in the azacitidine group and 65% in the intensive chemotherapy group. The median overall survival was 13.2 months in azacitidine-treated patients compared with 9.2 months in patients receiving intensive chemotherapy (Goldberg, 2006). All of the above mentioned studies used the standard azacitidine dose of 75 mg/m$^2$/day for 7 days.

Patients with lower-risk MDS have also been evaluated for response to therapy with azacitidine. In a retrospective study of 74 patients enrolled in an Italian named patient program, 77% of responses observed occurred within the first 6 cycles; most patients achieved their best response between the fourth and sixth cycle of treatment (Musto, 2010). Most responses to azacitidine occur upon completion of 6 cycles of treatment, but responses may still occur beyond completion of 6 courses (Silverman, 2006; Musto, 2010). Elderly patients (>70 years of age) respond as well as younger patients, and failure to respond to prior ESA therapy does not preclude possible responses to azacitidine (Musto, 2010). Overall response rates in lower-risk MDS subjects have been reported as approximately 50% in various studies (Silverman, 2002; Grinblatt, 2008; Lyons, 2009; Musto, 2010). There is minimal direct evidence available to indicate that treatment with azacitidine in the lower-risk disease setting improves survival. However, in the study conducted by Musto et al, a favorable trend toward improved overall survival (OS) was observed in the lower-risk MDS patients who responded to treatment with azacitidine (Musto, 2010).

An oral formulation of azacitidine has been evaluated in 3 clinical studies to date. Results from a pilot study (AZA PH US 2007 PK 004) indicated that azacitidine in an oral formulation was bioavailable (Garcia-Manero, 2008b). This was confirmed when evaluating several different formulations of the drug in a Phase 1 study (AZA PH US 2008 CL 008). Results from another Phase 1 study of oral azacitidine in subjects with MDS, CMML, or AML (AZA PH US 2007 CL 005) indicated that administration on different treatment schedules (7-, 14-, and 21-day once a day [QD], and 14- and 21-day twice a day [BID]) was feasible, generally well-tolerated, and exhibited biologic and clinical activity (Garcia-Manero, 2009; Garcia-Manero, 2010).

### 1.3 Study Rationale

This clinical study will evaluate the efficacy and safety of oral azacitidine plus best supportive care versus placebo and best supportive care in subjects with RBC transfusion-dependent anemia

and thrombocytopenia due to lower-risk MDS. The primary endpoint is the proportion of subjects achieving RBC transfusion independence with duration ≥ 56 days (8 weeks). The key secondary endpoint is overall survival. Additional secondary endpoints include HI-P, proportion of subjects in the overall population achieving RBC transfusion independence with duration of ≥ 84 days (12 weeks), duration of RBC transfusion independence, [≥ 84 days (12 weeks) and ≥ 56 days (8 weeks)], time to RBC transfusion independence [≥ 84 days (12 weeks) and ≥ 56 days (8 weeks)], the proportion of subjects progressing to AML, time to AML progression, HI-E (IWG 2006 criteria; Cheson, 2006; Appendix D), duration of RBC transfusion reduction, the 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 D), and the proportion of subjects experiencing clinically significant bleeding events, safety, health-related quality of life (HRQoL), and healthcare resource utilization. [redacted]

The study population represents a subset of IPSS lower-risk MDS patients who have both RBC transfusion-dependent anemia and thrombocytopenia. Lower-risk MDS patients often become dependent on frequent RBC transfusions, which leads to decreased health-related quality of life and increased morbidity and mortality (Hellstrom-Lindberg, 2003; Malcovati, 2005). In addition, recent studies have shown that lower-risk MDS patients who are thrombocytopenic have a significantly worse prognosis compared to lower-risk MDS patients who are not thrombocytopenic. Lower-risk MDS patient with significant thrombocytopenia have a median OS of approximately 14 to 16 months (Garcia-Manero, 2008a; Cruz, 2010; Yong, 2010; Gonzalez-Porras, 2011).

While azacitidine and decitabine are approved for treatment of lower-risk MDS in some countries, these agents are not routinely administered and the mainstay therapy remains supportive treatment with ESAs and RBC and/or platelet transfusions. While administration of ESAs may be beneficial for some RBC transfusion-dependent subjects, this therapy has no effect on thrombocytopenia. Bone marrow transplant is an option for only a subset of MDS patients that are good candidates for such an intensive procedure. In addition, the outcome of patients with lower-risk MDS is not improved by early introduction of allogeneic stem cell transplantation (Cutler, 2004). As a result, this treatment modality is recommended at the time of disease progression for lower-risk MDS patients. No currently approved therapies have been shown to improve OS in IPSS lower-risk MDS patients with both RBC transfusion-dependent anemia and thrombocytopenia.

In addition to the absence of a demonstrated survival benefit in lower-risk MDS for currently approved therapies, other limitations include the association of clinically significant neutropenia and worsening thrombocytopenia in a high proportion of patients receiving parenteral azacitidine

or decitabine, and the need for injections involving inconvenient drug product preparation and administration schedules for patients and health care providers. The association of neutropenia with azacitidine is well established and dose-related, with the highest proportion of patients experiencing neutropenia in the first few cycles of treatment (Silverman, 2006; Lyons, 2009). The requirement to receive SC or IV azacitidine for 7 consecutive days in a clinic or hospital setting often presents a challenge and may be a deterrent to patients who might otherwise benefit from treatment intervention before they develop higher-risk disease. Even in higher-risk MDS or AML studies, clinical sites sometimes decline study participation due to the inconvenience of the preparation, administration, and treatment schedule requirements of azacitidine. Injection and catheter site reactions for both azacitidine and decitabine can cause patient discomfort and morbidity. In addition, SC administration of either agent can be problematic in subjects with thrombocytopenia.

An oral formulation of azacitidine provides an opportunity to deliver the drug at lower doses over a more prolonged schedule than can be practically achieved with parenteral therapy. In addition, an oral formulation that can be taken at home rather than in the hospital/clinic setting represents an opportunity for subjects with lower-risk MDS disease to have a more convenient route of administration, thus alleviating the morbidity of injection and catheter-site reactions, and avoiding the inconvenience and resource utilization costs associated with frequent hospital/clinic visits. In addition, intervention with azacitidine in IPSS lower-risk MDS subjects with both RBC transfusion-dependent anemia and thrombocytopenia may offer better quality of life and possibly a survival advantage.

[redacted]

Please refer to the Investigator's Brochures (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IP. The study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) and the applicable regulatory requirements.

## 1.4 Risk/Benefit Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Azacitidine may be found in the Investigator's Brochure (IB), and/or package insert.

### *1.4.1 Risk Assessment*

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention - Azacitidine** | | |
| Neutropenia and severe infections | In subjects randomized to oral azacitidine 300 mg at 21-day treatment schedule, the most frequent hematological AEs were neutropenia, febrile neutropenia, | To mitigate risk of severe infections, during Cycles 1 and 2 (higher risk period for severe infections) the subjects will receive oral azacitidine for 14 days of a 28-day cycle |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | and associated infections. There was an imbalance in incidence of death between the drug and placebo treatment groups. Most of the death cases in the oral azacitidine-treated subjects occurred during the first 56 days on treatment with infections being the leading cause of death. Affected subjects showed lower median ANC at baseline, which could have made them more susceptible for severe infections. | schedule. The treatment can be extended to a 21-day schedule after Cycle 2, if a subject did not experience Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement on 14-day dosing schedule.<br><br>During the first 2 cycles on treatment subjects' blood counts will be monitored on weekly basis, reducing to biweekly monitoring up to Cycle 12.<br><br>Guidance for IP dose modification due to toxicities including neutropenia and febrile neutropenia is provided in Section 8.2.4 and Table 2 of the Protocol.<br><br>A **strong recommendation** regarding administration of prophylactic fluoroquinolone antibiotics or other recognized prophylactic antibiotics was provided for subjects who develop Grade 4 neutropenia (see Section 9.1). |
| Other known risks with oral azacitidine treatment observed in ≥ 10% of subjects include: thrombocytopenia; nausea; vomiting, diarrhea; abdominal or upper abdominal pain; constipation; asthenia or fatigue; pyrexia; decreased appetite; weight decreased; and pain (arthralgia, back pain, pain in extremity). | These risks are consistent with the established safety profile of azacitidine. | The proposed exclusion criteria (Section 7.3), safety monitoring, and dose adjustment (Section 8.2.4), will minimize the risks for the participants participating in this study.<br><br>An external independent Data Monitoring Committee (DMC) will monitor safety during the course of the study. |
| **Study Procedures** | | |
| Participants could be randomized to the placebo control arm. | This study is randomized, double blinded, and placebo controlled in order to eliminate bias in assignment of Investigational Product (IP) and data interpretation. This will allow for a more accurate assessment of study endpoints. | There is no current standard-of-care for patients with the transfusion-dependent anemia and thrombocytopenia due to International Prognostic Scoring System (IPSS) Lower-risk Myelodysplastic Syndromes. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | The placebo arm is also necessary to clearly recognize the possible short- or long-term side effects of oral azacitidine. | |

### *1.4.2 Benefit Assessment*

Azacitidine has demonstrated clinical benefit in myelodysplastic syndromes (MDS) with a decreased risk of progression to acute myeloid leukemia (AML) and a potential correction of the peripheral blood cytopenias, including the correction of red blood cell (RBC) or platelet transfusion dependence. While a benefit of overall survival has not been demonstrated by using oral azacitidine, it has shown that it can elicit packed red blood cell (pRBC) transfusion independence in heavily pre-transfused MDS patients. Therefore, the development of oral azacitidine offers an oral alternative to conventional hypomethylating agents (HMA), including injectable azacitidine, and provides a treatment option for patients who have exhausted symptomatic treatments (such as erythropoiesis stimulating agent [ESA] and Luspatercept) and are in need for a disease modifying treatment.

### *1.4.3 Overall Benefit Risk Conclusion*

The study population represents a subset of subjects with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS. The safety profile of azacitidine has been well characterized and is generally, taking into account the measures taken to minimize risk to participants in this study, manageable with appropriate monitoring and dosing adjustments as specified in the study protocol and the azacitidine Investigator's Brochure.

In conclusion, it is considered safe and of potential therapeutic benefit to continue with the proposed study in the patient population at the dose regimen(s) as specified in the protocol.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of the study 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.

## 2.2 Secondary Objectives

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.

# 3 STUDY ENDPOINTS

## 3.1 Primary Endpoint(s)

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

## 3.2 Secondary Endpoint(s)

The secondary endpoints of the study are:

- OS;
- HI-P (IWG 2006 criteria; Cheson, 2006; Appendix D);
- Proportion of subjects in the overall population achieving RBC transfusion independence with duration of ≥ 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 D)
- 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 D);
- 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; Appendix E) and EuroQoL Group EQ-5D (EQ-5D-3L; Appendix F) instruments; and
- Measures of healthcare resource utilization.

[redacted]

# 4 OVERALL STUDY DESIGN

## 4.1 Study Design

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 $\leq 75 \times 10^9$/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.

Confirmation of MDS disease, WHO classification (Appendix A), and IPSS risk classification (Appendix B) 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. Slides with smears from the bone marrow aspirate and touch preps from the biopsy are sent together with slides with peripheral blood smear and a bone marrow biopsy to the central pathology reviewer for morphologic assessment. Samples of the bone marrow aspirate or biopsy (if adequate aspirate is not attainable) are sent to the central cytogenetic reviewer for processing and analysis. Please refer to the study's Central Laboratory Manual for details on the required samples and handling instructions. 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. Hemoglobin (Hgb) levels at the time of or within 7 days prior to administration of an RBC transfusion must have been $\leq$ 10.0 g/dL in order 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 and including 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

‡ As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

immediately preceding and including 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 should include the type, number of units, reason and date of transfusion. Transfusion data must include the platelet value for which the transfusion was administered. This data must be accurately and completely recorded. Platelet transfusions administered during the 56 days immediately preceding and including the date of randomization will be used to establish baseline requirements. Platelet transfusions administered during the treatment period will be used in the efficacy analysis.

Platelet transfusion-dependence at baseline is defined for this protocol as at least 2 separate transfusion episodes during the 56 days immediately preceding and including 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 $\leq 75 \times 10^9$/L and $\geq$ 21 days apart. The second confirmatory platelet count must be obtained $\leq$ 14 days prior to randomization.

- At least one platelet count must be centrally analyzed within the 56 day screening period with results of $\leq 75 \times 10^9$/L; the second platelet count may be centrally or locally analyzed, with results that are also $\leq 75 \times 10^9$/L.
- Prior documented medical history of thrombocytopenia may be used to demonstrate eligibility for the study if at least one historical platelet count of $\leq 75 \times 10^9$/L was obtained within 56 days of randomization and $\geq$ 21 days apart from the centrally analyzed platelet count.
- If additional platelet counts were obtained during the interim period, these must also have been $\leq 75 \times 10^9$/L. If platelet counts within the interim period are $> 75 \times 10^9$/L, this would be acceptable only if directly associated with a platelet transfusion administered within 7 days prior to the date of the platelet count.

Additional screening assessments include demographics and medical history, prior treatments for MDS (and other malignancy, if applicable), prior medications, physical examination, vital signs, weight and height measurements, Eastern Cooperative Oncology Group (ECOG) performance status (Appendix C), electrocardiogram (ECG), urinalysis, coagulation, Coombs' test, reticulocyte count, serum erythropoietin (EPO) level, serum ferritin level, hematology, serum chemistry, pregnancy testing (females of childbearing potential [FCBP] only), [redacted] Adverse events (AEs) will be collected beginning on the date the informed consent is signed.

### *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 QD for 21 days. Randomization will occur by a central

randomization procedure using Interactive Response Technology (IRT, including an Interactive Voice Response System [IVRS] and an Interactive Web Response System [IWRS]) with stratification as described in Section 8.3. As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle.

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 for details). Dose modifications may occur for managing toxicity if necessary during treatment (Section 8.2.4).

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 fever/infections (Section 9.1). Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors (granulocyte colony stimulating factors are allowed only for subjects experiencing neutropenic fever/infections as well as for secondary prophylaxis under certain conditions as described in Section 9.1).

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 AEs, monitoring for progression to AML and second primary malignancy, physical examination, vital signs and weight measurement, ECOG performance status, hematology and serum chemistry, serum ferritin level, pregnancy testing (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 (IWG 2006 criteria; Cheson, 2006; Appendix D), disease status assessment, [redacted] IP administration and accountability, HRQoL, and healthcare resource utilization.

Disease Status Assessment

Because a hematologic response to treatment with azacitidine may frequently be delayed, it is recommended that subjects receive at least 6 cycles of treatment with IP; however, subjects may

be discontinued from treatment at the investigator's discretion prior to reaching the recommended minimum number of cycles for any of the reasons detailed in Section 12. Subjects will be assessed for disease status at the end of Cycle 6, prior to starting Cycle 7.

- If subjects have met any of the following criteria, subjects can continue on to Cycle 7 and beyond, and will be assessed for disease status at the end of every cycle:
  - RBC transfusion independence, or
  - platelet transfusion-independence for those subjects who were platelet transfusion dependent at baseline, or
  - Hematologic Improvement (HI; Cheson, 2006; Appendix D), or
  - ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
  - any other clinical benefit, including no evidence of progressive disease (see Section 12 for definitions of progressive disease).

  Thereafter, subjects may be discontinued from protocol-prescribed therapy for any of the reasons detailed in Section 12.
- If subjects have failed to meet any of the above criteria at the end of Cycle 6, subjects will be discontinued from protocol-prescribed therapy.

The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects who have received at least one dose of IP should undergo Treatment Discontinuation procedures (Section 6.13) when treatment is discontinued.

The reason for discontinuation will be recorded in the case report form (CRF) and in the source document for all randomized subjects, regardless of whether they are dosed or not.

### *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 had 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.

Details for the EP are provided in Appendix J.

### 4.1.5 Study Closure

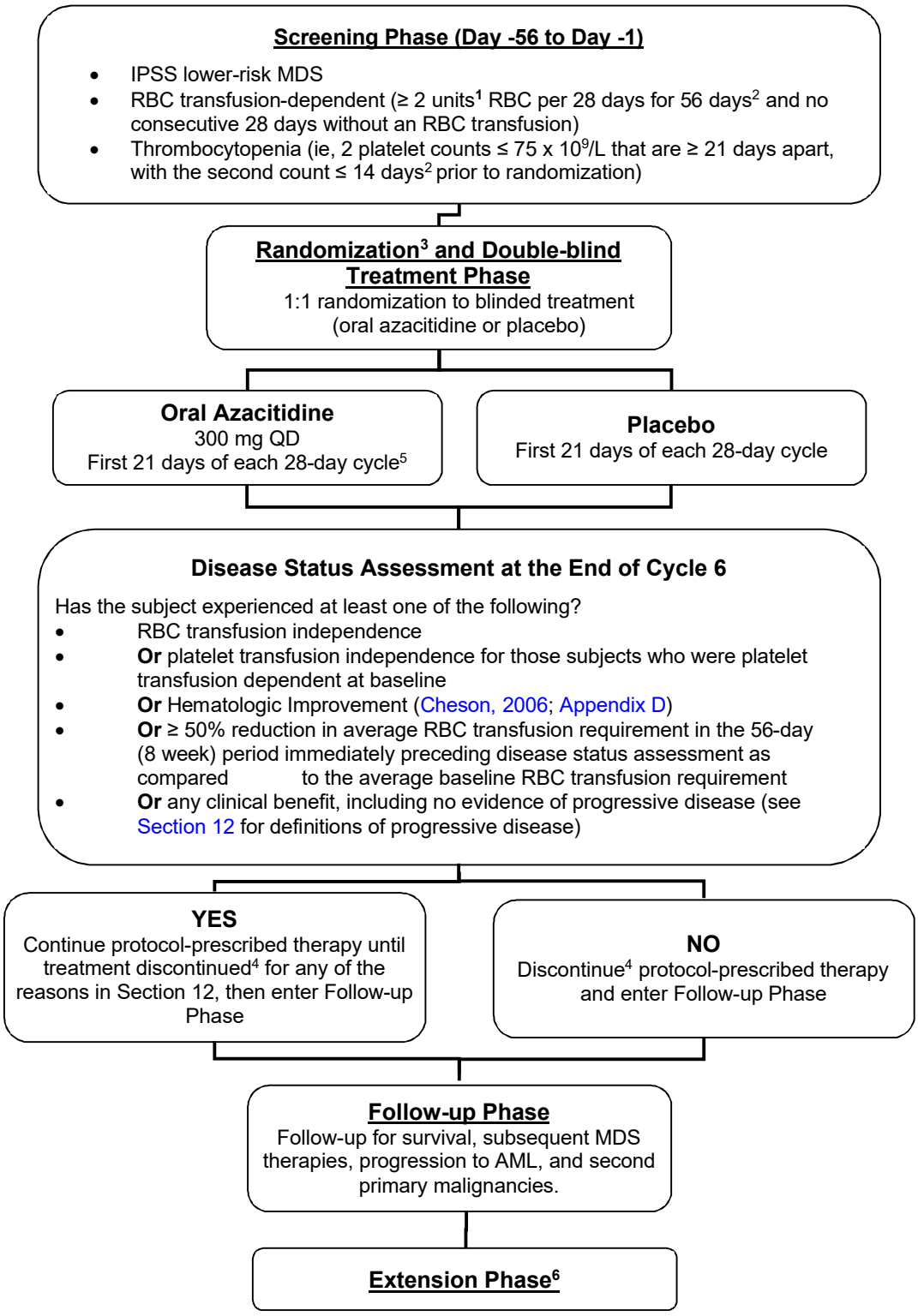
The study will conclude once all subjects have completed or discontinued from the extension phase.

### 4.1.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) with multidisciplinary representation will evaluate safety during the course of the study in compliance with a prospective charter. The DMC will be comprised of medical oncologists/hematologists with experience treating MDS and a statistician, all of whom are not otherwise involved in the study as investigators. An independent statistician will generate critical safety reports for the DMC to review periodically. The DMC chairperson may convene formal DMC meetings if there are safety concerns. The sponsor can also request a DMC review of safety data. The sponsor will not have access to the unblinded data. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter which will be endorsed and signed by DMC members before the first data review meeting.

Figure 1 provides a schematic of the overall study design.

**Figure 1: Overall Study Design**



[1] As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

[2] Immediately preceding and including the date of randomization (see Section 7.2 for details).

[3] Stratification factors: average baseline RBC transfusion requirement (≤ 4 units[1] versus > 4 units of RBC per 28 days), baseline platelet transfusion status (dependent versus independent), country of enrollment (ie, Japan versus Rest of World) and ECOG performance status (0 to 1 versus 2).

[4] The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

[5] As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle.

[6] Following unblinding, subjects could enter the Extension Phase to continue to receive oral azacitidine and/or be followed for survival. See details for EP in Appendix J.

## 4.2 Study Design Rationale

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

The study population represents a subset of IPSS lower-risk MDS patients who have both RBC transfusion-dependent anemia and thrombocytopenia, and has a worse prognosis. No currently approved therapies have been shown to improve OS in this population. So this study is designed to establish additional treatment options that could offer better quality of life and survival advantage for lower-risk MDS subjects who have both RBC transfusion-dependent anemia and thrombocytopenia.

This study is randomized, double-blinded, placebo-controlled, and parallel-group in order to eliminate bias in assignment of IP as well as data interpretation. This will allow for a more accurate assessment of study endpoints and especially allow an improved assessment of overall survival according to blinded treatment assignment. Best supportive care in both treatment arms will include, but is not limited to RBC (pRBC and whole blood) and platelet transfusions (single donor or pooled donor), antibiotic, antiviral and antifungal therapy, nutritional support as needed, and granulocyte colony stimulating factors for subjects experiencing neutropenic fever/infections (as detailed in Section 9.1). Best supportive care for this study excludes the use of ESAs and other hematopoietic growth factors as these therapies are not approved for the treatment of MDS and do not increase platelet counts in patients with concomitant thrombocytopenia associated with their MDS (granulocyte colony stimulating factors are allowed only for subjects experiencing neutropenic fever/infections as well as for secondary prophylaxis under certain conditions as described in Section 9.1). Furthermore, ESAs are less effective for RBC transfusion-dependent anemia than for RBC transfusion-independent anemia (Hellstrom-Lindberg, 2003). Thus, the best supportive care for this study should minimize the risk of not providing subjects with appropriate care, while providing the potential benefit of achieving RBC transfusion independence and/or having improvement in platelet counts. Further consideration of excluding the use of ESAs from best supportive care is the theoretical possibility that the combination of ESA with azacitidine may

have an additive effect on response and this could cloud the specific question relating to efficacy of oral azacitidine itself. Thus, excluding the use of ESAs from best supportive care would negate any possible bias in data interpretation, and allow accurate assessment of study endpoints.

Although parenteral azacitidine and decitabine are approved for treatment of lower-risk MDS in some countries, these agents are not routinely used. The mainstay therapy remains supportive care with ESAs and RBC and/or platelet transfusions. Also, in the EU azacitidine is only approved for treatment of patients with higher-risk MDS disease. Placebo is therefore the appropriate comparator for this study. The placebo arm is also necessary because should oral azacitidine have possible short or long term side effects, it would be difficult to clearly recognize these effects without a comparator arm, especially considering that the underlying MDS has a myriad of possible manifestations that could be misconstrued as secondary to the IP. The propensity to develop AML is a further reason for the inclusion of a placebo arm, because it is important to establish that AML occurrence is not induced more frequently and at an earlier time point than what would be expected from the underlying MDS. Furthermore, the use of historical data is not regarded as an accurate and reliable comparator.

The starting dose and schedule for subjects is 300 mg oral azacitidine (or placebo) once a day for the first 21-days of each 28-day treatment cycle. This oral azacitidine dose and schedule has demonstrated tolerability and shown signs of clinical activity in a prior study (Garcia-Manero, 2010). As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle.

Subjects should continue to receive IP for at least 6 cycles of treatment before being assessed for disease status because, based on prior studies with parenteral azacitidine therapy, response to treatment may be significantly delayed (Silverman, 2006). While on double-blinded treatment, subjects will continue to receive best supportive care, thus the requested 6-month minimum treatment period does not represent an undue risk to subjects. In addition, because overall survival is one of the endpoints, the effect of extended therapy is being evaluated; suspension of therapy at an early time point may blunt any possible extended survival. Crossover between the treatment groups is not allowed so as not to compromise the overall survival endpoint.

The primary endpoint, RBC transfusion independence, is defined as the absence of any RBC transfusion during any consecutive “rolling” 56 days during the treatment period compared with an average transfusion requirement of ≥ 2 units/28 days of RBCs confirmed for a minimum of 56 days immediately preceding and including the date of randomization. Achieving RBC transfusion independence is likely to be a substantial clinical benefit in a patient population with a median overall survival of approximately 14 to 16 months (Garcia-Manero, 2008a; Cruz, 2010; Yong, 2010).

Analysis of the primary endpoint will be conducted only once after full (100%) information is available for RBC transfusion independence rates (ie, after all subjects have completed 12 months of double-blind treatment or discontinued before reaching 12 months of double-blind treatment). Twelve months was selected as the duration of double-blind treatment based on the same reason mentioned above that a hematologic response to azacitidine treatment may frequently be delayed (Silverman, 2006).

## 4.3 Study Duration

The expected duration of the study is 134 months, including a 56-month enrollment followed by 78 months of subject treatment and/or observation, including EP. The study is planned to conclude 78 months after the last subject is randomized.

# 5 TABLE OF EVENTS

Table 1 provides a detailed description of all study events or procedures by time point for each 28-day treatment cycle.

**Table 1: Table of Events**

| Procedure | Screening ≤ 56 days prior to Randomization | Random-ization[b] | Double Blind Treatment Phase[a] | | | | | | Follow-up[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cycles 1 – 2 | | Cycles 3 – 12 | | Cycles 13 and Beyond | Treatment Discon-tinuation[c] | |
| | | | Day 1[b] | Days 8, 15, 22 | Day 1 | Day 15 | Day 1 | | |
| Informed Consent | × | -- | -- | -- | -- | -- | -- | -- | -- |
| Inclusion and Exclusion Criteria | × | -- | -- | -- | -- | -- | -- | -- | -- |
| MDS Diagnosis, WHO Classification and IPSS Score | ×[d] | -- | -- | -- | -- | -- | -- | -- | -- |
| RBC and Platelet Transfusion History | ×[e] | | -- | -- | -- | -- | -- | -- | -- |
| Thrombocytopenia History | ×[f] | | -- | -- | -- | -- | -- | -- | -- |
| Demographics and Medical History | × | -- | -- | -- | -- | -- | -- | -- | -- |
| Prior Treatment for MDS (and other malignancy, if applicable) | ×[g] | -- | -- | -- | -- | -- | -- | -- | -- |
| Prior Medications | ×[h] | -- | -- | -- | -- | -- | -- | -- | -- |
| Physical Examination | × | -- | ×[i] | -- | × | -- | × | × | -- |
| Vital Signs (blood pressure, pulse, temperature, respiratory rate) | × | -- | × | -- | × | -- | × | × | -- |
| Body Weight Measurement | × | -- | × | -- | × | -- | × | × | -- |
| Height | × | -- | -- | -- | -- | -- | -- | -- | -- |
| ECOG Performance Status | × | -- | ×[i] | -- | × | -- | × | × | -- |
| ECG – Local | ×[j] | -- | -- | -- | -- | -- | -- | -- | -- |
| Urinalysis | ×[k] | -- | -- | -- | -- | -- | -- | -- | -- |

**Table 1: Table of Events**

| Procedure | Screening ≤ 56 days prior to Randomization | Random-ization[b] | Double Blind Treatment Phase[a] | | | | | | Follow-up[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cycles 1 – 2 | | Cycles 3 – 12 | | Cycles 13 and Beyond | Treatment Discon-tinuation[c] | |
| | | | Day 1[b] | Days 8, 15, 22 | Day 1 | Day 15 | Day 1 | | |
| **Coagulation** | ×[l] | -- | -- | -- | -- | -- | -- | -- | -- |
| **Coombs' Test (Direct/Indirect) - Local** | ×[m] | -- | -- | -- | -- | -- | -- | -- | -- |
| **Reticulocyte Count - Local** | ×[n] | -- | -- | -- | -- | -- | -- | -- | -- |
| **Serum EPO Level** | ×[o] | -- | -- | -- | ×[o] | -- | -- | -- | -- |
| **Serum Ferritin[p]** | × | -- | × | -- | × | -- | × | × | -- |
| **Serum Transferrin Saturation (Fe/TIBC)** | × | -- | -- | -- | -- | -- | -- | -- | -- |
| **Hematology[q]** | × | -- | ×[i] | × | × | × | × | × | -- |
| **Serum Chemistry[r]** | × | -- | ×[i] | × | × | -- | × | × | -- |
| **Pregnancy Testing (FCBP only)[s]** | × | -- | × | -- | × | -- | × | × | -- |
| **Assessing Adverse Events** | After signing ICD and until 28 days after the last IP dose or until the last study visit, whichever period is longer. | | | | | | | | |
| **Monitoring for Progression to AML and Second Primary Malignancy** | After signing ICD and until death, lost to follow-up, withdrawal of consent for further data collection, or study closure. | | | | | | | | |
| **Concomitant Medications, Therapy, and Procedures** | -- | From the date of randomization and until 28 days after the last dose of IP or until the last study visit, whichever period is longer | | | | | | | |
| **Bone Marrow Aspirate and/or Biopsy (Biopsy mandatory at Screening)** | ×[d] | -- | -- | -- | ×[t] | -- | ×[t] | -- | -- |
| **Peripheral Blood Smear** | | | | | | | | | |
| **Cytogenetic Testing** | | | | | | | | | |
| [redacted] | | | | | | | | | |

**Table 1: Table of Events**

| Procedure | Screening ≤ 56 days prior to Randomization | Random-ization[b] | Double Blind Treatment Phase[a] | | | | | | Follow-up[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cycles 1 – 2 | | Cycles 3 – 12 | | Cycles 13 and Beyond | Treatment Discon-tinuation[c] | |
| | | | Day 1[b] | Days 8, 15, 22 | Day 1 | Day 15 | Day 1 | | |
| [redacted] | | | | | | | | | |
| FACT-An and EQ-5D[x] | -- | -- | × | -- | × | -- | × | × | -- |
| Healthcare Resource Utilization | After signing ICD and until 28 days after the last IP dose or until the last study visit, whichever period is longer | | | | | | | | |
| Randomization | -- | × | -- | -- | -- | -- | -- | -- | -- |
| IP Dispensation[y] | -- | -- | × | -- | × | -- | × | -- | -- |
| IP Administration | -- | -- | Day 1 to Day 21 of 28-day treatment cycles[z] | | | | | -- | -- |
| IP Accountability | -- | -- | ×[aa] | -- | × | -- | × | × | -- |
| [redacted] | | | | | | | | | |
| Transfusion Assessment[cc] | -- | -- | After the date of randomization and until 28 days after the last dose of IP or until the last study visit, whichever period is longer | | | | | | |
| Assessment of Bleeding Events[dd] | -- | -- | × | × | × | × | × | × | -- |
| IWG Response/Improvement[ee] | -- | -- | -- | -- | ×[t] | -- | ×[t] | -- | -- |
| Disease Status Assessment | -- | -- | -- | -- | ×[ff] | -- | ×[ff] | × | -- |
| Subsequent MDS Therapies | -- | -- | -- | -- | -- | -- | -- | × | ×[gg, hh] |
| Survival Follow-up | -- | -- | -- | -- | -- | -- | -- | -- | ×[gg, hh] |

Key: AML=acute myeloid leukemia; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EPO=erythropoietin; EQ-5D=EuroQol Group EQ-5D-3L; FACT-An=Functional Assessment of Cancer Therapy-Anemia; FCBP=female of childbearing potential; ICD=informed consent document; IP=investigational product; IPSS=International Prognostic Scoring System; IWG= International Working Group; MDS=myelodysplastic syndromes; RBC=red blood cell; WHO=World Health Organization.

[a] The study visit window for visit related assessments in the double-blind treatment phase is ± 3 days for Cycles 1 and 2; ± 7 days for Cycle 3 and beyond, unless noted otherwise for a particular assessment. **However, please note that in all circumstances a drug holiday of 7 days needs to be maintained for the treatment schedules of 300 mg and 200 mg for 21 days /28-day-cycle (14 and 21 days, respectively, for modified treatment schedules of 200 mg for 14 days/28-day-cycle and 7 days/28-day-cycle.** Study visits should also take into account the subject's IP supply. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each cycle. Day 1 of Cycles 2 and beyond may be delayed from Day 28 of the prior cycle in order for subjects to recover from toxicity and meet criteria for re-treatment (Section 8.2.5). During follow-up, the study visit window is ± 7 days for visits scheduled monthly (including the follow-up visit 28 days after last dose if necessary) or ± 14 days for visits scheduled every 3 month. One cycle (one month) is considered as 28 days (ie, 4 weeks).

[b] First dose of IP in Cycle 1 should be administered within 3 days of randomization and can be on the same day of randomization.

[c] All subjects who have received at least one dose of IP should undergo Treatment Discontinuation procedures detailed in Section 6.13 when treatment is discontinued. The reason for discontinuation will be recorded in the CRF and in the source document for all randomized subjects, regardless of whether they are dosed or not. Reasons for discontinuation are provided in Section 12.

[d] MDS diagnosis, WHO classification (Appendix A), and IPSS risk classification (Appendix B) will be prospectively determined by independent central pathology and cytogenetics review, and applicable central laboratory results. Thus bone marrow aspirate and biopsy samples together with peripheral blood samples must be collected at screening as detailed in Section 6.1.1. At all later time points a biopsy is only needed if adequate aspirate is not attainable. Blood samples at screening should be collected on the same day as the bone marrow aspirate/biopsy procedure. Instructions for submission of bone marrow slides, sample collection, processing, storage, and shipment procedures are provided in the study's Central Laboratory Manual.

[e] Red blood cell transfusion history must be available for the 56 days immediately preceding and including the date of randomization and platelet transfusion history must be available for the 56 days immediately preceding and including the date of randomization. Transfusion history data can be gathered during the 56-day screening period as detailed in Section 6.1.2.

[f] Thrombocytopenia at baseline must be confirmed by two platelet counts that are $\leq 75 \times 10^9$/L and $\geq 21$ days apart. The second confirmatory platelet count must be obtained $\leq 14$ days prior to randomization. At least one platelet count must be centrally analyzed within the 56 day screening period with results of $\leq 75 \times 10^9$/L; the second platelet count may be centrally or locally analyzed, with results that are also $\leq 75 \times 10^9$/L . If additional platelet counts are obtained during the interim period, these must also have been $\leq 75 \times 10^9$/L. If platelet counts within the interim period are $> 75 \times 10^9$/L, this would be acceptable only if associated with a platelet transfusion administered within 7 days prior to the date of the platelet count (Section 6.1.3).

[g] Prior Treatment for MDS includes all prior treatments for MDS regardless of discontinuation date of treatment as detailed in Section 6.1.5.

[h] All medications taken in the 8 weeks (56 days) prior to randomization are to be collected on the appropriate Case Report Form (CRF).

[i] The assessment does not need to be performed if the screening examination was performed within 7 days of the first dose of IP in the treatment phase.

[j] Electrocardiogram will be performed locally at screening and whenever clinically indicated. The investigator will review and assess the results as detailed in Section 6.1.9.

[k] Urinalysis is conducted at the central laboratory at screening and whenever clinically indicated as detailed in Section 6.1.10.

[l] Coagulation is conducted at the central laboratory at screening and whenever clinically indicated as detailed in Section 6.1.11.

[m] A direct or indirect Coombs' test at screening is performed at the local laboratory.

[n] The screening reticulocyte count is performed at the local laboratory.

[o.] Ideally, the screening serum EPO level (Section 6.1.14) should be collected on the same day as a planned RBC transfusion, and should not be collected within 1 week after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Serum EPO level should also be tested on Day 1 of Cycle 6. However, if possible, the sample should not be collected within 1 week after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Therefore in the event that Day 1 of Cycle 6 would be scheduled within a week of a RBC transfusion, EPO sampling may be performed on Day 1 of the following cycle (Section 6.7.7). Serum EPO level is tested at the central laboratory.

[p.] Serum ferritin level must be collected at screening, on Day 1 of Cycle 1, on Day 1 of every 3 cycles thereafter (eg, Day 1 of Cycles 4, 7, 10, 13, etc.) (Section 6.6.6), and at Treatment Discontinuation. Serum ferritin level is tested by the central laboratory.

[q.] Hematology includes a complete blood count as detailed in Section 6.1.17. Any or all laboratory assessments may be repeated more frequently if clinically indicated. All samples will be analyzed by the central laboratory. The samples are to be collected at screening and prior to IP administration as detailed in Section 6.6.5, and at Treatment Discontinuation.

[r.] Serum chemistry parameters are detailed in Section 6.1.18. All samples will be analyzed by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. The samples are to be collected at screening and prior to IP administration as detailed in Section 6.6.5, and at Treatment Discontinuation.

[s.] For females of childbearing potential (FCBP, please refer to Section 6.1.19 for definition of FCBP) a medically supervised serum pregnancy test (conducted at the central laboratory or locally) is to be obtained and verified negative at screening (Section 6.1.19). During the treatment phase a serum or urine pregnancy test (investigator's discretion; sensitivity of at least 25 mIU/mL) is to be done within 72 hours prior to Day 1 of every cycle and at the Treatment Discontinuation visit (Section 6.6.7). Note that the screening pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour timeframe. The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative.

[t.] Day 1 of Cycles 3, 6, and 12 and every 6 months thereafter (eg, Day 1 of Cycles 18, 24, etc.). See Section 6.7.3, Section 6.10.1 and Section 6.10.2 for detail.

[redacted]

[x.] FACT-An and EQ-5D questionnaires must be completed prior to interaction with study personnel (when feasible) and prior to IP administration at the start of every Cycle, and at Treatment Discontinuation (Section 6.8). If blood is drawn in advance of Day 1 of a particular cycle or in advance of the treatment discontinuation visit, the questionnaires will still be completed at the first visit with the site staff at that particular cycle or treatment discontinuation visit.

[y.] IP should only be dispensed on Day 1 of each treatment cycle after all Day 1 procedures have been completed and all IP from the previous cycle has been accounted for (where applicable). Only 1 cycle of IP will be dispensed to the subject on Day 1 of each cycle (Section 8.2.1).

[z.] IP is scheduled to be taken on Day 1 to Day 21 of each cycle, unless there has been a schedule modification of IP administration due to toxicity. As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle. On [redacted] days, IP will be administered by the study site personnel in the clinic. Subject will self-administer all other IP doses in the treatment phase. Antiemetic medication (not supplied by the sponsor) may be administered 30 minutes prior to IP administration at the investigator´s discretion (Section 8.2.2).

[aa.] Day 1 of Cycle 2 only.

[redacted]

[cc.] The type, number of units, reason and date of transfusions are to be collected after randomization and until 28 days after the last dose of IP or until the last study visit, whichever occurs later as detailed in Section 6.7.1.

[dd.] Assessment of all bleeding events should be performed during the treatment phase starting on Day 1 of Cycle 1, as detailed in Section 6.7.2, and at Treatment Discontinuation. Information for each bleeding event should be recorded on the appropriate CRF.

[ee.] International Working Group Response/Improvement Assessment is scheduled to be performed on Day 1 of Cycles 3, 6, and 12, and every 6 cycles thereafter (eg, Day 1 of Cycles 18, 24, etc.), and could be done at any time prior to starting the next cycle (eg, prior to starting Cycles 4, 7, 13, etc., respectively) (Section 6.7.5).

[ff.] An assessment of disease status must be performed at the end of Cycle 6, prior to starting Cycle 7.

- If subjects have met any of the following, subjects can continue on to Cycle 7 and beyond, and will be assessed for disease status at the end of every cycle:
  - RBC transfusion independence, or
  - platelet transfusion-independence for those subjects who were platelet transfusion dependent at baseline, or
  - Hematologic Improvement (HI; Cheson, 2006; Appendix D), or
  - ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
  - any other clinical benefit, including no evidence of progressive disease (see Section 12 for definitions of progressive disease).

  Thereafter, subjects may be discontinued from protocol-prescribed therapy for any of the reasons detailed in Section 12.
- If subjects have failed to meet any of the above criteria at the end of Cycle 6, subjects will be discontinued from protocol-prescribed therapy (Section 6.7.6).

The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

[gg.] All subjects discontinued from protocol-prescribed therapy for any reason should be followed for survival and subsequent MDS therapies (Section 6.7.9).

[hh.] Following unblinding, subjects could enter the Extension Phase to continue to receive oral azacitidine and/or be followed for survival. See details for EP in Appendix J.

# 6 PROCEDURES

All of the required assessments are indicated in Table 1 with an "X" on the visits to be performed. All data obtained from these assessments must be present in the subject's source documentation. All routine assessments of Cycles 1 and 2 must be performed ± 3 days of the scheduled day indicated in the table. All routine assessments of Cycles 3 and beyond must be performed ± 7 days of the scheduled day indicated in the table. However, please note that in all circumstances a drug holiday of 7 days needs to be maintained for the treatment schedules of 300 mg and 200 mg for 21 days /28-day cycle (14 and 21 days, respectively, for modified treatment schedules of 200 mg for 14 days/28-day cycle and 7 days/28 day-cycle. During follow-up, the study visit window is ± 7 days for visits scheduled monthly (including the follow-up visit 28 days after last dose if necessary) or ± 14 days for visits scheduled every 3 month. One cycle (one month) is considered as 28 days (ie, 4 weeks). Procedures are described in detail below.

## 6.1 Screening

Written informed consents must be obtained before any study-specific procedures are performed [redacted] during the course of the study.

Screening procedures are to occur during the screening phase (see Table 1). Screening assessments to confirm eligibility must take place within 56 days prior to randomization, unless otherwise specified. Subject eligibility is to be established by confirming all inclusion/exclusion criteria. Failure to meet any entry criterion excludes a subject from enrolment into the study. Refer to Section 6.2 for information to be collected on screen failures.

If a subject is screen failed and then re-screened, subject must be re-consented in writing.

### *6.1.1 MDS Diagnosis, WHO Classification, and IPSS Risk Classification*

MDS diagnosis, WHO classification (Appendix A), and IPSS risk classification (Appendix B) will be prospectively determined by independent central pathology and cytogenetics review, and applicable central laboratory results. Thus at screening bone marrow aspirate and biopsy samples together with peripheral blood samples must be collected. At all later time points a biopsy is only needed if adequate aspirate is not attainable.

- Morphological assessment: Slides of the bone marrow aspirate (bone marrow aspirate smears, including one for iron stain) and biopsy (touch prep smears), and peripheral blood smear will be prepared locally and sent to the central pathology reviewer for assessment.
- Cytogenetic analysis: Bone marrow aspirate (or biopsy if adequate aspirate is not attainable - note that specific handling of the biopsy is required if also to be used for cytogenetic testing [see the study's Central Laboratory Manual for handling instructions]) will be sent to the central cytogenetic reviewer for processing and analysis prior to randomization. At least 20 analyzable metaphases are required for standard G-banding cytogenetic analyses. If, after two bone marrow aspirate and/or biopsy procedures, 20 metaphases cannot be obtained, at least 10 analyzable metaphases are required for standard G-banding cytogenetic analysis at screening.

- Peripheral blood sample: A peripheral blood sample will be sent to the central laboratory for a complete blood count (CBC) with white blood cell (WBC) differential and platelet count.

The screening bone marrow aspirate and biopsy samples for central pathology and central cytogenetic review, and the screening hematology samples for central laboratory analysis should be collected no later than 14 days prior to randomization in order to allow sufficient time for central review and a repeat bone marrow assessment, if necessary.

Every attempt should be made to send the screening bone marrow aspirate and/or biopsy samples (if adequate aspirate is not attainable) to the central cytogenetic reviewer for processing and analysis prior to randomization. In the event that cytogenetic analysis cannot be performed by the central cytogenetic reviewer prior to randomization, a cytogenetic analysis by the local laboratory may suffice for randomization. The sponsor must be consulted prior to randomizing a subject using cytogenetic results from a local laboratory. A central "over read" of the cytogenetic report and photographs will be performed at a later date by the central cytogenetic reviewer. If, in the case of a patient who undergoes 2 bone marrow procedures on 2 separate occasions (aspirate and/or biopsy), and the IPSS score is still not able to be determined due to a lack of metaphases (dividing cells), FISH analysis of bone marrow aspirate utilizing a sponsor-determined probe panel may be used for the determination of IPSS score at screening. Additionally, if a definitive diagnosis of MDS is not determined via cytomorphologic analysis of the bone marrow aspirate or pathologic examination of bone marrow biopsies, local samples or prepared slides may be sent to the central reviewer to perform a potential "over read" of the samples. These samples may be obtained outside of the 56 day screening period, but should not be from more than 3 months prior to the date of the first screening bone marrow procedure.

Instructions for submission of bone marrow slides and samples to central reviewers are provided in the study's Central Laboratory Manual.

### *6.1.2 RBC and Platelet Transfusion History*

Red blood cell and platelet transfusion history should be recorded on the appropriate CRF at screening. Transfusion history data can be gathered during the 56-day screening period. All transfusion data should include the type, number of units, reason and date of transfusion.

Red Blood Cell Transfusion History

Red blood cell transfusion history must be available for the 56 days immediately preceding and including the date of randomization. Data must include the Hgb value for which the RBC transfusion was administered. The Hgb value can be from the central or a local laboratory. Hemoglobin levels at the time of or within 7 days prior to administration of an RBC transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards RBC transfusion-dependent status. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of providing evidence of RBC transfusion-dependent status. All RBC transfusion records for the 56 days immediately preceding and including the date of randomization should be collected, regardless of Hgb levels (see Section 7.2).

Platelet Transfusion History

Platelet transfusion history must be available for the 56 days immediately preceding and including the date of randomization. Data must include the platelet value for which the platelet transfusion was administered. The platelet value can be from the central or a local laboratory. Platelet transfusions administered for elective surgery will not qualify as a transfusion episode for the purpose of determining baseline platelet transfusion status.

### 6.1.3 Thrombocytopenia History

Thrombocytopenia must be confirmed by two platelet counts that are $\leq 75 \times 10^9$/L and $\geq 21$ days apart. The second confirmatory platelet count must be obtained within 14 days of randomization.

- At least one platelet count must be centrally analyzed within the 56 day screening period with results of $\leq 75$ x 109/L; the second platelet count may be centrally or locally analyzed, with results that are also $\leq 75$ x 109/L.
- Prior documented medical history of thrombocytopenia may be used to demonstrate eligibility for the study if at least one historical platelet count of $\leq 75$ x 109/L was obtained within 56 days of randomization and $\geq$ 21 days apart from the centrally analyzed platelet count.
- If additional platelet counts were obtained during the interim period, these must also have been $\leq 75 \times 10^9$/L. If platelet counts within the interim period are $> 75 \times 10^9$/L, this would be acceptable only if directly associated with a platelet transfusion administered within 7 days prior to the date of the platelet count.

(See Section 7.2)

### 6.1.4 Demographics and Medical History

The subject's date of birth, sex, race and ethnicity will be recorded on the appropriate CRF. Relevant medical history and current medical conditions, including those symptoms related to MDS, must be recorded on the appropriate CRF at screening. History of prior malignancy and treatment(s) administered will also be recorded on the appropriate CRF.

### 6.1.5 Prior Medications and MDS Treatments

All medications taken in the 8 weeks (56 days) prior to randomization will be recorded on the appropriate CRF.

All prior treatments for MDS (detailed in Section 9) will be recorded on the respective CRF(s) regardless of discontinuation date of treatment.

### 6.1.6 Physical Examination

Information about the screening physical examination must be present in the subject's source documentation. Significant findings must be included on the appropriate CRF.

### 6.1.7 Vital Signs, Body Weight and Height Measurements

Vital signs (blood pressure, pulse, temperature, and respiratory rate) and body weight will be assessed at screening. Please refer to Section 6.6.3 for assessment schedule during the treatment phase. Height is only collected once at screening.

### 6.1.8 Eastern Cooperative Oncology Group Performance Status

Performance status at screening will be assessed using ECOG criteria provided in Appendix C. Refer to Section 6.6.9 for timing of assessing ECOG performance status during the study.

### 6.1.9 Electrocardiogram

Electrocardiogram (ECG) at screening is conducted by the local laboratory. ECG will be performed using the internationally recognized 12-leads. The investigator will review the results and assess as normal, abnormal - not clinically significant, or abnormal - clinically significant, and report the abnormal finding(s) on the appropriate CRF. If the ECG is abnormal, the investigator should consult a cardiologist if deemed appropriate.

### 6.1.10 Urinalysis

Urinalysis at screening is conducted by the central laboratory. Urinalysis includes examination by a standard stick test for specific gravity, glucose, ketones, blood, pH, and protein, and microscopic analysis if indicated.

### 6.1.11 Coagulation

Coagulation at screening is conducted by the central laboratory. Coagulation includes prothrombin time (PT), activated partial thromboplastin time (PTT) and international normalized ratio (INR).

### 6.1.12 Coombs' Test

A direct or indirect Coombs' test at screening is performed at the local laboratory.

### 6.1.13 Reticulocyte Count

The screening reticulocyte count is performed at the local laboratory.

### 6.1.14 Serum EPO Level

If possible, the screening serum EPO level should be collected on the same day as a planned RBC transfusion, prior to the transfusion. The screening serum EPO level should not be collected within 1 week after any RBC transfusion due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Serum EPO level is tested by the central laboratory. Refer to Section 6.7.7 for timing of serum EPO level testing during the study.

### 6.1.15 Serum Ferritin

Serum ferritin level at screening is to be tested by the central laboratory. Refer to Section 6.6.6 for timing of serum ferritin testing during the study.

### 6.1.16 Serum Transferrin Saturation

Transferrin saturation is to be tested at screening only by the central laboratory as the percentage of serum iron/serum total iron binding capacity (Fe/TIBC).

### 6.1.17 Hematology

Hematology assessment includes a complete blood count (CBC, RBC count, hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW], WBC count

with differential, absolute neutrophil count [ANC], and platelet count). The sample will be analyzed by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Refer to Section 6.6.5 for timing of hematology assessments during the study.

### 6.1.18 Serum Chemistry

The screening serum chemistry assessment includes sodium, potassium, chloride, bicarbonate (if available), calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, direct/indirect/total bilirubin, Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT), lactate deyhydrogenase (LDH), and uric acid. The sample will be analyzed by the central laboratory. Any or all laboratory assessments may be repeated more frequently if clinically indicated. Refer to Section 6.6.5 for timing of serum chemistry assessments during the study.

### 6.1.19 Pregnancy Testing

This protocol defines a FCBP as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). The investigator will appraise a female subject as a FCBP according to this definition. Justification must be recorded in the CRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

A medically supervised serum pregnancy test (conducted at the central laboratory or locally) is to be obtained and verified negative in all female subjects of childbearing potential at screening. Refer to Section 6.6.7 for details regarding pregnancy tests during the study and to Section 7.2 for contraception information as required by the protocol.

[redacted]

## 6.2 Information to be Collected on Screening Failures

The informed consent date, [redacted] demographics, reason subject did not qualify for the study and the investigator's signature will be collected for all subjects determined to be screen failures. The adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed to be a screen failure. This

information will be captured in the subject's source documents and appropriate CRF(s). Relevant information will also be recorded on the Screening Log.

## 6.3 Entering a Subject Into the Study

Written consent must be obtained, all the screening evaluations must be completed and eligibility criteria must be verified by the investigator. In addition the sponsor will review key eligibility criteria including central lab, pathology and cytogenetic reports *prior* to randomization of a subject. Randomization will occur by a central randomization procedure using IRT with stratification as described in Section 8.3. Specific contact information and instructions will be provided individually to each study site.

Randomization should be as close to the planned first dose of IP in the treatment phase as possible to avoid randomizing subjects who ultimately do not participate in the study.

The first dose of IP should be administered within 3 days of Randomization and can be on the same day of randomization.

## 6.4 Baseline

Refer to Section 10.4 for baseline definitions of vital signs, weight and laboratory assessments, unless noted otherwise for a particular assessment.

Physical examination, ECOG performance status, hematology or serum chemistry does not need to be performed if the screening examination was performed within 7 days of the first dose of IP in the treatment phase. Assessment of bleeding events, and the FACT-An and EQ-5D questionnaires start on Day 1 of Cycle 1. The FACT-An and EQ-5D questionnaires should always be completed prior to IP administration and, when feasible, prior to interaction with study personnel.

## 6.5 Treatments

Refer to Sections 8.2.1, 8.2.2, and 8.2.3 for details regarding IP dispensation, administration, and accountability.

## 6.6 Safety

Safety assessments include AEs, monitoring for progression to AML and second primary malignancy, physical examination, vital signs and body weight measurement, ECOG performance status, hematology (CBC with WBC differential and platelets) and serum chemistry, serum ferritin level, and concomitant medications, therapies and procedures, and pregnancy testing (for FCBP subjects).

ECG, urinalysis and coagulation testing will be repeated as clinically indicated during the double-blind treatment phase.

### *6.6.1 Adverse Events*

All subjects will be monitored for AEs during the study. Refer to Section 11.1 for details regarding monitoring, recording, and reporting of AEs, including SAEs.

Information about common side effects already known about azacitidine will be included in the subject informed consent document and should be discussed with the subject as needed during the study. This information can also be found in the IB or will be communicated between IB updates in the form of Investigator Notifications.

### 6.6.2 Progression to AML and Second Primary Malignancies

Progression to AML and second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report progression to AML and any second primary malignancy, regardless of causal relationship to IP (oral azacitidine or placebo), occurring at any time from signing of informed consent until death, lost to follow-up, or withdrawal of consent for further data collection. Events of progression to AML and second primary malignancy are to be reported as a serious adverse event (SAEs; considered to be an adverse event of special interest (AESI) even if no other seriousness criteria apply). This information must also be documented on the appropriate pages of the CRF and in the subject's source documents. Documentation on the diagnosis of progression to AML and/or the second primary malignancy (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.) must be provided at the time of reporting as an SAE. Refer to Section 11.2 for evaluation of AEs.

### 6.6.3 Physical Examination, Vital Signs and Weight

During the treatment phase physical examinations, vital signs (blood pressure, pulse, temperature and respiratory rate) and weight measurements are to be performed on Day 1 of each cycle and the Treatment Discontinuation visit. Significant findings must be included on the appropriate CRF.

### 6.6.4 Urinalysis, 12-Lead Electrocardiogram or Coagulation

Urinalysis, ECG or coagulation should be performed as required by the protocol and whenever clinically indicated.

### 6.6.5 Hematology and Serum Chemistry Laboratory Evaluations

Hematology and serum chemistry laboratory analyses must be performed according to Table 1. The same parameters as required at screening should be evaluated (see Section 6.1 for details regarding the parameters for hematology and serum chemistry, respectively).

The hematology samples will be collected prior to IP administration and will be analyzed by the central laboratory. The frequency of hematology assessment in the treatment phase is as such: weekly on Day 1, 8, 15 and 22 in Cycles 1-2, and biweekly on Day 1 and 15 in Cycles 3-12, and monthly on Day 1 thereafter and at Treatment Discontinuation.

The serum chemistry samples will be collected prior to IP administration and will be analyzed by the central laboratory. The frequency of serum chemistry assessment in the treatment phase is as such: weekly in Cycles 1-2 and monthly on Day 1 thereafter, and at Treatment Discontinuation.

On a case-by-case basis and at the investigator's discretion, the Day 8, 15, and 22 hematology and serum chemistry draws may be performed at the subject's local/primary physician office and shipped to the central laboratory for analysis or obtained via an in-home nursing service (where

available). In these specific cases, the sponsor needs to be consulted prior to performing these blood draws to assess logistics and obtain local laboratory details. In addition, to ensure the medical care of the individual study subject is maintained, the investigator remains responsible for all subject procedures performed during the study and communication with the subject must be continued. Proper documentation is required in the source documents at the investigative site in these cases.

Any or all laboratory assessments may be repeated more frequently if clinically indicated. In the event that an immediate laboratory assessment is required to acutely manage a subject, local laboratory tests may be used. In addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory.

Refer to Section 11.3 for guidance on abnormal laboratory values and test results.

### *6.6.6 Serum Ferritin*

Samples for testing serum ferritin level are collected on Day 1 of Cycle 1, on Day 1 of every 3 cycles thereafter (eg, Day 1 of Cycles 4, 7, 10, 13, etc.) and at Treatment Discontinuation. The serum ferritin is tested by the central laboratory.

### *6.6.7 Pregnancy Test*

For females of childbearing potential (FCBP, please refer to Section 6.1.19 for definition of FCBP) a serum or urine pregnancy test (investigator's discretion; sensitivity of at least 25 mIU/mL) is to be done within 72 hours prior to Day 1 of every cycle in the treatment phase and at the Treatment Discontinuation visit (note that the screening serum pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour timeframe).

The subject may not receive IP until the investigator has verified that the result of the pregnancy test is negative.

Pregnancy testing at screening is provided in Section 6.1.19.

### *6.6.8 Concomitant Medications/Significant Non-drug Therapies/Concomitant Procedures*

All concomitant over-the-counter/prescription medications/procedures, taken from the date of randomization until 28 days after the last dose of the IP or until the last study visit, whichever period is longer, must be recorded on the appropriate CRF page. See Section 9 for details regarding concomitant medications and procedures.

### *6.6.9 Eastern Cooperative Oncology Group Performance Status*

Eastern Cooperative Oncology Group Performance status is to be assessed before IP administration on Day 1 of each cycle in the treatment phase and at Treatment Discontinuation.

## 6.7 Efficacy

### *6.7.1 Transfusion Assessment*

The type, number of units, reason and date of transfusions are to be collected after the date of randomization and until 28 days after the last dose of IP or until the last study visit, whichever

occurs later. The Hgb value for which any RBC transfusion is given, and the platelet value for which any platelet transfusion is given, must also be recorded on the CRF. Red blood cell and/or platelet transfusions administered for elective surgery will not count toward baseline requirement, efficacy assessment, or progressive disease status.

### 6.7.2 Assessment of Bleeding Events

An assessment of all bleeding events during the treatment phase should be performed weekly on Day 1, 8, 15 and 22 of Cycles 1-2, biweekly on Day 1 and 15 of Cycles 3-12, and on Day 1 of each treatment cycle thereafter and at Treatment Discontinuation. Information for each bleeding event should be recorded on the appropriate CRF.

The investigative site may inquire about signs and symptoms of bleeding events via a phone call made to the subject. All phone calls made to the subject should be performed by a medically-qualified person (eg, principal investigator or sub-investigator) at the investigative site and adequately documented in the subject's medical record.

### 6.7.3 Bone Marrow Aspirate, Biopsy and Peripheral Blood Smear

[redacted]

Additional bone marrow samples should be collected as clinically indicated. A bone marrow biopsy must be collected if adequate aspirate is not attainable. Whenever a bone marrow sample is collected, a peripheral blood smear is to be prepared.

Instructions for submission of bone marrow samples are provided in the study's Central Laboratory Manual.

### 6.7.4 Cytogenetics

Bone marrow cytogenetic testing is to be completed whenever a bone marrow aspirate (or biopsy if adequate aspirate is not attainable - note that specific handling of the biopsy is required if to be used for cytogenetics testing [see the study's Central Laboratory Manual for handling instructions]) is obtained for efficacy assessment.

### 6.7.5 International Working Group Response/Improvement

Response/improvement assessment according to the International Working Group (IWG) criteria (Cheson, 2006; Appendix D) is to be performed on Day 1 of Cycles 3, 6, and 12, and every 6 cycles thereafter (eg, Day 1 of Cycles 18, 24, etc.) and recorded on the CRF. Due to the turnaround time required to obtain results from the central review of bone marrow aspirate (or biopsy if adequate aspirate is not attainable), peripheral blood smear and cytogenetics, IWG response/improvement assessment could be done at any time prior to starting the next cycle (eg, prior to starting Cycles 4, 7, 13, etc., respectively).

### 6.7.6 Disease Status Assessment

An assessment of disease status must be performed at the end of Cycle 6, prior to starting Cycle 7.

- If subjects have met any of the following criteria, subjects can continue on to Cycle 7 and beyond, and will be assessed for disease status at the end of every cycle:
  - RBC transfusion independence, or
  - platelet transfusion-independence for those subjects who were platelet transfusion dependent at baseline, or
  - Hematologic Improvement (HI; Cheson, 2006; Appendix D), or
  - ≥ 50% reduction in average RBC transfusion requirement in the 56-day (8-week) period immediately prior to disease status assessment as compared to the average baseline RBC transfusion requirement, or
  - any other clinical benefit, including no evidence of progressive disease (see Section 12 for definitions of progressive disease).

  Thereafter, subjects may be discontinued from protocol-prescribed therapy for any of the reasons detailed in Section 12.
- If subjects have failed to meet any of the above criteria at the end of Cycle 6, subjects will be discontinued from protocol-prescribed therapy.

The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

Confirmation of response requires the investigator to document the Hgb and platelet levels in the subject's medical records demonstrating the required increase from the baseline measurement according to Appendix D; and the dates and units of the RBC/platelet transfusions that validate the erythroid/platelet response, respectively. In the event that immediate laboratory assessment is needed for disease status assessment, local laboratory measurement is acceptable pending the outcome of the central laboratory assessment (ie, in addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory).

### 6.7.7 Serum EPO Level

Serum EPO level should be tested on Day 1 of Cycle 6. However, if possible, the serum EPO level should not be collected within 1 week after any RBC transfusion (if applicable) due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion. Therefore in the event that Day 1 of Cycle 6 would be scheduled within a week of a RBC transfusion, EPO sampling may be performed on Day 1 of the following cycle. Refer to Section 6.1.14 for guidance on serum EPO level testing at screening.

### 6.7.8 Progression to AML

Refer to Section 6.6.2 for guidance on monitoring progression to AML.

### 6.7.9 Survival and Subsequent MDS Therapies

All subjects discontinued from protocol-prescribed therapy for any reason should undergo Treatment Discontinuation procedures (Section 6.13) and be followed for survival and subsequent MDS therapies (Section 6.14).

## 6.8 Health-related Quality of Life

The FACT-An (Cella, 1997) is a validated HRQoL measure applicable to subjects with any cancer diagnosis. In addition to general quality of life concerns, it provides specific information regarding fatigue and anemia. It is composed of 47 questions that address physical, social/family, emotional, and functional well-being, as well as other concerns (Appendix E). The FACT-An is available in many languages and it takes approximately 10 to 15 minutes to complete.

The EQ-5D (EQ-5D-3L) is a standardized instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status, and is applicable to a wide range of health conditions and treatments (Appendix F). The EQ-5D is available in many languages and it takes approximately 5 minutes to complete.

The FACT-An and EQ-5D questionnaires should be completed prior to interaction with study personnel (when feasible) and prior to IP administration on Day 1 of every Cycle and at the Treatment Discontinuation visit. It is important that every subject completes all of the FACT-An and EQ-5D at every specified time point to minimize the amount of missing data.

## 6.9 Healthcare Resource Utilization

Healthcare utilization data will also be collected. Information on each hospitalization will be collected utilizing a CRF designed specifically for this purpose. Information to be collected will include, but not be limited to, the reason for hospitalization (eg, disease progression, MDS-related illness, treatment-related AE), and days of hospitalization by treatment setting (inpatient, special care unit). Other disease- and treatment-related forms of healthcare utilization will be collected through routine study activities. These include diagnostic procedures and treatment interventions not requiring hospitalization such as those required for MDS-related illness (eg, RBC or platelet transfusions for anemia or thrombocytopenia, infection), or for treatment-related adverse events. Additionally, information on all concomitant medications (eg, G-CSF, anti-infective treatments, etc.) and resource use associated with treatment administration for MDS will be collected.

Healthcare resource utilization information should be collected after a subject signs informed consent through 28 days after the last dose of IP or until the date of last study visit, whichever period is longer.

[redacted]

## 6.12 Unscheduled Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests, vital signs, etc.), the results of the repeat evaluation should be entered as appropriate in an additional unscheduled visit page of the CRF.

## 6.13 Discontinuation

The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

All subjects who have received at least one dose of IP should undergo Treatment Discontinuation procedures when treatment is discontinued. The Treatment Discontinuation procedures include AEs, monitoring for progression to AML and second primary malignancy, physical examination, vital signs and weight measurements, ECOG performance status, hematology and serum blood chemistry, serum ferritin level, pregnancy test (FCBP only), concomitant medications, therapies and procedures, transfusions administered, clinically significant bleeding events, disease status assessment, subsequent MDS therapies, IP accountability, HRQoL, and healthcare resource utilization.

If a subject is discontinued during a regular scheduled visit, all Treatment Discontinuation procedures should be complete at that visit. If a procedure had been performed within 7 days of the Treatment Discontinuation visit, it does not need to be repeated.

The reason for discontinuation will be recorded in the CRF and in the source document for all randomized subjects, regardless of whether they are dosed or not. Reasons for discontinuation are provided in Section 12.

## 6.14 Follow-up

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 is later, for the collection of AEs, concomitant medications, therapies 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, or withdrawal of consent for further data collection. The investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up. Survival follow-up can be performed via the telephone.

## 6.15 Extension Phase

Following unblinding, subjects could enter the Extension Phase to continue to receive oral azacitidine and/or be followed for survival. See details for EP in Appendix J.

# 7 STUDY POPULATION

## 7.1 Number of Subjects and Sites

The study population consists of 216 subjects who are ≥ 18 years old with RBC transfusion-dependent anemia and thrombocytopenia (platelet count ≤ 75 x $10^9$/L) due to IPSS lower-risk MDS.

The study will be conducted at approximately 150 clinical study sites worldwide.

## 7.2 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Age ≥ 18 years§ at the time of signing the informed consent document
2. Have a documented diagnosis of MDS according to WHO 2008 classification (Appendix A)
3. Be RBC transfusion-dependent as defined by:
   - Average transfusion requirement of ≥ 2 units** per 28 days of RBCs confirmed for a minimum of 56 days immediately preceding randomization (please note that the period covering the transfusion history overlaps with the screening phase)
     - Hemoglobin levels at the time of or within 7 days prior to administration of an RBC transfusion must have been ≤ 10.0 g/dL in order for the transfusion to be counted towards RBC transfusion-dependent status. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL and/or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of providing evidence of RBC transfusion-dependent status
   - No consecutive 28 days that are RBC-transfusion-free during the 56 days
   - immediately preceding randomization
4. Have thrombocytopenia as defined 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
   - At least one platelet count must be centrally analyzed within the 56 day screening period with results of ≤ 75 x $10^9$/L; the second platelet count may be centrally or locally analyzed, with results that are also ≤ 75 x $10^9$/L.
   - Prior documented medical history of thrombocytopenia may be used to demonstrate eligibility for the study if at least one historical platelet count of ≤ 75 x $10^9$/L was obtained within 56 days of randomization and ≥ 21 days apart from the centrally analyzed platelet count.
   - If additional platelet counts were obtained during the interim period, these must also have been ≤ 75 x $10^9$/L. If platelet counts within the interim period are > 75 x $10^9$/L, this would be acceptable only if directly associated with a platelet transfusion administered within 7 days prior to the date of the platelet count.

§ In Japan, both the subject and the subject's legal representative must sign an informed consent document in case the age of the subject has not reached 20 years.
** As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

5. Have an ECOG performance status of 0, 1, or 2 (Appendix C)
6. Females of childbearing potential (FCBP)[††] may participate, providing they meet the following conditions:
   - Agree to use at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study, and for 3 months following the last dose of IP and
   - Have a negative serum pregnancy test at screening (Section 6.1.19); and
   - Have a negative serum or urine pregnancy test (investigator's discretion; sensitivity of at least 25 mIU/mL) within 72 hours prior to starting IP in the treatment phase (note that the screening serum pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour timeframe) (Section 6.6.7)
7. Male subjects with a female partner of childbearing potential must agree to the use of at least two physician-approved contraceptive methods throughout the course of the study and should avoid fathering a child during the course of the study and for 3 months following the last dose of IP
8. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted
9. Able to adhere to the study visit schedule and other protocol requirements

## 7.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. IPSS higher-risk (INT-2 or High risk) MDS (Appendix B)
2. Secondary MDS, ie MDS that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases, unless subject received last dose from prior antineoplastic therapy ≥ 24 weeks prior to randomization
3. Hypoplastic MDS or other subtype with eligibility for treatment with immunotherapy based on investigator's judgment, unless subject received last dose from prior Chemo~ or Immunotherapy ≥ 24 weeks prior to randomization
4. CMML, atypical chronic myeloid leukemia (CML) and unclassifiable myeloproliferative disease (MPD)
5. Prior treatment with any of the following:
   - Azacitidine (any formulation), decitabine or other hypomethylating agent
   - Lenalidomide, unless the subject received the last dose ≥ 8 weeks prior to randomization
6. Prior allogeneic or autologous stem cell transplant
7. History of inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), celiac disease (ie, sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal

†† A woman of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).

disorder or defect that would interfere with the absorption, distribution, metabolism or excretion of the IP and/or predispose the subject to an increased risk of gastrointestinal toxicity

8. Thrombocytopenia secondary to other possible causes, including medication(s), congenital disorder(s), immune disorder(s) (eg, idiopathic thrombocytopenic purpura [ITP]), or microvascular disorder(s) (eg, disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)
9. Use of any of the following within 28 days prior to randomization:
   - cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
   - thrombopoiesis-stimulating agents (TSAs; eg, Romiplostim, Eltrombopag, Interleukin-11)
   - ESAs and other RBC hematopoietic growth factors (eg, Interleukin-3)
   - hydroxyurea
10. Ongoing medically significant adverse events from previous treatment, regardless of the time period
11. Concurrent use of any of the following:
    - iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks (56 days) prior to randomization
    - corticosteroid, except for subjects on a stable or decreasing dose for ≥ 1 week prior to randomization for medical conditions other than MDS
12. Prior history of malignancies, other than MDS, unless the subject has been free of the disease for ≥ 3 years. However, subjects with the following history/concurrent conditions are allowed:
    - Basal or squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
13. Significant active cardiac disease within the previous 6 months, including:
    - New York Heart Association (NYHA) class IV congestive heart failure (see Appendix G);
    - Unstable angina or angina requiring surgical or medical intervention; and/or
    - Myocardial infarction
14. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment)
15. Known Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) infection, or evidence of active Hepatitis B Virus (HBV) infection
16. Abnormal coagulation parameters (PT > 15 seconds, PTT > 40 seconds, and/or INR > 1.5). After consultation with the medical monitor, higher than normal range levels may be acceptable if the subject is being treated with a stable dose of anticoagulants for thrombotic

prophylaxis (ie with atrial fibrillation, previous thromboembolic event, mechanical cardiac valve replacement or presence of lupus or antiphospholipid antibodies). The decision to include such patients would be the responsibility of the investigator.

17. Any of the following laboratory abnormalities:
    - Serum AST/SGOT or ALT/SGPT > 2.5 x upper limit of normal (ULN) unless these abnormal liver function test(s) can be attributed to iron overload as demonstrated by a serum transferrin saturation of > 65% and a serum ferritin of > 1000 µg/L
    - Serum bilirubin > 1.5 x ULN. Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis) or in the presence of known history of Gilbert Syndrome. Subjects are excluded if there is evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count of > 2% with either a positive Coombs' test or over 50% of indirect bilirubin
    - Serum creatinine > 2.5 x ULN
18. Known clinically significant anemia due to iron, vitamin $B_{12}$, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding. Iron deficiency would be determined by a bone marrow aspirate stain for iron, the transferrin saturation (iron/total iron binding capacity [Fe/TIBC] ≤ 20%), or serum ferritin ≤ 15 ng/mL
19. Known or suspected hypersensitivity to azacitidine or mannitol
20. Pregnant or lactating females
21. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
22. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
23. Any condition that confounds the ability to interpret data from the study

# 8 DESCRIPTION OF STUDY TREATMENTS

## 8.1 Description of Investigational Product(s)

### *8.1.1 Azacitidine and Placebo*

Celgene Corporation will supply azacitidine 150- and/or 200-mg tablets and matching placebo tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products. Details of the specific formulations will be provided in the azacitidine IB.

All tablets will be packaged in blister cards. Only sufficient IP for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed.

No modification of tablets is necessary to preserve blinding as both placebo and azacitidine tablets are identical in appearance.

Shelf-life evaluation of the intact blister card is ongoing. IP will be monitored for stability for the duration of the study.

## 8.2 Treatment Administration and Schedule

As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle as described in Section 8.3. In the event of toxicity, dose and schedule may be modified (see Section 8.2.4). Subjects may continue to receive the protocol-prescribed therapy for as long as they benefit from the treatment or until treatment is discontinued for reasons detailed in Section 12. The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

### *8.2.1 Investigational Product Dispensation*

Investigational product will be dispensed on Day 1 of each treatment cycle. Only 1 cycle of IP will be dispensed to the subject on Day 1 of each treatment cycle.

The subject may not receive IP for each treatment cycle until all Day 1 procedures have been completed and all IP from the previous cycle are to be accounted for (where applicable).

For FCBP subjects, a pregnancy test must be verified negative when performed within 72 hours prior to IP administration on Day 1 of Cycle 1.

### 8.2.2 Investigational Product Administration

Investigational product administration will be accurately recorded including, but not limited to, date of administration, dose and any changes in dose administration (eg, interruption or reduction in dose due to an adverse event).

Investigational product is scheduled to be taken on the first 21 days of each 28-day treatment cycle, unless there has been a schedule modification of IP administration due to toxicity. On [redacted] days, IP will be administered by the study site personnel in the clinic. Subjects will self-administer all other IP doses in the treatment phase.

Antiemetic medication (not supplied by the sponsor) may be taken 30 minutes prior to IP administration at the investigator´s discretion (Section 9.1).

The subject will ingest IP with approximately 240 mL (8 ounces) of room temperature water. Investigational product may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories can be provided as a guidance).

Refer to Section 8.6 for details regarding IP accountability.

### 8.2.3 Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each 28-day treatment cycle. Any missed doses during that period should not be taken after the last scheduled day of administration, but should be returned by the subject for IP accountability.

### 8.2.4 Dose Modifications

All subjects in Cycle 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule (Level +1) at the conclusion of Cycle 2 if no Grade 3 or 4 toxicities requiring dose delay or reductions and if no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor.

When the dose level is adjusted, weekly hematology monitoring is required for 2 cycles including the cycle in which the adjusted dose or dosing schedule was applied as well as the following cycle, see Section 8.2.5 Re-treatment Criteria.

The dose/treatment schedule modifications steps for 14 days schedule are:

| | Dose/schedule | | |
|---|---|---|---|
| | 300 mg/21d | | Level +1 |
| Dose escalation step | 300 mg/14d | | Level 1 |
| Dose escalation step | 200 mg/14d | Dose reduction step | Level -1 |
| Dose escalation step | 200 mg/7d | Dose reduction step | Level-2 |

All efforts should be made to dose IP according to schedule without cycle delay, dose interruption and reduction. Subjects will be monitored for hematologic toxicity and non-hematologic toxicity with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) used as a guide for the grading of severity.

If a certain level of toxicity is observed (eg, Table 2) and considered by the investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. The investigator may contact the Medical Monitor prior to any treatment adjustment. Please note that in the event neutropenia Grade 4 is observed, or any adverse event that would put a subject at unacceptable risk in the investigator´s opinion, IP dosing may be interrupted, delayed or modified even if not considered by the investigator to be at least possibly related to treatment.

A maximum of one dose reduction step to 200 mg is permitted in the event of toxicity. A maximum of two treatment schedule modifications, stepwise first from 21 to 14 days and then from 14 days to 7 days, at a dose of 200 mg once a day are permitted in the event of continuing toxicity. Subjects are not allowed to receive less than 200 mg IP or be scheduled to receive treatment for less than 7 days.

Subjects who have their IP dose reduced or treatment schedule modified may return to their original dose and/or schedule in a step-wise fashion upon discussion and agreement between the investigator and the Medical Monitor provided that the increased dose or treatment schedule is tolerable and at least two additional treatment cycles have occurred since the dose reduction or treatment schedule modification. The treatment schedule should first be increased from 7 to 14 days and then 14 to 21 days, followed by a dose escalation step from 200 to 300 mg.

The dose/treatment schedule modifications steps for 21 days schedule are:

| | Dose/schedule | | |
|---|---|---|---|
| | 300 mg/21d | | Level 1 |
| Dose escalation step | 200 mg/21d | Dose reduction step | Level -1 |
| Dose escalation step | 200 mg/14d | Dose reduction step | Level -2 |
| Dose escalation step | 200 mg/7d | Dose reduction step | Level -3 |

Refer to Section 8.2.5 if, despite the temporary interruption, delay or modification of study treatment, the toxicity persists for more than 42 days and is considered by the investigator to be at least possibly related to study treatment.

Following any modification of study treatment or if a dose is missed, the subject should stay on the visit schedule as specified in Table 1. Unscheduled visits may occur to monitor the subject's toxicities if necessary.

**Dose Modification for Febrile Neutropenia**

Any subject who experiences febrile neutropenia ≥ Grade 3 will have IP held until fever has resolved; must be afebrile for 3 days before re-starting IP, see Table 2. Administration of antibiotic, antiviral and antifungal therapy is strongly recommended.

**Dose Modification for Neutropenia Grade 4**

- Grade 4 ANC at Day 1 of a cycle:

  Subjects with Grade 4 ANC at Day 1 of a cycle are going to be dosed for a maximum of 14 days on the respective dose level 300 mg or 200 mg or a maximum of 7 days when already on a 14-day dosing schedule. If a subject is stable or improving over several cycles, a discussion with the Medical Monitor is necessary to determine the dose schedule, see Table 2.

- ANC change during a cycle:

  Subjects who experience a drop in the ANC during a cycle (e.g. from Grade 3 to Grade 4 or for > 50% drop for subject with Grade 4 at Day 15 or Day 8 [Day 8 during the 1st two cycles]) will hold the dose for the remaining cycle. If subject is stable or improving for several cycles, a discussion with the Medical Monitor is necessary to determine the dose schedule, see Table 2.

- If dose was held, the start of next cycle is based on ANC recovery, see flow chart in Section 8.2.5 Re-Treatment Criteria, and see dosing table above.

**Dose Modification for Diarrhea**

It is recommended that subjects experiencing diarrhea be managed according to the guidelines provided in Appendix H. Anti-diarrhea medication may be administered as prophylaxis against diarrhea and for treatment of any adverse events of diarrhea. Dose modifications for diarrhea (≥ Grade 3) are summarized in Table 2.

**Dose Modification for Nausea and Vomiting**

A serotonin (5-$HT_3$) receptor antagonist (eg, ondansetron) (or other comparable medication) may be administered as an antiemetic approximately 30 minutes prior to IP administration at the investigator´s discretion. Antiemetic medication(s) may be administered for treatment of any adverse events of nausea and/or vomiting. Dose modifications for nausea and vomiting (≥ Grade 3) are summarized in Table 2.

**Dose Modification for Renal Dysfunction and Abnormal Serum Electrolytes**

If unexplained elevations of serum creatinine or electrolyte disturbances occur, dose or schedule modifications may be implemented as summarized in Table 2.

**Dose Modification for Weight Change**

No dose adjustment should be made for weight loss or gain alone; however, the reason for weight loss (eg, significant nausea, vomiting, anorexia, etc.) or weight gain (eg, peripheral edema) should be investigated and may require a dose modification as specified in Table 2.

**Dose Modification for Other Treatment-Related Non-hematologic Toxicity**

Any subject who experiences a treatment-related non-hematologic toxicity ≥ Grade 3, that is an escalation from baseline status (see Section 10.4 for baseline definition), may have IP dosing temporarily interrupted until the toxicity returns to ≤ Grade 2. Dose modifications for ≥ Grade 3 non-hematologic toxicity are summarized in Table 2.

**Dose modification for hematologic or non-hematologic adverse events that would put a subject at unacceptable risk in the investigator´s opinion (independent of IP relationship)**

Any subject who experiences any hematologic or non-hematologic adverse event ≥ Grade 2, that is an escalation from baseline status (see Section 10.4 for baseline definition) and would put a subject at unacceptable risk in the investigator´s opinion, may have IP dosing temporarily interrupted until the adverse event returns to ≤ Grade 1. Dose modifications for ≥ Grade 2 hematologic or non-hematologic adverse events, that would put a subject at unacceptable risk in the investigator´s opinion (independent of IP relationship), are summarized in Table 2.

**Table 2: Guidelines for Dose Modifications**

| NCI CTCAE Toxicity Grade | Action |
|---|---|
| **Febrile Neutropenia (≥ Grade 3)** | • Hold IP until fever has resolved.<br>  • Antibiotic, antiviral and antifungal therapy is strongly recommended.<br>  • Resume IP at next lower dose level (see dosing table above) after the fever has resolved and ANC recovery. Contact Medical Monitor. Must be afebrile for 3 days before re-starting IP.<br>• Secondary prophylaxis with G-CSF is strongly recommended. |
| **Neutropenia Grade 4** (related or unrelated to IP) | **Pre-existing Neutropenia Grade 4**<br>• Subjects with G4 ANC at D1 of a cycle are going to be dosed for a maximum of 14 days on the respective dose level 300 mg or 200 mg or a maximum of 7 days when already on a 14-day dosing schedule.<br>If subjects are stable or improving for several cycles, a discussion with the Medical Monitor is necessary to determine the dose schedule.<br>• If dose was held, the start of next cycle is based on ANC recovery, see flow chart in Section 8.2.5 Re-Treatment Criteria<br>• If the subject continues to experience neutropenia Grade 4 during 2 consecutive cycles, the treatment schedule may be reduced one step. Secondary prophylaxis with G-CSF is strongly recommended.<br>**Subjects experiencing worsening of Neutropenia to Grade 4 under IP treatment**<br>• Subjects that experience a drop in the ANC during a cycle (e.g., from G3 to G4 or for > 50% drop for subject with G4 at Day 15 or Day 8 [Day 8 during the 1st two cycles]) will hold the dose for the remaining cycle.<br>If subject is stable or improving for several cycles, a discussion with the Medical Monitor is necessary to determine the dose schedule.<br>• If dose was held, the start of next cycle is based on ANC recovery, see flow chart in Section 8.2.5 Re-Treatment Criteria. |
| | • If the subject continues to experience neutropenia Grade 4 during 2 consecutive cycles, the treatment may be reduced one step. Secondary prophylaxis with G-CSF is strongly recommended. |

**Table 2: Guidelines for Dose Modifications**

| NCI CTCAE Toxicity Grade | Action |
|---|---|
| **Diarrhea (≥ Grade 3)** | • Interrupt IP and provide adequate/maximum medical intervention<br>• Resume IP at same dose when toxicity resolves to ≤ Grade 1<br>• If event reoccurs upon re-challenge or during next treatment cycle, reduce IP dose to 200 mg.<br>• If event reoccurs at same intensity once IP dose is reduced to 200 mg, follow the steps above and modify the treatment schedule at a dose of 200 mg once a day. |
| **Nausea and/or Vomiting (≥ Grade 3)** | • Interrupt IP and provide adequate/maximal medical intervention<br>• Resume IP at same dose when toxicity resolves to ≤ Grade 1<br>• If event reoccurs upon re-challenge or at same intensity during next treatment cycle, reduce dose to 200 mg<br>• If event reoccurs at same intensity once IP dose is reduced to 200 mg, follow the steps above and modify the treatment schedule at a dose of 200 mg once a day. |
| **Renal Dysfunction** | • For unexplained elevations of serum creatinine, delay the start of the next cycle of treatment until values return to baseline. Reduce IP dose in the next cycle of treatment to 200 mg.<br>• The treatment schedule at a dose of 200 mg once a day can be modified if the elevation of serum creatinine recurs in the subsequent cycle.<br>• Discontinue IP if similar unexplained renal and/or electrolyte disturbances subsequently persist or recur during the next cycle of treatment. |
| **Other ≥ Grade 3 non-hematologic treatment-related toxicities** | • Interrupt IP dosing and provide medical intervention as appropriate<br>• Resume IP at same dose when toxicity resolves to ≤ Grade 2<br>• If event reoccurs upon re-challenge or at same intensity during next treatment cycle, IP dose may be reduced to 200 mg once a day<br>• If event reoccurs at same intensity once IP dose is reduced to 200 mg once a day, follow the steps above and modify the treatment schedule at a dose of 200 mg once a day. |
| **≥ Grade 2 hematologic or non-hematologic AEs putting a subject at unacceptable risk in the investigator´s opinion** | • Interrupt IP dosing and provide medical intervention as appropriate<br>• Resume IP at same dose when toxicity resolves to ≤ Grade 1 |

**Table 2: Guidelines for Dose Modifications**

| NCI CTCAE Toxicity Grade | Action |
|---|---|
| (related or unrelated to IP) | • If event reoccurs upon re-challenge or at same intensity during next treatment cycle, IP dose may be reduced to 200 mg once a day<br>• If event reoccurs at same intensity once IP dose is reduced to 200 mg, follow the steps above and consider modifying the treatment schedule at a dose of 200 mg once a day. |

Key: AE=Adverse Event; ANC=Absolute Neutrophil Count; D=Day; G=Grade; IP=Investigational Product; NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.

### *8.2.5 Re-treatment Criteria*

In order to proceed to the next cycle, subjects must continue to meet entry criteria regarding renal and hepatic function (see Section 7.3). Thus, subjects will have laboratory assessments performed to evaluate organ function prior to starting each cycle (including Cycle 1). Because of the time it takes to obtain results from the central laboratory, samples should be collected early enough prior to starting the next cycle in order to allow sufficient time for review. In the event that immediate laboratory assessment is needed, local laboratory measurement is acceptable for starting the next cycle pending the outcome of the central laboratory assessment (ie, in addition to collecting the local laboratory sample, a second sample should be collected and sent to the central laboratory).

The start of the next cycle will be delayed if the subject does not meet entry criteria regarding renal and hepatic function. If there is a delay of more than 42 days (6 weeks) in the start of the next cycle, the Medical Monitor must be consulted. Study treatment should be discontinued if there is a delay of more than 56 days (8 weeks) in the start of the next cycle, unless, in the opinion of the investigator and the Medical Monitor, the subject is experiencing clinical benefit. Justification of the subject continuing in the study must be recorded in the source documents.

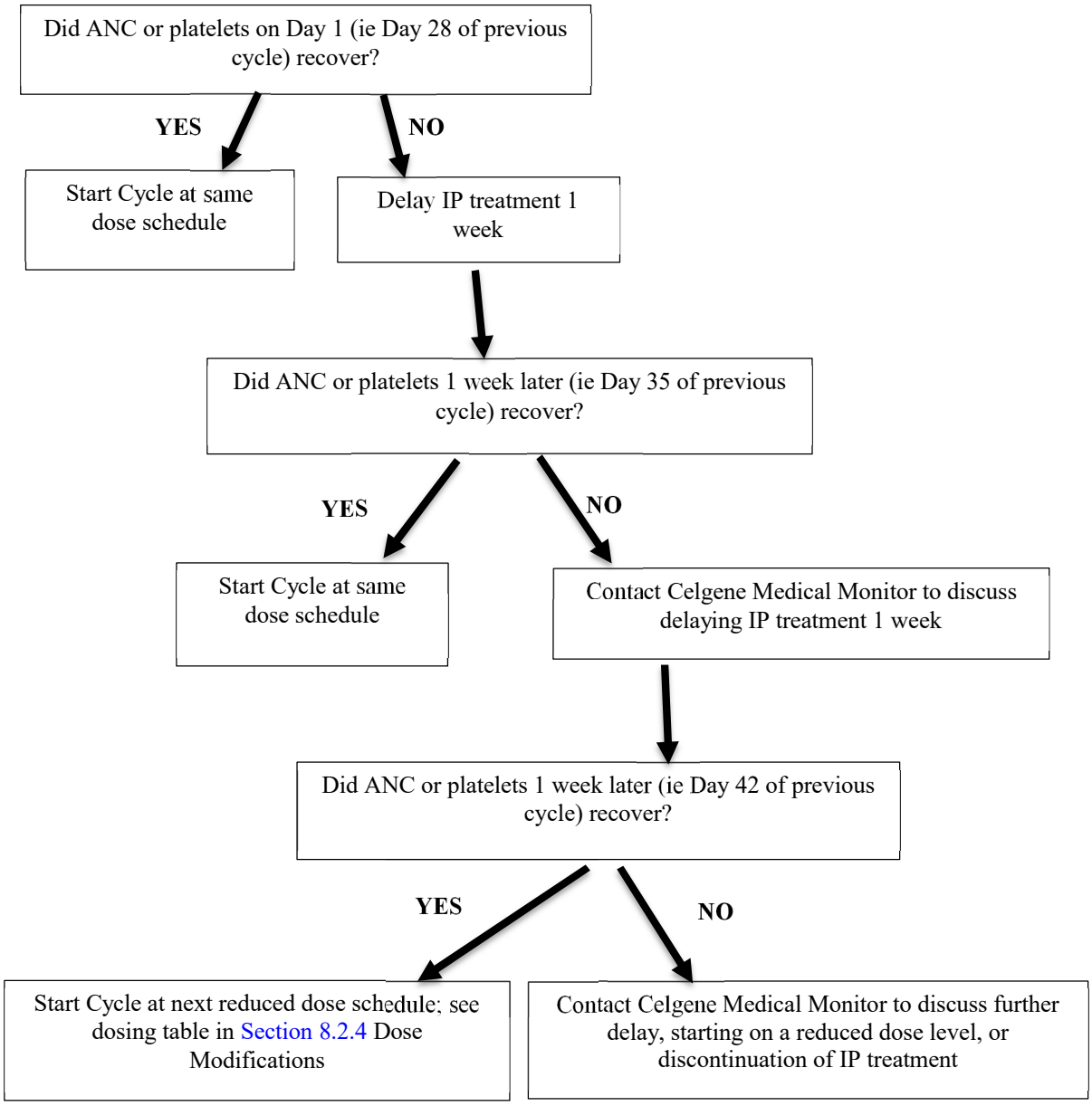
For subjects that experience hematotoxicity (ANC or platelet drop to Grade 4, or 50% drop within Grade 4) hematologic recovery is required before starting the next cycle at Day 28. When this occurs later than Cycle 6, contact the Celgene Medical Monitor to discuss if the re-treatment criteria are met.

Hematologic recovery defined as:

ANC or platelets Day 1 $\geq$ ANC or platelets nadir from previous Cycle + (0.5 x [ANC or platelets Day 1 – ANC or platelets nadir from previous Cycle])

Note: Following dose adjustments, cycle duration should return to 28 days.

**Figure 2: Decision Tree for Hematologic Recovery**




ANC=Absolute Neutrophil Count; IP=Investigational Product.

When the dose level is adjusted, weekly hematology monitoring is required for 2 cycles including the cycle in which the adjusted dose or dosing schedule was applied as well as the following cycle. During those 2 cycles, the following dose modification rule, based on ANC or platelets, is applied:

- Subjects that experience a drop in the ANC or platelets during a cycle (drop to Grade 4 or for > 50% drop for subject with Grade 4 at Day 15 or Day 8) will hold the dose for the remaining cycle.

- If dose was held, the start of next cycle is based on ANC or platelet recovery, see flow chart in Section 8.2.5 Re-Treatment Criteria.

## 8.3 Method of Treatment Assignment

Subjects will be randomized to receive oral azacitidine or placebo in a 1:1 ratio. Randomization will be accomplished by IRT to ensure timely registration and randomization.

Investigator or designated site staff will be assigned password protected, coded identification numbers that give them authorization to access the IRT system to enroll subjects. At screening, the investigator or designated staff will access the IRT system and provide the requested identifying information for the subject. The IRT system will then confirm the assignment of a 2-part unique subject number. The first part is the center number and the second part is one of a series of numbers allocated to subjects at that center. Once assigned to a subject, the subject number will not be reused. If the subject is not randomized, the IRT system must be notified.

Randomization will be performed using the following procedure to insure that treatment assignment is unbiased and concealed from subjects and investigators. A subject randomization list will be produced by the IRT system provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment groups. The randomization scheme for subjects will be reviewed and approved by the Biostatistics Group of the sponsor, Celgene Corporation. Written consent must be obtained, all the screening evaluations must be completed and eligibility criteria must be verified by the investigator. In addition the sponsor will review key eligibility criteria including central lab, pathology and cytogenetic reports *prior* to randomization of a subject. Then the investigator or designated staff will access the IRT system and confirm that the subject fulfills all the inclusion and exclusion criteria prior to randomization. The IRT system will assign a randomization number to the subject, which will be used to link the subject to a treatment group.

A stratified randomization schedule will be implemented. Subjects will be stratified by 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). The stratification on country of enrollment is due to the different transfusion treatment practices in Japan versus those in other countries. The random treatment assignment will be concealed so that investigators and subjects will not know in advance the next treatment assignment.

After randomization, no crossover between the treatment arms will be permitted. Subjects may continue to receive randomized study treatment for as long as it is appropriate, provided that all protocol-specified re-treatment criteria are met.

## 8.4 Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage

‡‡ As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

## 8.5 Clinical Supplies

The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying IP shipping order form. The investigator(s) or designee(s) will verify the accuracy of the information on the form and access the IRT system to register the IP received at the site.

At the study site, all IPs will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on package label at controlled temperature and a temperature log must be maintained in the source documents.

## 8.6 Investigational Product Accountability and Disposal

Investigational Product accountability will be assessed by the investigator or designee. Applicable information such as lot number, tablet count and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary).

Investigational Product accountability should be assessed before drug dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the Treatment Discontinuation visit.

The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining IP will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Celgene representative (or designee). The Celgene representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the investigator study file and the central clinical study file.

Celgene will instruct the investigator(s) on the return, disposal and destruction of IP. A copy of the site's Standard Operating Procedure (SOP) for drug destruction may be collected by the sponsor (or designee). Any revisions to a site's destruction process must be provided and approved by the sponsor (or designee) prior to implementation on this protocol. Any site without a sponsor (or designee) approved destruction SOP and process will be required to return IP to Celgene.

## 8.7 Investigational Product Compliance

IP will be administered by the study site personnel in the clinic on [redacted] days. Subjects will self-administer all other IP doses in the treatment phase. Documentation of dosing during treatment will be recorded in a study specific diary card. Investigational product administration

diary cards will be provided by the sponsor to study site personnel, who will in turn distribute them to study subjects. Study site personnel will enter the scheduled daily doses, the number of tablets to be taken each day and any other applicable information. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Subjects (or legally authorized representative) will be asked to record IP dosing information and anti-emetic medication taken at home in the diary card and to bring the diary card and unused tablets in the blister card (or the blister card packaging even if it is empty) with them to scheduled clinic visits (ie, prior to the start of the next treatment cycle). A diary card and tablet compliance check will be performed by study personnel. Diary cards must be saved and kept with the source documentation. Study site personnel will perform an IP administration compliance check and record this information in the subject's source documentation and on the appropriate CRF.

Administration of all IP will be recorded including dispensing, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

## 8.8 Blinding

This is a double-blind study. Subjects, investigators, site staff and Celgene Corporation clinical and medical personnel will be unaware of treatment assignments until all subjects randomized have received at least 12 months of treatment, or have discontinued from the study, whichever occurs first. At this point specific Celgene Corporation clinical and medical personnel may be unblinded to treatment assignment information in order to perform a final analysis on the primary efficacy endpoint and an interim analysis for the key secondary endpoint of OS. The decision to unblind when all randomized subjects have completed 12 months of treatment or discontinued from the study, whichever occurs first, will depend upon the total number of deaths that have occurred at that time. Refer to protocol Sections 10.3 and 10.8 for further details.

## 8.9 Emergency Unblinding

In order to maintain the integrity of the study design, the blind must not be broken during the course of the study unless, in the opinion of the investigator, it is absolutely required to safely treat the subject. There should only be rare instances when breaking the blind would be required, such as the development of pregnancy, for example. In most instances of treatment-related toxicity, interrupting treatment and/or dose reduction of IP is all that would be required.

For more information on the unblinding process, please refer to Section 13.2.

# 9 CONCOMITANT MEDICATIONS AND PROCEDURES

All prior and concomitant medications (prescription and non-prescription), treatments and therapies taken from the 8-week period (56 days) prior to randomization up to 28 days after the last dose of IP or up to the last study visit, whichever period is longer, must be recorded on the appropriate CRF.

All prior treatments for MDS, including ESAs, TSAs, iron-chelating agents, chemotherapy, cytotoxic therapy, investigational agents or other medications considered supportive care for MDS should be recorded on the respective CRF(s) regardless of discontinuation date of treatment.

Concomitant medications should be kept to a minimum during the study. However, if considered necessary for the subject's welfare and are unlikely to interfere with the IP, they may be given at the discretion of the investigator.

## 9.1 Permitted Concomitant Medications and Procedures

Best supportive care may be used in combination with study therapy if deemed necessary. Best supportive care in both treatment arms for this study includes, but is not limited to, treatment with RBC or whole blood transfusions, fresh frozen plasma transfusions, 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 fever/infections. The use of granulocyte colony stimulating factors is also allowed for secondary prophylaxis under certain conditions as described further below. The use of these products will be considered as concomitant treatment and documented as concomitant medications, therapies or procedures. Additional details on the permitted treatments are detailed below.

Subjects who are currently using iron-chelating agents should be on a stable or decreasing dose for at least 8 weeks (56 days) prior to randomization.

Blood product support (RBCs and platelets) may be administered according to institutional standards. Consider platelet transfusion if platelet counts are $< 25 \times 10^9$/L. If appropriate administration of platelets does not correct the platelet counts, contact the Medical Monitors to consider IP dosing delay. The use of these products will be considered as concomitant treatment, and should be collected on the appropriate CRF.

Subjects may be administered supportive and palliative care (eg, pain control) as clinically indicated throughout the study.

Nausea and vomiting are commonly reported adverse reactions associated with azacitidine treatment and subjects may be pre-medicated for nausea and vomiting prior to IP administration at the investigator´s discretion. Serotonin ($5\text{-}HT_3$) receptor antagonists (eg, ondansetron) or other antiemetics may be administered approximately 30 minutes prior to IP administration. Additional doses of serotonin ($5\text{-}HT_3$) receptor antagonists or other antiemetics may be administered if required. Pre-treatment or post-treatment with antiemetic medication will be considered as concomitant treatment and should be recorded on the appropriate CRF.

Treatment with antidiarrheal medications is recommended at the first sign of diarrhea as per the guidelines in Appendix H. Pre-medication with antidiarrheal medication for subsequent doses of

azacitidine may be appropriate. Pre- and post-treatment with an antidiarrheal must be recorded in the CRF as concomitant medication.

Myeloid growth factors (G-CSF and granulocyte macrophage colony-stimulating factor [GM-CSF]) may be given per investigator's discretion for the treatment of neutropenic fever/infections as well as for secondary prophylaxis (ie, prophylactic use of myeloid growth factors if the subject had a previous event of neutropenic fever/infection or neutropenia Grade 4 during the treatment phase of the study) and the safety of the patient is considered jeopardized by subsequent episodes of neutropenic fever/infections or Grade 4 neutropenia.

For subjects who develop an ANC $< 0.5 \times 10^9$/L, administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin or other recognized prophylactic antibiotics) is strongly recommended and should be documented as a concomitant medication on the appropriate CRF. If neutropenic fever/infection occurs, treatment should consist of a broad spectrum antibiotic, and if the investigator deems the use of a myeloid growth factor to be medically important, myeloid growth factors may also be administered. In case of use of secondary prophylaxis with myeloid growth factors, the dose modification guidelines detailed in Section 8.2.4 remain applicable. Discontinuation of secondary prophylaxis with myeloid growth factors should be considered by the investigator as clinically appropriate.

Concurrent corticosteroids for medical conditions other than MDS is allowed provided subject is on a stable or decreasing dose for ≥ 1 week prior to randomization.

## 9.2 Prohibited Concomitant Medications and Procedures

Best supportive care for this study specifically excludes cancer surgery, immunotherapy, biologic therapy, radiotherapy, anticancer hormonal therapy, and systemic chemotherapy where the goal is to eradicate or slow the progression of the disease.

The following concomitant medications are specifically **excluded** during the course of the study:

- Cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
- Azacitidine, decitabine or other demethylating agents
- Lenalidomide, thalidomide and other immunomodulating drugs (IMiDs)
- Erythropoietin stimulating agents and other RBC hematopoietic growth factors (eg, Interleukin-3).
- Romiplostim and other TSAs (eg, Interleukin-11, Eltrombopag)
- Hydroxyurea
- Androgens, unless to treat hypogonadism
- Oral retinoids (topical retinoids are permitted)
- Arsenic trioxide
- Interferon

Refer to Section 7.3 for exclusion criteria pertaining to prohibited concomitant medications.

## 9.3 Required Concomitant Medications and Procedures

Not applicable.

# 10 STATISTICAL ANALYSES

The sections below provide an overview of the proposed statistical considerations and analyses.

## 10.1 Overview

This phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study is designed to compare the efficacy and safety of oral azacitidine plus best supportive care versus placebo plus best supportive care in subjects with RBC transfusion-dependent anemia and thrombocytopenia (platelet count $\leq 75 \times 10^9$/L) due to IPSS lower-risk MDS.

All data will be summarized by treatment group. In addition, where appropriate, a total column will be included to summarize subjects across treatment groups. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SDev) of the mean, the median, the minimum, and the maximum statistics. Counts and percentages will be presented in summaries of categorical variables. The denominator for each percentage will be the number of subjects in the population treatment group unless otherwise specified. In general, missing data will not be imputed unless otherwise specified.

All statistical analyses specified in this protocol will be conducted using SAS® Version 9.2 or higher unless otherwise specified.

## 10.2 Study Population Definitions

### *10.2.1 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. Subjects will be analyzed based on randomized treatment group.

### *10.2.2 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. Subjects will be analyzed based on randomized treatment group.

### *10.2.3 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. Subjects will be analyzed according to the treatment actually received.

## 10.3 Sample Size and Power Considerations

The basis for the power and sample size determination will be a test of the equality of the overall survival curves between the 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 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 an 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 may 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 10.8).

While 56 days (8 weeks) is the standard duration a response must be maintained in order to meet the current IWG response criteria (IWG 2006 criteria; Cheson, 2006; Appendix D), limited information is available on the target population for estimating the response rate for RBC transfusion independence maintained for ≥ 84 days (12 weeks). [redacted]

For the primary efficacy endpoint RBC transfusion independence with a duration ≥ 56 days (8 weeks), the response rate for oral azacitidine is assumed to be similar as the above findings. 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).

## 10.4 Background and Demographic Characteristics

Demographic and baseline disease characteristics will be summarized by treatment group for the ITT, mITT, and safety populations. Subjects' age, height, weight, body mass index (BMI), and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, SDev, median, minimum, maximum), while age group, gender, race and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group. Summaries of baseline disease characteristics will include WHO MDS diagnosis classification, IPSS risk classification, time since initial MDS diagnosis, ECOG performance status, bone marrow blasts (%), Hgb (g/dL), platelet counts ($10^9$/L), average baseline RBC transfusion requirement

(unit of RBC per 28 days), platelet transfusion status (dependent or independent), and IPSS cytogenetic classification. For laboratory and vital sign measures, the most recent assessment on or prior to the date of randomization will be used for baseline. Baseline transfusion history will include all transfusions up to and including the date of randomization.

Medical history data (coded by the Medical Dictionary for Regulatory Affairs [MedDRA] dictionary) will be summarized using frequency tabulations by treatment group, system organ class and preferred term for the ITT, mITT, and safety populations.

## 10.5 Subject Disposition

Subject disposition (analysis population allocation, discontinued, along with primary reason for discontinuation) will be summarized using frequency tabulation for both treatment and follow-up phases. A summary of subjects enrolled by site and by country will be provided. Major protocol violations will be summarized using frequency tabulations for the ITT population. Supportive corresponding subject listings will also be provided.

## 10.6 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. Refer to Section 3.1 and Section 3.2 for the primary and secondary efficacy endpoints, respectively.

A sequential gate-keeping approach will be used to control the overall type I error rate in order 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 given, 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 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 analysis of the OS endpoint will also be conducted at the time of the analysis of the primary efficacy endpoint. This analysis of the OS endpoint may be an interim analysis or it may be the final analysis, depending on the maturity of the survival data (eg, the required 205 deaths have occurred) at 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 in the event that OS is analyzed twice.

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.

### 10.6.1 Primary Efficacy Analysis

The primary efficacy endpoint of RBC transfusion independence is defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period, ie, Day 1 to 56, Day 2 to 57, Day 3 to 58, etc. Subjects with less than 56 days of assessment during the double-blind treatment period will be counted as non-responders. 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), country of enrollment (ie, Japan versus ROW) 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 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 analysis of the primary endpoint will be repeated for the mITT population as the supportive analysis. Additionally, the following sensitivity analyses will be conducted:

- In subjects considered baseline transfusion dependent based on transfusions given for a hemoglobin value ≤ 9.0 g/dL for 56 days;
- In subjects considered baseline transfusion dependent based on transfusions given for a hemoglobin value ≤ 9.0 g/dL for 84 days.

### 10.6.2 Secondary Efficacy Analyses

#### 10.6.2.1 Key Secondary Efficacy Analyses

**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 from any cause 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 10.8]) will have their OS times censored at the time of last contact, 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,

[§§] As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

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), country of enrollment (ie, Japan versus ROW) 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 in order to preserve the overall alpha level at 0.05 (see Section 10.8 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 25$^{th}$ and 75$^{th}$ 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, 25$^{th}$, and 75$^{th}$ percentiles between the two treatment groups will be presented for the un-stratified 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 azacitidine relative to placebo. 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.

In order 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.

The key secondary study endpoint of OS will be assessed as an interim analysis at the time of the primary analysis and in the final analysis at the time of study closure.

#### *10.6.2.2 Additional Secondary Efficacy Analyses*

For secondary efficacy analyses, KM methods will be used to estimate curves for time to event secondary variables. Counts and percentages will be used to describe categorical secondary variables. Secondary efficacy analyses will be performed on the ITT population unless otherwise specified.

**Platelet response (HI-P)** is defined according to IWG 2006 criteria (Cheson, 2006; Appendix D). HI-P rates will be summarized and compared between the two treatment groups using the same methods as the primary endpoint (see Section 10.6.1).

**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, ie, Day 1 to 84, Day 2 to 85, Days 3 to 86, etc. Frequency cross-tabulations of RBC transfusion dependency status for 84 days at baseline versus on-treatment will be presented by treatment group.

**Duration of RBC transfusion independence for 56 days** will be determined only for subjects who achieve RBC transfusion independence on treatment. Duration of RBC transfusion independence is defined as the time from the date transfusion independence is first observed (day 1 of 56 or more days without a transfusion) until the date the subject has a subsequently documented transfusion of RBC. Subjects who maintain RBC transfusion independence through the end of the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Duration of RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using a log-rank test.

**Time to RBC transfusion independence for 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 date of treatment discontinuation or death, whichever occurs first. Time to RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using a log-rank test. A Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI.

**Duration of RBC transfusion independence for 84 days** will be determined only for subjects who achieve RBC transfusion independence on treatment. Duration of RBC transfusion independence is defined as the time from the date transfusion independence is first observed (day 1 of 84 or more days without a transfusion) until the date the subject has a subsequently documented transfusion of RBC. Subjects who maintain RBC transfusion independence through the end of the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Duration of RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using a log-rank test.

**Time to RBC transfusion independence for 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). Subjects who do not achieve RBC transfusion independence during the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Time to RBC transfusion independence curves will be estimated using KM methods and treatment groups will be compared using a log-rank test. A Cox proportional hazards model will be used to estimate the corresponding hazard ratio and 95% CI.

**Progression to AML** is defined as bone marrow blast count ≥ 20%. Number and percentage of subjects progressing to AML will be presented by treatment group.

**Time to AML Progression** is defined as the time from the date of randomization until the date the subject has documented progression to AML. 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. [redacted]

**Erythroid response (HI-E)** is defined according to IWG 2006 criteria (Cheson, 2006; Appendix D). HI-E response will be presented descriptively, by treatment group, using counts and percents.

**Duration of RBC transfusion reduction**. A subject will be considered as a RBC transfusion reduction responder if the subject had at least 4 units reduction in transfusion units over a consecutive 56 days period compared to the baseline transfusion units in 56 days. The duration of response will be determined for RBC transfusion reduction responders. Subjects who maintain the response through the end of the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Duration of RBC transfusion reduction response will be analyzed descriptively using KM methods.

**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. Frequency cross-tabulations of platelet transfusion status (dependent or independent) at baseline versus on-treatment will be presented by treatment group.

**Duration of platelet transfusion independence** will be determined only for subjects who are platelet transfusion dependent at baseline and achieve platelet transfusion independence on treatment. Duration of platelet transfusion independence is defined as the time from the date transfusion independence is first documented (day 1 of 56 or more days without a transfusion) until the date the subject has a subsequently documented transfusion of platelets. Subjects who maintain platelet transfusion independence through the end of the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. Duration of platelet transfusion independence will be analyzed descriptively using KM methods.

**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). Subjects who were platelet transfusion dependent at baseline and who do not achieve platelet transfusion independence during the treatment period will be censored at the date of treatment discontinuation or death, whichever occurs first. 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.

**Hematologic response** (Complete Remission [CR], Partial Remission [PR], Marrow CR [mCR], Stable Disease [SD], Failure, Relapse after CR or PR, and Cytogenetic Response) is defined according to IWG 2006 criteria (Cheson, 2006; Appendix D). Subjects will be classified according to their best response achieved during treatment for the response categories of CR, PR, mCR, SD, 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 percents.

**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.

#### *10.6.2.3 Exploratory Efficacy Analyses*

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 and OS endpoints:

- Age group (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race (white, Asian, others)
- WHO MDS diagnosis classification
- baseline % of bone marrow blasts (< 5, ≥ 5)
- Geographic region (North America, Europe, Japan, ROW)
- Average baseline RBC transfusion requirements (≤ 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)
- Prior lenalidomide use (yes, no)
- Subject enrolled under Amendment 2 (yes, no)

[***] As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

RBC transfusion independence and OS will be analyzed separately within each subgroup using the appropriate analysis methods as described in Sections 10.6.1 and 10.6.2.1. The odds ratios (ORs) for RBC transfusion independence and the hazard ratios (HRs) for OS will be presented graphically in Forest plots. Exploratory analyses for the OS endpoint will be performed at the time of the final analysis of OS only.

## 10.7 Safety Analysis

All safety analyses will be performed on the safety population.

Adverse events (AEs) will be coded using MedDRA. Adverse event listings will include the verbatim term and the MedDRA preferred term. Treatment-emergent AEs (TEAEs) will be summarized by worst severity grade, system organ class, and preferred term. Treatment-emergent AEs leading to death or to discontinuation from treatment, AEs classified as CTCAE (Version 4.0) Grade 3 or Grade 4, AEs related to IP and SAEs will be summarized separately. Listings of all deaths and all SAEs, regardless of when they occurred, will also be generated. Progression to AML and development of a second primary malignancy will be documented as an SAE (considered to be at least an AESI even if no other seriousness criteria apply) throughout a subject's duration in the study (from the time of signing ICD until death, lost to follow-up, or withdrawal of consent for further data collection). AESIs , based on appropriate Standardized MedDRA Queries (SMQs), will also be summarized.

Clinical laboratory results will be summarized descriptively by treatment group, which will also include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic and non-hematologic laboratory abnormalities that meet Grade 3 or Grade 4 criteria according to the CTCAE will be listed and summarized. Graphical display of select laboratory parameters over the course of the study will be provided.

Vital sign measurements and ECOG performance status will be listed for each subject at each visit. Descriptive statistics for vital signs and ECOG performance status, both observed values and changes from baseline, will be summarized by treatment group.

## 10.8 Interim Analysis

An interim analysis of the OS endpoint may be performed when all 216 subjects have completed 12 months of double-blind treatment or have 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. In the event an interim analysis of OS is performed, 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, 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

azacitidine is demonstrated for the primary efficacy endpoint, RBC transfusion independence, at the two-sided 0.05 significance level.

## 10.9 Other Analyses

### *10.9.1 Health-related Quality-of-life*

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.

Scoring for the FACT-An and EQ-5D and methods to address missing values will be accomplished according to directions provided by each separate instrument developer. [redacted]

### *10.9.2 Healthcare Resource Utilization*

The medical resource utilization and cost-effectiveness/cost utility analyses will be outlined in a separate Statistical Analysis Plan for health economic endpoints.

[redacted]

[redacted]

## 10.10 Other Topics

**Data Monitoring Committee**

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

# 11 ADVERSE EVENTS

## 11.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP or until the last study visit, whichever period is longer. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

## 11.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

### *11.2.1 Seriousness*

An SAE is any AE occurring at any dose that:

- Results in death
- Is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an AESI

AESI are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical

intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Progression to AML and development of second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of the treatment arm the subject is in (see Section 11.5).

For the purposes of this study, progressive disease (PD) from Int-1 MDS to Int-2 or high risk MDS will not require reporting as an SAE unless one or more of the above SAE criteria has been met.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study) must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

### *11.2.2 Severity / Intensity*

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the currently active minor version of Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);

http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

### *11.2.3 Causality*

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

| | |
|---|---|
| Not suspected: | The temporal relationship of the AE to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event. |
| Suspected: | The temporal relationship of the AE to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event. |

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

### *11.2.4 Duration*

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

### *11.2.5 Action Taken*

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

### *11.2.6 Outcome*

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

## 11.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

## 11.4 Pregnancy

### *11.4.1 Females of Childbearing Potential*

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 3 months of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form.

The female should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other

appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### *11.4.2 Male Subjects*

If a female partner of a male subject taking IP becomes pregnant while the male subject is on IP, or within 3 months of the male subject's last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Where applicable, the IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the investigator and medical monitor.

## 11.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Progression to AML and development of second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of the treatment arm the subject is in. This includes progression to AML or any second primary malignancy, regardless of causal relationship to IP (oral azacitidine or placebo), occurring at any time for the duration of the study, from the time of signing the ICD until death, lost to follow-up, or withdrawal of consent for further data collection. Events of progression to AML and second primary malignancy are to be reported using the SAE report form and must be considered an AESI even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of progression to AML and/or the second primary malignancy must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to 28 days after the last dose of IP or until the last study visit, whichever period is longer), and those made known to the investigator at anytime thereafter that are suspected of being related to IP. Serious AEs occurring prior to treatment but after informed consent will be collected.

The SAE report should provide a detailed description of the SAE and include a summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety

as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

### *11.5.1 Safety Queries*

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

## 11.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to oral azacitidine based on the Azacitidine IB.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the investigator of the following information (in Japan, Celgene KK shall notify the heads of the institutes in addition to the investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR).
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

**Celgene Drug Safety Contact Information:**

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form/Completion Guidelines or to the Pregnancy Report Form/Completion Guidelines.

# 12 DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Lack of Efficacy
- Progressive Disease (Table 3)
- Adverse event(s)
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation

Although lack of efficacy or progressive disease is considered a sufficient reason for discontinuing a subject from protocol-prescribed therapy, the investigator should continue to treat the subject until the investigator considers protocol-prescribed therapy to be no longer beneficial to the subject, or the change of disease state renders the subject unacceptable for further treatment in the judgment of the investigator. The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The reason for discontinuation will be recorded in the CRF and in the source document for all randomized subjects, regardless of whether they are dosed or not.

Subjects discontinued from the investigational product will not be replaced.

All subjects discontinued from protocol-prescribed therapy for any reason should undergo Treatment Discontinuation procedures (Section 6.13), and 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 as described in Section 6.14.

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 as described in Section 6.14.

**Table 3: Definitions of Progressive Disease for Clinical Decision on Discontinuing Subjects from the Investigational Product and/or from the Study**

| Category | Progression/Relapse††† Criteria |
|---|---|
| Progression in Bone Marrow | For subjects with:<br><br>Less than 5% blasts at baseline: > 50% increase in blasts to > 5% blasts<br><br>5%-10% blasts at baseline: ≥ 50% increase to > 10% blasts<br><br>Note: A 2nd bone marrow sample should be collected within 4 weeks to confirm progression before discontinuing subjects from treatment. |
| Progression in RBC Transfusion Requirement | For subjects RBC transfusion-dependent at baseline:<br><br>Who do not achieve RBC transfusion independence ≥ 56 "rolling" days (8 weeks) during study treatment, a > 50% increase in the average RBC transfusion requirement during any 56-day (8-week) period during study treatment compared to the average RBC transfusion requirement in the 56 days (8 weeks) prior to randomization. |
| Relapse in RBC Transfusion Requirement | For subjects RBC transfusion-dependent at baseline:<br><br>Who achieve RBC transfusion independence ≥ 56 "rolling" days (8 weeks) during study treatment, a relapse to RBC transfusion-dependent status. Relapse is defined as a return to baseline requirements. |
| Progression in Platelet Transfusion Requirement | For subjects platelet transfusion-dependent at baseline:<br><br>Who do not achieve platelet transfusion independence ≥ 56 days (8 weeks) during study treatment, a > 50 % increase in platelet transfusion requirement during any 56-day (8-week) period during study treatment compared to the 56-day (8-week) period prior to randomization.<br><br>For subject not platelet transfusion-dependent at baseline:<br><br>Development of platelet transfusion dependence, ie ≥ 2 platelet transfusions in any 56-day (8-week) period during study treatment. |
| Relapse in Platelet Transfusion Requirement | For subjects platelet transfusion-dependent at baseline:<br><br>Who achieve platelet transfusion independence ≥ 56 days (8 weeks) during study treatment, a relapse to platelet transfusion-dependent status. Relapse is defined as a return to baseline requirements. |

††† RBC and/or platelet transfusions administered for elective surgery should not be counted toward determination of progressive disease or relapse status.

# 13 EMERGENCY PROCEDURES

## 13.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Clinical Research Organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

## 13.2 Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless, in the opinion of the investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued (Section 8.9).

The investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject. However, the decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor.

The investigator should ensure that the code is broken only in accordance with the protocol. The investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the investigator in the subject´s source documentation.

Emergency unblinding should only be performed by the investigator through the IRT system by using an emergency unblinding personal identification number (PIN), and the investigator should access the IRT system for unblinded dose information.

# 14 REGULATORY CONSIDERATIONS

## 14.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

## 14.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICD and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

## 14.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICD signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICD must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICD. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

## 14.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICD, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

## 14.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

## 14.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICD, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational Product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICD should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

## 14.7 Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

## 14.8 Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

The sponsor may consider closing this trial when data supporting key endpoints and objectives of the study have been analyzed. In the case where there are subjects in the Extension Phase still being administered the investigational product, and it is the opinion of the investigator(s) that these subjects would continue to receive benefit from treatment, the sponsor may choose to initiate an open-label roll-over study under a separate protocol to allow these subjects to continue receiving oral azacitidine.

# 15 DATA HANDLING AND RECORDKEEPING

## 15.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

## 15.2 Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

## 15.3 Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICDs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

# 16 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

## 16.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, IP storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and GCP.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

## 16.2 Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

# 17 PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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# 19 APPENDICES

## APPENDIX A MYELODYSPLASTIC SYNDROMES WORLD HEALTH ORGANIZATION CLASSIFICATION SYSTEM

| Myelodysplastic Syndromes World Health Organization 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]<br>No or rare blasts (< 1%)[b] | Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage<br>< 5% blasts<br>< 15% of erythroid precursors are ringed sideroblasts |
| Refractory anemia with ringed sideroblasts (RARS) | Anemia<br>No blasts | ≥ 15% of erythroid precursors are ringed sideroblasts<br>Erythroid dysplasia only<br>< 5% blasts |
| Refractory cytopenia with Multilineage dysplasia (RCMD) | Cytopenia(s)<br>No or rare blasts (< 1%)[b]<br>No Auer rods<br>< $1x10^9$/L monocytes | Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes)<br>< 5% blasts in marrow<br>No Auer rods<br>± 15% ringed sideroblasts |
| Refractory anemia with excess blasts-1 (RAEB-1) | Cytopenia(s)<br>< 5% blasts[b]<br>No Auer rods<br>< $1x10^9$/L monocytes | Unilineage or multilineage dysplasia<br>5%-9% blasts[b]<br>No Auer rods |
| Refractory anemia with excess blasts-2 (RAEB-2) | Cytopenia(s)[c]<br>5%-19% blasts<br>Auer rods[c]<br>< $1x10^9$/L monocytes | Unilineage or multilineage dysplasia<br>10%-19% blasts[c]<br>Auer rods ±[c] |
| Myelodysplastic syndrome - unclassified (MDS-U) | Cytopenias<br>< 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[d] for a diagnosis of MDS<br>< 5% blasts |
| MDS associated with isolated del(5q) | Anemia<br>Usually normal or increased platelet count<br>No or rare blasts (< 1%) | Normal to increased megakaryocytes with hypolobated nuclei<br>< 5% blasts<br>Isolated del(5q) cytogenetic abnormality<br>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.

# Appendix A: Myelodysplastic Syndromes World Health Organization Classification System (Continued)

[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 lymphoid 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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# APPENDIX B 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 < 1.8 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.

Sources: 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.

# APPENDIX C EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

| Eastern Cooperative Oncology Group (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.

# APPENDIX D HEMATOLOGIC RESPONSE AND IMPROVEMENT ACCORDING TO THE INTERNATIONAL WORKING GROUP FOR MYELODYSPLASTIC SYNDROMES

| Hematologic Response According to IWG Criteria for MDS (Cheson, 2006) | |
|---|---|
| **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]<br>Persistent dysplasia will be noted[a,b]<br>Peripheral blood[c]<br>Hgb ≥ 11 g/dL<br>Platelets ≥ 100 X $10^9$/L<br>Neutrophils ≥ 1.0 X $10^9$/L[b]<br>Blasts 0% |
| Partial Remission (PR) | All CR criteria if abnormal before treatment except:<br>– Bone marrow blasts decreased by ≥ 50% over pre-treatment but still > 5%<br>– Cellularity and morphology not relevant |
| Marrow CR[b] | Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment[b]<br>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 pre-treatment. |
| Relapse After CR or PR | At least 1 of the following:<br>– Return to pre-treatment bone marrow blast percentage<br>– Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets<br>– Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence |
| Cytogenetic Response | Complete:<br>– Disappearance of the chromosomal abnormality without appearance of new ones<br>Partial:<br>– At least 50% reduction of the chromosomal abnormality |
| Disease Progression | For subjects with:<br>– Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts<br>– 5%-10% blasts: ≥ 50% increase to > 10% blasts<br>– 10%-20% blasts: ≥ 50% increase to > 20% blasts<br>– 20%-30% blasts[d]: ≥ 50% increase to > 30% blasts<br>Any of the following:<br>– ≥ 50% decrease from maximum remission/response in granulocytes or platelets<br>– Reduction in Hgb by ≥ 2 g/dL<br>– Transfusion dependence |
| Survival | Endpoints:<br>– Overall: death from any cause<br>– Event free: failure or death from any cause<br>– PFS: disease progression or death from MDS<br>– DFS: time to relapse<br>– Cause-specific death: death related to MDS |

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

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

[b] Modification to IWG (2000) response criteria.

# Appendix D: Hematologic Response and Improvement According to the International Working Group for Myelodysplastic Syndromes (Continued)

[c] 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.

[d] 20 – 30% blasts is considered AML according to WHO classification (Vardiman, 2009).

Notes: 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.

| **Hematologic Improvement According to IWG Criteria (Cheson, 2006)** | |
|---|---|
| **Hematologic improvement**[a] | **Response criteria (responses must last at least 8 week)**[b] |
| Erythroid Response (HI-E) (pre-treatment, <11 g/dL) | – Hemoglobin increase by ≥ 1.5 g/dL<br>– Relevant Reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk<br>Note: Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL on treatment will count in the RBC transfusion response evaluation.[b] |
| Platelet Response (HI-P) (pre-treatment, <100 X $10^9$/L) | – Absolute increase of ≥ 30 X $10^9$/L for subjects starting with > 20 X $10^9$/L platelets<br>– Increase from < 20 X $10^9$/L to > 20 X $10^9$/L and by at least 100%[b] |
| Neutrophil Response (HI-N) (pre-treatment, <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:<br>– At least 50% decrease from maximum response levels in granulocytes or platelets<br>– Reduction in Hgb by ≥ 1.5 g/dL<br>– Transfusion dependence |

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

[a] Pre-treatment counts averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for 2 weeks and no platelet transfusions for 1 week) ≥ 1 week apart (modification).

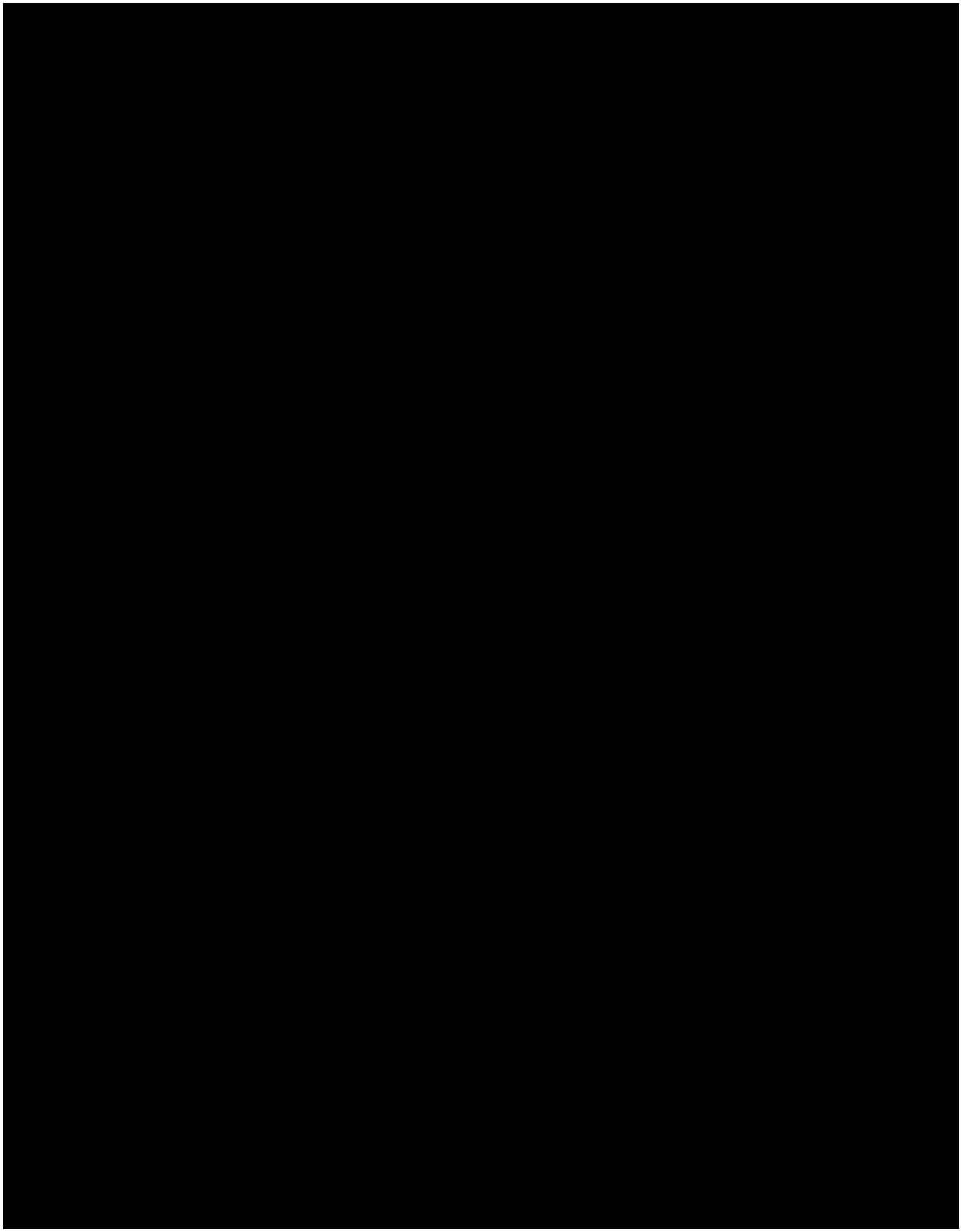
[b] Modification to IWG (2000) response criteria.

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.

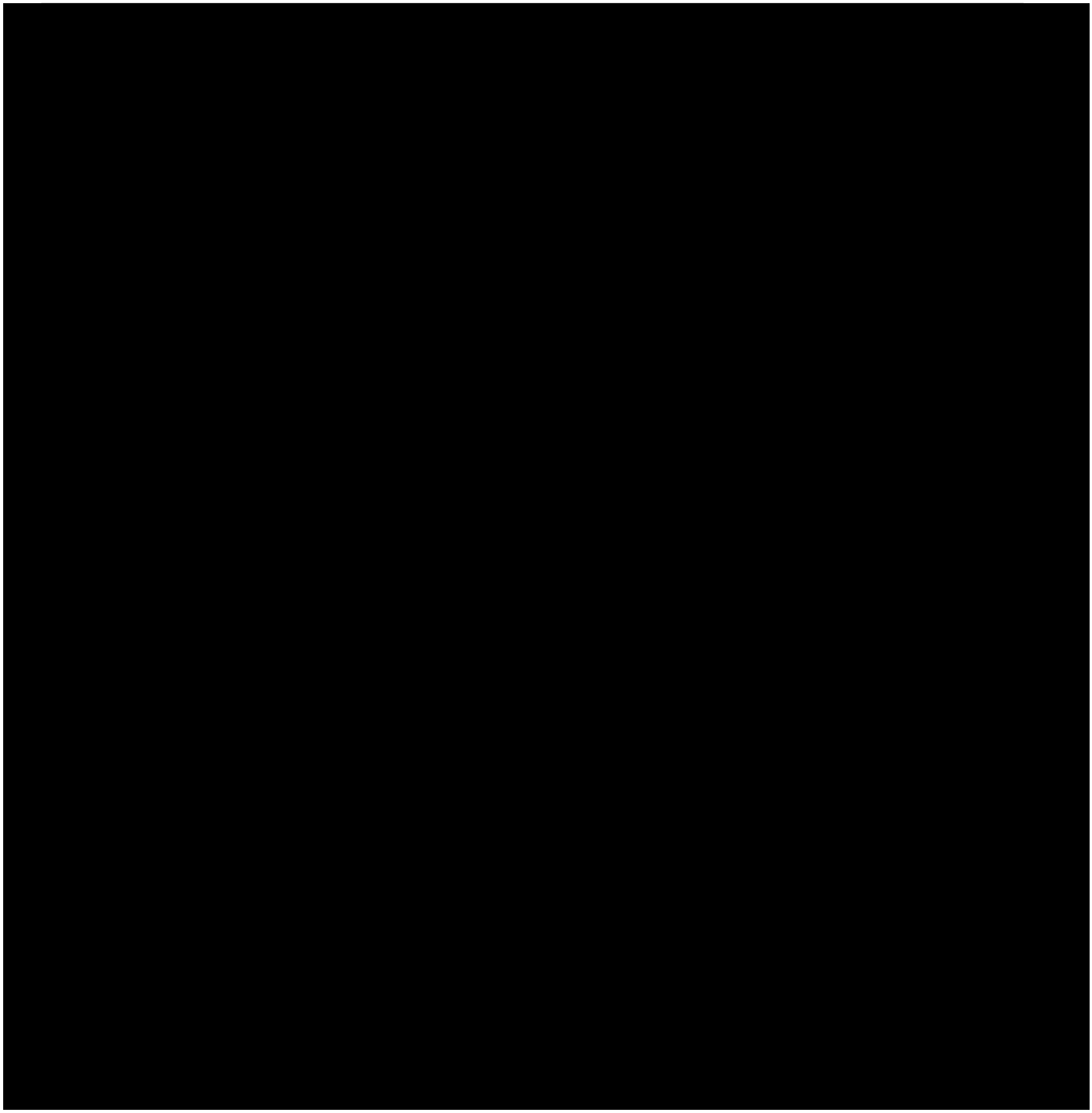
Note: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

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.

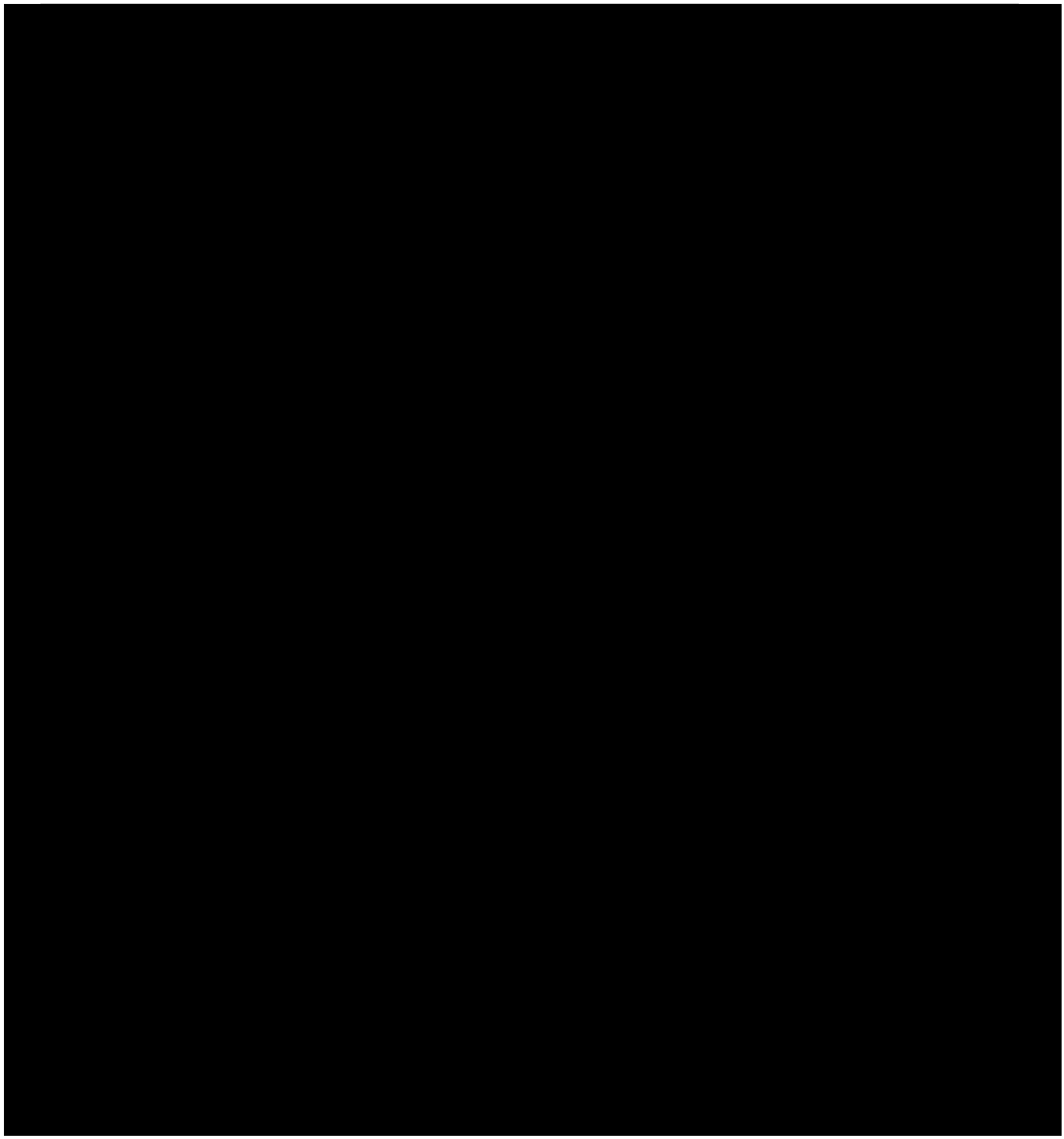
## APPENDIX E FACT-AN (VERSION 4)



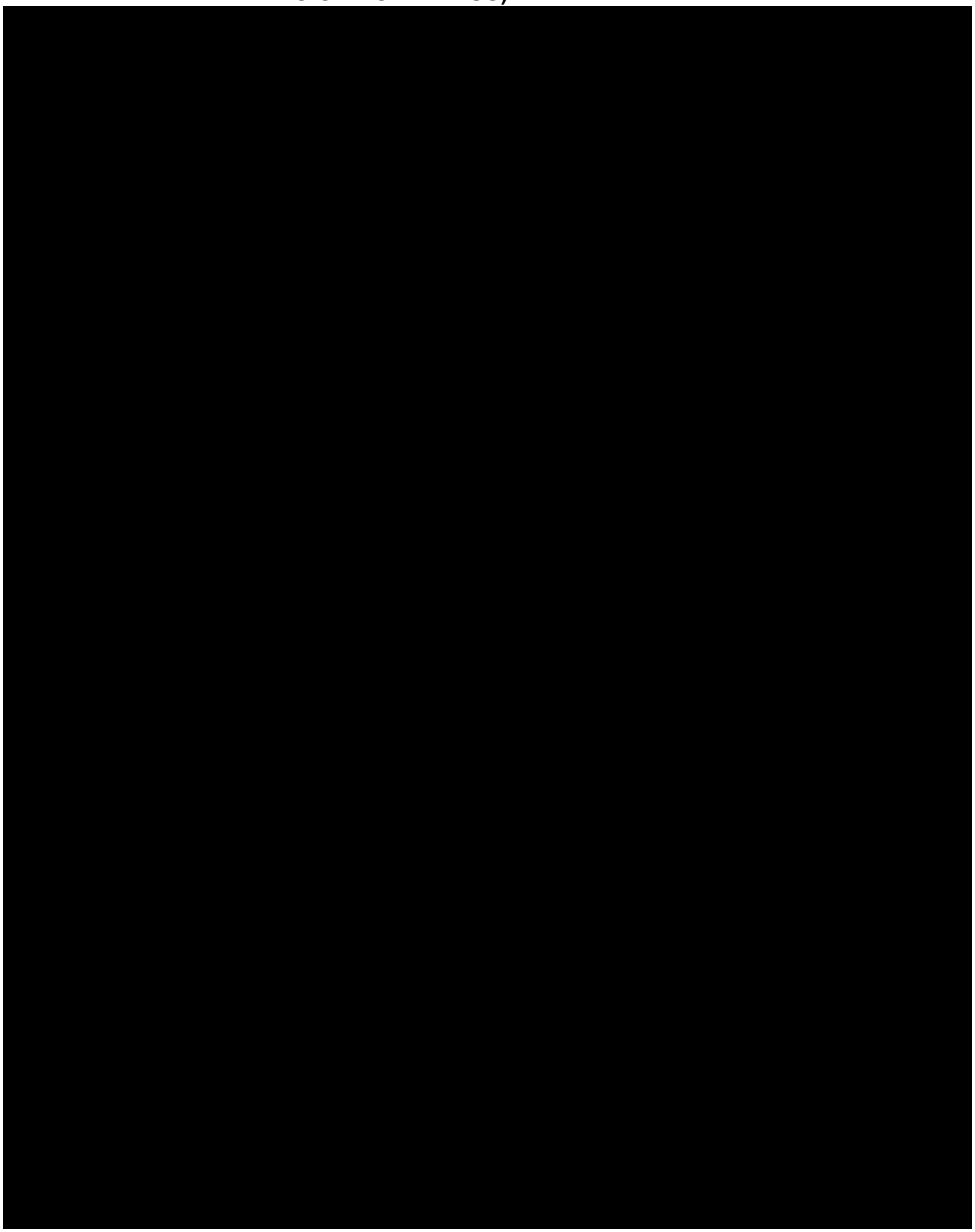
# Appendix E: FACT-An (Version 4) (Continued)



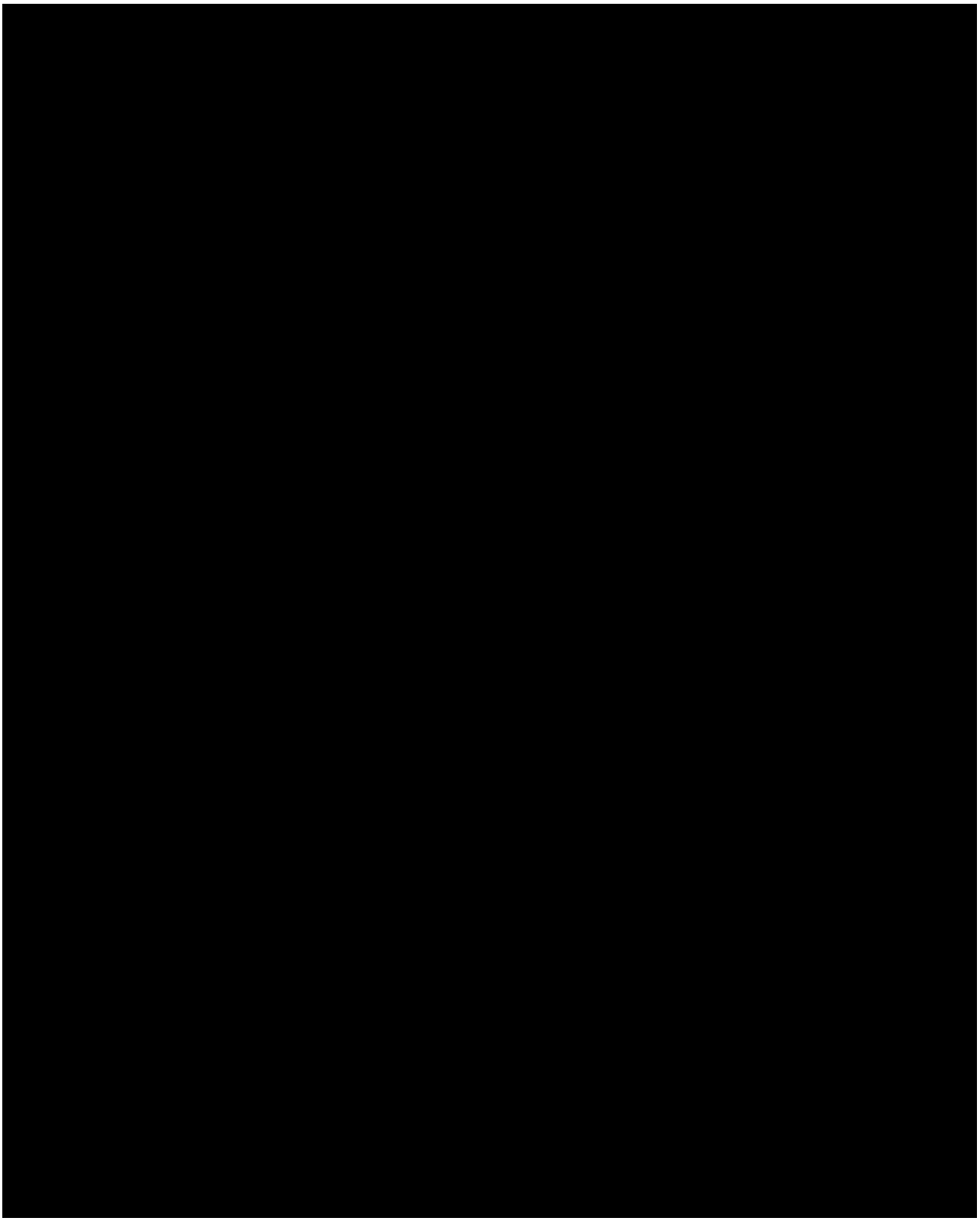
# Appendix E: FACT-An (Version 4) (Continued)



## APPENDIX F EQ-5D HEALTH QUESTIONNAIRES (EQ-5D-3L; ENGLISH VERSION FOR THE US)



# Appendix F: EQ-5D Health Questionnaires (EQ-5D-3L; English Version for the US) (Continued)



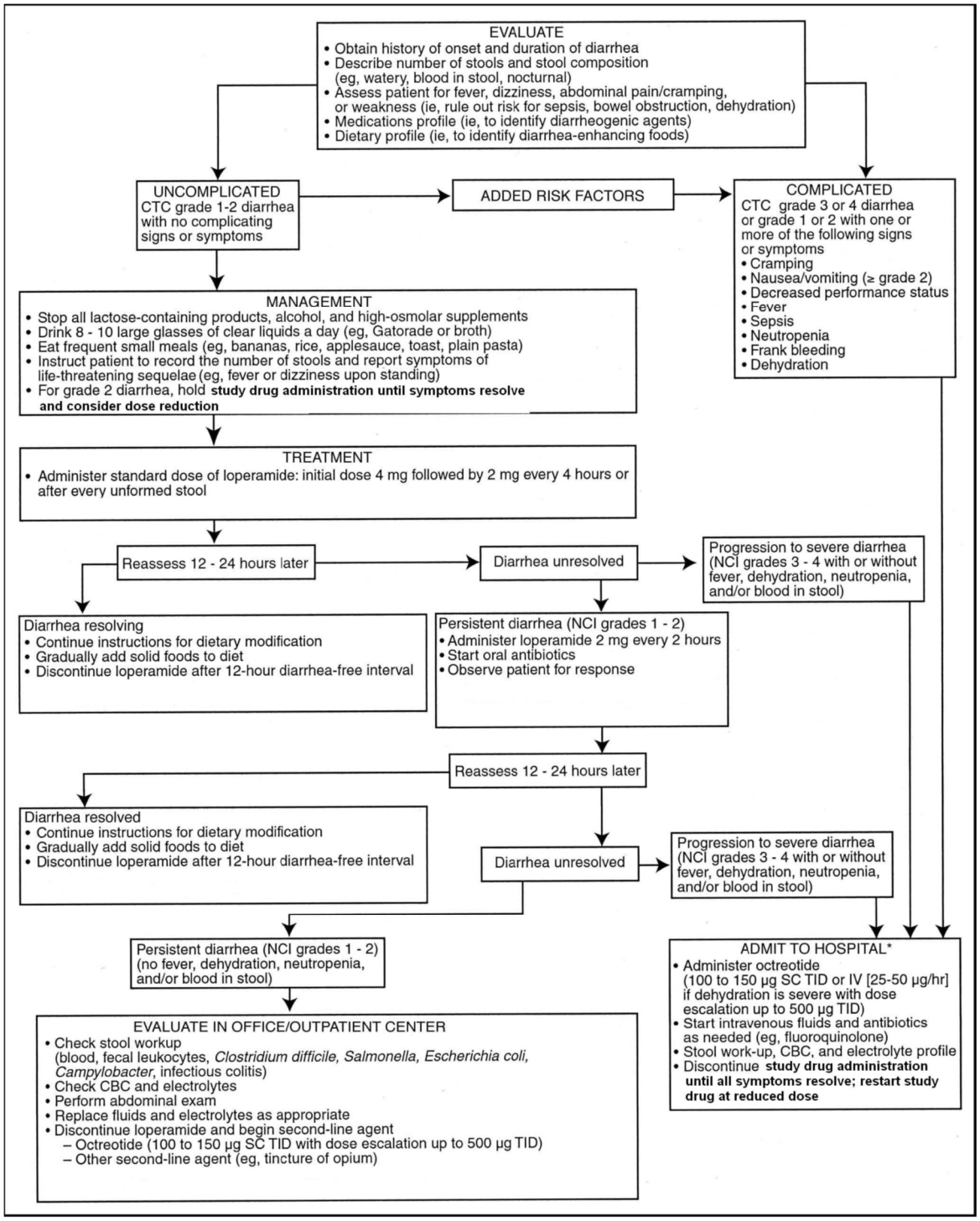
# APPENDIX G NEW YORK HEART ASSOCIATION CLASSIFICATION FOR CONGESTIVE HEART FAILURE

| **Functional Capacity** |
|---|
| **Class I.** Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. |
| **Class II.** Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. |
| **Class III.** Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. |
| **Class IV.** Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

Source: 1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients With Diseases of the Heart. American Heart Association website. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1712. Accessed 02 Mar 2011.

# APPENDIX H RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED DIARRHEA

The following published guidelines (Benson, 2004) were modified in order to be consistent with the clinical study protocol.



# APPENDIX I LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine transaminase (also SGPT) |
| AML | Acute myeloid leukemia |
| ANC | Absolute neutrophil count |
| AST | Aspartate transaminase (also SGOT) |
| BID | Twice a day |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CCR | Conventional care regimen |
| CI | Confidence interval |
| CML | Chronic myeloid leukemia |
| CMML | Chronic myelomonocytic leukemia |
| CR | Complete remission |
| CRF | Case report form |
| CRO | Clinical research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EEA | European Economic Area |
| EP | Extension Phase |
| EPO | Erythropoietin |
| EQ-5D | EuroQol Group 5D |
| EMA | European Medicines Agency |
| ESA | Erythropoiesis stimulating agent |
| EU | European Union |
| FAB | French-American-British |
| FACT-An | Functional Assessment Cancer Therapy-Anemia |
| FCBP | Female of childbearing potential |
| FDA | Food and Drug Administration |

# Appendix I:List of Abbreviations and Definitions of Terms (Continued)

| | |
|---|---|
| Fe/TIBC | Serum iron/serum total iron binding capacity |
| FISH | Florescent in situ hybridization |
| GCP | Good clinical practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GM-CSF | Granulocyte macrophage colony-stimulating factor |
| Hgb | Hemoglobin |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HI | Hematologic improvement |
| HI-E | Hematologic improvement-erythroid response |
| HI-N | Hematologic improvement-neutrophil response |
| HI-P | Hematologic improvement-platelet response |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| HR | Hazard ratio |
| HRQoL | Health-related Quality of Life |
| IB | Investigator's Brochure |
| ICD | Informed Consent Document |
| ICH | International Conference on Harmonization |
| IMiD | Immunomodulating drugs |
| INR | International normalized ratio |
| INT-1 | Intermediate-1 |
| INT-2 | Intermediate-2 |
| IP | Investigational Product |
| IPSS | International Prognostic Scoring System |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ITP | Idiopathic thrombocytopenic purpura |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| IWG | International Working Group |
| IWRS | Interactive Web Response System |

# Appendix I:List of Abbreviations and Definitions of Terms (Continued)

| [redacted] | [redacted] |
|---|---|
| LDH | Lactic dehydrogenase |
| KM | Kaplan-Meier |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| mCR | Marrow complete response |
| MCV | Mean corpuscular volume |
| MDS | Myelodysplastic syndromes |
| MDS-U | Myelodysplastic syndrome -unclassified |
| MedDRA | Medical Dictionary for Regulatory Affairs |
| MH | Mantel-Haenszel |
| mITT | Modified intent-to-treat |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| MPD | Myeloidproliferative disease |
| NCI | National Cancer Institute |
| NYHA | New York Heart Association |
| OR | Odds ratio |
| OS | Overall survival |
| PIN | Personal Identification Number |
| PK | Pharmacokinetics |
| PR | Partial remission |
| pRBC | Packed red blood cells |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| QD | Once a day |
| RA | Refractory anemia |
| RAEB | Refractory anemia with excess blasts |
| RAEB-T | Refractory anemia with excess blasts in transformation |
| RARS | Refractory anemia with ringed sideroblasts |
| RCMD | Refractory cytopenia with multilineage dysplasia |
| RCUD | Refractory cytopenia with unilineage dysplasia |
| RDW | Red cell distribution width |

# Appendix I:List of Abbreviations and Definitions of Terms (Continued)

| | |
|---|---|
| RBC | Red blood cell |
| ROW | Rest of world |
| RN | Refractory neutropenia |
| RNA | Ribonucleic acid |
| RT | Refractory thrombocytopenia |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SD | Stable disease |
| SDev | Standard deviation |
| SGOT | Serum glutamic oxaloacetic transaminase (also AST) |
| SGPT | Serum glutamic pyruvate transaminase (also ALT) |
| SMQ | Standardized MedDRA Query |
| SOP | Standard operating procedure |
| [redacted] | [redacted] |
| SUSAR | Suspected unexpected serious adverse reactions |
| TEAE | Treatment-emergent adverse event |
| TNM | Tumor nodes metastasis |
| TRALI | Transfusion-related lung injury |
| TSA | Thrombopoiesis-stimulating agent |
| ULN | Upper limit of normal |
| US | United States |
| WBC | White blood cell |
| WHO | World Health Organization |

# APPENDIX J EXTENSION PHASE

Once all 216 subjects enrolled have completed 12 months of double-blind treatment or have discontinued before reaching 12 months of double-blind treatment and Amendment 5 of the protocol is approved at the respective sites, and after study unblinding by Celgene, eligible subjects can enter the Extension Phase.

**Subject Eligibility**

At the Investigator's discretion and following confirmation of eligibility criteria below, subjects can enter the extension phase:

- Subjects who have signed the informed consent for the EP of the study;
- Subjects randomized to the oral azacitidine treatment arm and continuing in the Treatment Phase demonstrating clinical benefit as assessed by the Investigator are eligible to receive oral azacitidine in the EP;
- Subjects randomized into the placebo arm of the study will not receive oral azacitidine in the EP, but will be followed for survival in the EP;
- Subjects currently in the Follow-up Phase, after permanent study treatment discontinuation, will continue to be followed for survival in the EP;
- Subjects who do not meet any of the criteria for study discontinuation (see Section 12).

**Treatment Assignment**

Subjects will start the EP at the start of their next regularly scheduled dosing cycle for oral azacitidine and align Cycle 1 Day 1 with the Treatment Discontinuation visit, so they occur on the same day. The dose and schedule will follow the study treatment administration and schedule (Section 8.2).

Cycles should be repeated every 28 days. Subjects should be monitored locally for hematology and chemistry testing, pregnancy testing for FCBP and dose limiting toxicities before the dosing of the next cycle. Dosage delay or reduction as described below may be necessary.

**Management of Toxicities and Dose Modifications**

Subjects should be monitored for toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0), as a guide for the grading of severity. If a certain level of toxicity is observed and considered by the investigator to be at least possibly related to treatment, IP dosing may be interrupted, delayed or modified. In all cases, the reason for dose modification must be recorded in the subject's medical record. If the subject discontinues the protocol-prescribed therapy because of an AE, this event must be reported in accordance with the procedures outlined in Section 12.

Oral azacitidine dose modifications due to nonhematological and hematological toxicities during oral azacitidine treatment should be managed as described in Section 8.2.4 for dose modification guidelines due to toxicity.

**Adverse Events**

Adverse events (non-serious and serious) will continue to be collected in the EP AE CRF. Refer to Section 11. Adverse Events for reporting requirements, responsibilities and procedures.

**Concomitant Medications**

All concomitant medications that are necessary for the subject's welfare may be given at the Investigator's discretion during the EP and recorded onto the CRF. However, treatment with any other investigational medication is not permitted. Refer to Section 9 for prohibited concomitant medications/therapy for subjects on oral azacitidine.

**Survival Follow-up**

All subjects participating in the EP will be followed for survival, subsequent MDS therapies, progression to AML and secondary malignancy for 35 days ± 7 days, including 28-day safety follow-up (refer to Section 11.1: Monitoring, Recording, and Reporting of Adverse Events) following Treatment Discontinuation or until death, withdrawal of consent for further data collection, lost to follow-up, or study termination, whichever is earlier. The investigator must make every effort to obtain information regarding the subject's survival status before determining the subject is lost to follow-up.

Survival follow-up may be conducted via telephone contact with the subject, family, or the subject's treating physician or via record review (including public records, if admissible by law in the participating countries).

**Monitoring of Subjects**

The monitoring of subjects is as per the local standard of care, and at least:

- Complete blood count with WBC differential and platelet count as required, and at a minimum, prior to each dosing cycle
- For FCBP, pregnancy testing must be done prior to initiating a new cycle
- Bone marrow biopsy and aspirate as clinically indicated
- Additional tests or more frequent monitoring are at the Investigator's discretion based on the subject's clinical status.

**Investigator's Responsibility**

- Obtain subject's signature of the informed consent form to enter the EP phase
- Complete Extension Phase Case Report Form pages
- Document all adverse events (serious and non-serious) on the adverse event log page of the Extension Phase Case Report Form as required by the protocol (Section 8.2.4)
- Report serious adverse events and other immediately reportable events, as required by the protocol (see Section 11 ). A completed SAE form must be faxed to Celgene Drug Safety, as detailed in the Serious Adverse Event Report Form Completion Guidelines, immediately (ie, within 24 hours of the Investigator's knowledge of the event)
- Report drug accountability to the sponsor

- Report to the sponsor and complete the case report form page for extension phase termination when the subject terminates treatment with oral azacitidine.
- The subject should stop treatment with oral azacitidine if any of the following occur:
  - Additional investigational treatment is started;
  - Subject is no longer receiving clinical benefit, as per Investigator's discretion;
  - Subject withdraws consent;
  - A positive pregnancy test in a FCBP, at any time; or
  - At the specific request of the sponsor or its authorized representative.
- The Investigator must be available for periodic monitoring visits and allow the sponsor access to all medical records.
- The Investigator will maintain source documents on the subject for all case report form data points, which include the following:
  - Informed consent;
  - Adverse events;
  - Dosing information (date of administration, dose, number of tablets used, and lot number);
  - Concomitant-medications; and
  - Termination date and reason.

Safety evaluation for the EP will include monitoring for adverse events and recording of concomitant medications. Although physical examinations, vital sign measurements and laboratory assessments will be performed in the EP, these assessments will not be captured in the CRF. However, clinically significant findings from these assessments which meet the definition of an adverse event (see Section 11) will be reported as adverse events. Adverse events will be summarized as per Section 10.7 on the subjects entering the EP. Exposure to oral azacitidine as well as concomitant medications taken during the EP will also be summarized.

# 1. JUSTIFICATION FOR AMENDMENT

This protocol is being amended to change the primary endpoint to RBC transfusion independence with duration ≥ 56 days (8 weeks) and to add an extension phase of CC-486 treatment once the trial is unblinded.

**Significant changes included in this amendment are summarized below:**

- The primary efficacy endpoint, "proportion of subjects in the overall population achieving RBC transfusion independence with duration ≥ 84 days (12 weeks)", is switched with the secondary endpoint, "proportion of subjects in the overall population achieving RBC transfusion independence with duration ≥ 56 days (8 weeks)."

  Revised sections: Protocol Summary, Sections 3.1 Primary Endpoint(s), 3.2 Secondary Endpoint(s), 10.6.1 Primary Efficacy Analysis, and 12 Discontinuations.

- A description of the Extension Phase is presented in Appendix J and mentioned throughout the protocol.

  Revised sections: Protocol Summary, Sections 4.1.4 Extension Phase and 6.15 Extension Phase, and Appendix J: Extension Phase; and several minor editorial changes throughout the protocol to reflect the addition to the extension phase.

- The following secondary endpoint was added: Duration of RBC transfusion reduction.

  Revised sections: Protocol Summary, Sections 3.2 Secondary Endpoint(s) and 10.6.2.2 Additional Secondary Efficacy Analyses

- Deletion of Section 1.4 Protocol Amendment 4.0 Rationale

  Revised sections: Section 1.4.

- To reflect the switch in primary endpoint, the following paragraph was updated to (*italic* - new text, ~~strikethrough~~ - deleted text):
  "(…) The primary endpoint, RBC transfusion independence, is defined as the absence of any RBC transfusion during any consecutive "rolling" ~~84~~ *56* days during the treatment period compared with an average transfusion requirement of ≥ 2 units/28 days of RBCs confirmed for a minimum of 56 days immediately preceding and including the date of randomization. ~~The longer RBC transfusion-independent interval (ie, ≥ 84 days) is more conservative than the IWG 2006 criteria (ie, ≥ 56 days; Appendix D) and is significant in a patient population with 2 or more cytopenias which is indicative of poor bone marrow function at the start of study treatment.~~ Achieving RBC transfusion independence ~~of at least 84 days~~ is likely to be a substantial clinical benefit in a patient population with a median overall survival of approximately 14 to 16 months (Garcia-Manero, 2008a; Cruz, 2010; Yong, 2010). (…)"

  Revised sections: Section 4.2 Study Design Rationale

- For clarification, the text in *italic* below was added:
  "(…) *While 56 days (8 weeks) is the standard duration a response must be maintained in order to meet the current IWG response criteria (IWG 2006 criteria; Cheson, 2006; Appendix D),* limited information is available on the target population for estimating the response rate for RBC transfusion independence maintained for ≥ 84 days (12 weeks).

[redacted] *For the primary efficacy endpoint RBC transfusion independence with a duration ≥ 56 days (8 weeks), the response rate for oral azacitidine is assumed to be similar as the above findings.* (…)"

Revised sections: Section 10.3 Sample Size and Power Considerations

- To reflect the switch in endpoints, the following paragraph was updated to (*italic* - new text, ~~strikethrough~~ - deleted text):
"**RBC transfusion independence for ~~56~~ *84* days** is defined as the absence of any RBC transfusion during any consecutive "rolling" ~~56~~ *84* days during the treatment period, ie, Day 1 to ~~56~~ *84*, Day 2 to ~~57~~ *85*, Days 3 to ~~58~~ *86*, etc. ~~Subjects who are RBC transfusion-dependent at baseline and are discontinued from double-blind treatment for lack of therapeutic efficacy will be counted as non-responders~~. Frequency cross-tabulations of RBC transfusion dependency status for ~~56~~ *84* days at baseline versus on-treatment will be presented by treatment group."

Revised sections: Section 10.6.2.2 Additional Secondary Efficacy Analyses

**The amendment also includes other minor clarifications and corrections:**

- Section 8.2.5, deletion of: "The decision to discontinue a subject, which will not be delayed or refused by the sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion." As already stated in Section 8.2.
- "Important medical event" replaced by "adverse event of special interest (AESI)" in Sections 6.6.2 Progression to AML and Second Primary Malignancies, 10.7 Safety Analysis, 11.2.1 Seriousness, and 11.5 Reporting of Serious Adverse Events.
- In Section 11.6 Expedited Reporting of Adverse Events, safety group recommended the deletion of: "Adverse events such as death related to disease progression (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities. These events will be captured as AEs on the CRF, reported to Celgene Drug Safety meeting SAE reporting criteria (within 24 hours) and reported to regulatory authorities in the annual report."

# 1. JUSTIFICATION FOR AMENDMENT

This protocol is being amended to address Celgene's decision to close enrollment into the study and revise sample size.

Significant changes included in this amendment are summarized below:

- To reflect the change in sample size and the decision to close enrollment into the study, "386 subjects" is replaced by "216 subjects" throughout the protocol.
- The following rationale for Amendment 4.0 was added:

  [redacted] Per protocol, the primary analysis will be conducted once all subjects enrolled have completed 12 months of double-blind treatment or have discontinued before reaching 12 months of double-blind treatment (100% information for the primary endpoint), whichever occurs first.

  The current sample size of 216 randomized subjects is sufficient to allow analysis of the planned primary study objective of red blood cell (RBC) transfusion independence for CC-486 versus placebo with approximately 99% power. The key secondary study endpoint of overall survival (OS) will also be assessed as an interim analysis at the time of the primary analysis and in the final analysis at the time of study closure."

  Revised sections: Addition to Section 1.4 Protocol Amendment 4.0 Rationale

- Per protocol, the study will conclude once all subjects have completed the follow-up phase.

  Revised sections: Protocol Summary and Section 4.1.4. Study Closure

- To reflect the study closure update, the Follow-up sections were updated as follows.
  Original text: "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, or study closure."
  Updated text: "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, or withdrawal of consent for further data collection."

  Also, when appropriate, "or study closure" was deleted from "(…) withdrawal of consent for further data collection, or study closure." to read "(…) or withdrawal of consent for further data collection."

  Revised sections: Protocol Summary and Sections 4.1.3. Follow-up Phase, 6.6.2. Progression to AML and Second Primary Malignancies, 6.14. Follow-up, 10.7. Safety Analysis, and 11.5 Reporting of Serious Adverse Events.

- The duration of the study and enrollment period were updated based on the closure of enrollment and revised sample size. Duration was changed from "122 months" to "134 months" and enrollment period from "81 months" to "56 months".
  The protocol language will read as follows:
  "The expected duration of the study is 134 months, including a 56-month enrollment followed by 78 months of subject treatment and/or observation. The study is planned to conclude 78 months after the last subject is randomized."

  Revised sections: Protocol Summary and Section 4.3 Study Duration.

- To clarify the timing of the OS analysis, the following sentence was added: "The key secondary study endpoint of OS will be assessed as an interim analysis at the time of the primary analysis and in the final analysis at the time of study closure."

  Revised sections: Section 1.4 Protocol Amendment 4.0 Rationale and Section 10.6.2.1. Key Secondary Efficacy Analyses

- To reflect the updated treatment administration and schedule, the following sentences were added in various sections: "As of Amendment 3.0, all subjects in Cycles 1 or 2 will receive CC-486 for 14 days of a 28-day cycle schedule. Subjects may increase to a 21-day schedule at the conclusion of Cycle 2 if there are no Grade 3 or 4 toxicities requiring dose delay or reductions and if there is no evidence of hematological improvement upon discussion and agreement between the investigator and the Medical Monitor. Subjects remaining beyond Cycle 2 will continue to receive 300 mg oral azacitidine or matching placebo QD for 21 days of each 28-day treatment cycle."

  Revised sections: Protocol Summary, Section 4.1.2. Randomization and Double-blind Treatment Phase, Figure 1 Overall Study Design (footnote 5), Section 4.2. Study Design Rationale, Table 1 Table of Events (in footnote z), and Section 8.2. Treatment Administration and Schedule

- To reflect the change in power percentage and number of deaths based on the 216 randomized subjects, Section 10.3. Sample Size and Power Considerations was updated to read:

  "The basis for the power and sample size determination will be a test of the equality of the overall survival curves between the 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 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 an 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 may 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 10.8).

  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). [redacted] 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)."

  Revised section: Section 10.3. Sample Size and Power Considerations

- To reflect the change in sample size, the Section 10.6. Efficacy Analysis was updated to read:
  "(…)

  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 analysis of the OS endpoint will also be conducted at the time of the analysis of the primary efficacy endpoint. This analysis of the OS endpoint may be an interim analysis or it may be the final analysis, depending on the maturity of the survival data (eg, the required 205 deaths have occurred) at 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 in the event that OS is analyzed twice.

  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."

  Revised section: Protocol Summary and Section 10.6. Efficacy Analysis

- To reflect the change in sample size, the Section 10.8. Interim Analysis was updated to read:
  "An interim analysis of the OS endpoint may be performed when all 216 subjects have completed 12 months of double-blind treatment or have 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. In the event an interim analysis of OS is performed, 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, 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 azacitidine is demonstrated for the primary efficacy endpoint, RBC transfusion independence, at the two-sided 0.05 significance level."

  Revised section: Section 10.8. Interim Analysis

**The amendment also includes other minor clarifications and corrections:**

- To clarify that the FACT-An and EQ-5D questionnaires can be completed following interaction with study personnel the following sentences were modified:
    - In Footnote x of Table 1. Table of Events, the words "when feasible" were added to read: "FACT-An and EQ-5D questionnaires must be completed prior to interaction with study personnel (when feasible) and prior to IP administration at the start of every Cycle, and at Treatment Discontinuation (Section 6.8). (…)"
    - In Section 6.4. Baseline, the last sentence now reads: "The FACT-An and EQ-5D questionnaires should always be completed prior to IP administration and, when feasible, prior to interaction with study personnel."
    - In Section 6.8. Health-related Quality of life, first sentence of last paragraph reads: "The FACT-An and EQ-5D questionnaires should be completed prior to interaction with study personnel (when feasible) and prior to IP administration on Day 1 of every Cycle and at the Treatment Discontinuation visit."

# 1. JUSTIFICATION FOR AMENDMENT

[redacted]

Significant changes included in this amendment are summarized below:

- The duration of the study and enrollment period was extended due to slow enrollment. Duration was extended from "60 months" to "122 months" and enrollment period from "26 months" to "81 months".
  The protocol language will read as follows:
  "The expected duration of the study is 122 months, including an 81-month enrollment followed by 41 months of subject treatment and/or observation. The study is planned to conclude 41 months after the last subject is randomized."

  Revised sections: Protocol Summary, Section 4.3 Study Duration, and Section 10.3 Sample Size and Power Consideration.

- [redacted] dose schedule was reduced to 14 days.

  Revised sections: Section 8.2.4. Dose Modifications

- [redacted] to enhance hematotoxicity monitoring, the following information was added to Section 8.2.4. Dose Modifications: "Any subject who experiences febrile neutropenia ≥ Grade 3 will have IP held until fever has resolved; must be afebrile for 3 days before re-starting study drug. Administration of antibiotic, antiviral and antifungal therapy is strongly recommended."

  Revised sections: Section 8.2.4. Dose Modifications and Table 2

- [redacted], to enhance hematotoxicity monitoring, dose modification for neutropenia Grade 4 was updated.

  Revised sections: Section 8.2.4. Dose Modifications and Table 2

- [redacted], to enhance hematotoxicity monitoring for Febrile Neutropenia, the following wording "Secondary prophylaxis with G-CSF may be considered" was changed to "Secondary prophylaxis with G-CSF is strongly recommended".

  Revised sections: Table 2

- [redacted], to enhance hematotoxicity monitoring, Section 8.2.5. Re-treatment Criteria was updated to reflect that for subjects that experience hematotoxicity (absolute neutrophil count [ANC] or platelet drop to Grade 4, or 50% drop within Grade 4), hematologic recovery is required before starting the next cycle at Day 28. Hematology recovery is defined and a decision tree for hematologic recovery presents the rules in a friendly manner.

  Revised sections: Section 8.2.5. Re-treatment Criteria

- [redacted], to enhance hematotoxicity monitoring, the following sentences were added: "Consider platelet transfusion if platelet counts are < 25 x $10^9$/L.

If appropriate administration of platelets does not correct the platelet counts, contact Medical Monitors to consider IP dosing delay."

Revised sections: Section 9.1. Permitted Concomitant Medications and Procedures

- [redacted], to enhance hematotoxicity monitoring, the following sentence: "For subjects who develop an ANC < 0.5 x $10^9$/L, administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin or other recognized prophylactic antibiotics) may be considered and documented as a concomitant medication on the appropriate case report form (CRF)." was updated to: "For subjects who develop an ANC < 0.5 x $10^9$/L, administration of prophylactic fluoroquinolone antibiotics (eg, ciprofloxacin or levofloxacin or other recognized prophylactic antibiotics) **is strongly recommended** and should be documented as a concomitant medication on the appropriate CRF."

  Revised sections: Section 9.1. Permitted Concomitant Medications and Procedures

**The amendment also includes other minor clarifications and corrections:**

- Change of Medical Monitor
- Change of Celgene Therapeutic Area Head
- In Section 6.1. Screening, the following sentence has been added for clarification: "If a subject is screen failed and then re-screened, subject must be re-consented in writing."

# 1. JUSTIFICATION FOR AMENDMENT

**Significant changes included in this amendment are summarized below:**

1. **Modification of Inclusion Criterion #3**

   - **Changed the definition of red blood cell (RBC) transfusion dependency for screening by increasing the maximum hemoglobin value threshold prior to transfusions when determining transfusion dependence from ≤ 9 g/dL to ≤ 10 g/dL.**

By increasing the maximum hemoglobin (Hgb) threshold to ≤ 10 g/dL from ≤ 9 g/dL when evaluating subjects for the inclusion criterion of transfusion dependency, this may allow patients to be randomized earlier into the trial. The median age of diagnosis of myelodysplastic syndrome (MDS) is 71 to 76 years, and 72% of patients are age 70 or older. Along with this older demographic in MDS, patients often develop overlapping co-morbidities. When erythrocyte production is affected in MDS, patients frequently present with signs and symptoms of anemia including pallor, tachycardia, hypotension, fatigue, headache and exercise intolerance, or with signs and symptoms of worsening of an underlying condition such as angina pectoris, heart failure, or a pulmonary disorder. Patients with such co-morbidities may have more symptoms at a higher baseline Hgb level than patient who do not have such co-morbidities. Due to this fact, some practitioners choose to transfuse their older MDS patients with multiple co-morbidities at a higher Hgb level of 10 g/dL than they would younger and/or more fit patients.

Increasing the Hgb threshold for the definition of transfusion dependence for eligibility does not change the overall survival (OS) of the target population of 17 months (Garcia-Manero, 2008), which is still in the range of the median OS of 18 months assumed for the placebo treated group used for the sample size calculation in the current protocol. Thus, no impact on the secondary endpoint of OS is expected.

This change also does not affect the definition of transfusion independence as described in the primary objective of the study, nor would it be applicable to the International Working group (IWG) response criteria for hematologic improvement as described in the secondary objective of hematologic improvement-erythroid response (HI-E, which uses ≤ 9 g/dL as the maximum threshold of hemoglobin values for transfusions to count towards transfusion independence response evaluation). However, to account for any potential impact a sensitivity analysis will be performed as specified in the modification of the Primary Efficacy Analysis (see further below).

- **Changed the definition of RBC transfusion dependency for screening assessment by decreasing the time of observation of dependency from 84 to 56 days.**

This modification has been made in order to change the definition of RBC transfusion dependence when evaluating a patient's eligibility to enroll in the study. The change to this part of the inclusion criteria is proposed to address the fact that the targeted study population are patients with MDS who have significant thrombocytopenia and are required to wait an

additional 28 days for the RBC transfusion definition to be met. This additional time required may result in some patients progressing to higher risk MDS or AML prior to randomization. Having a shorter observation time in which to define red blood cell transfusion dependence will shorten the time to enrollment in the study. This change is in line with the IWG Hematologic Response and Improvement Criteria for MDS (Cheson, 2006).

Revised Sections: 3.2, 4.1.1, 4.2, 6.1.2, 7.2, and Figure 1

2. **Modification of the primary efficacy analysis in accordance with the changes to the definition of red blood cell transfusion dependence at screening for the study.**

This includes the addition of a sensitivity analysis to account for any potential impact of increasing the RBC transfusion dependence requirement for the baseline hemoglobin (Hgb) level from ≤ 9.0 g/dL to ≤ 10.0 g/dL, as well as for those subjects considered transfusion dependent at baseline based on transfusions given for a hemoglobin value ≤ 9.0 g/dL for both 56 and 84 days

Revised Section: 10.6.1

3. **Modification of Inclusion Criterion #4**

- **Changed requirement for two centrally analyzed platelet counts that are ≤ 75 x $10^9$/L and ≥ 21 days apart to just one centrally analyzed platelet count if thrombocytopenia is already confirmed prior to screening or if locally analyzed platelet counts are ≤ 75 x $10^9$/L and are ≥ 21 days apart**

This modification has been made to potentially decrease the screening time for these patients who have both transfusion-dependent anemia and thrombocytopenia, as they are at risk to experience bleeding events, rapid progression of disease, as well as other complications. By allowing the use of locally analyzed platelet counts within 56 days prior to randomization that are ≤ 75 x $10^9$/L, in combination with a centrally analyzed platelet count, the screening period for a patient's entry into the study may be reduced. The current protocol requirement of 2 centrally analyzed platelet counts at least 21 days apart extends the time required to complete screening and delays treatment for these patients who are at risk of complications and/or progression, and for whom there are very few alternative treatment options.

Revised Sections: 3.2, 4.1.1, 6.1.3, 7.2, and Table 1 (footnote f)

4. **Modification of Exclusion Criterion #5**

- ***Changed the wash-out period for prior lenalidomide treatment from ≥ 24 weeks to ≥ 8 weeks.***

Under the current protocol, patients who have received lenalidomide previously have had to wait for 24 weeks since their last dose before being randomized into this study. Most of these patients have received other therapies in the interim, resulting in the loss of a population of patients due to this extended wash-out period.

[redacted]

[redacted]

Based on the data examined and described above, amending the protocol to allow the inclusion of subjects with prior lenalidomide treatment after ≥ 8 week wash-out period is warranted because the average time to recovery of platelet counts to > 50 x $10^9$/Lafter lenalidomide use is less than a month. Additionally, the platelet count at screening is unlikely to be affected by earlier treatment with lenalidomide. The overall study population would not be changed significantly.

Revised Section: 7.3

5. **Modification of Exclusion Criterion #16**

   - **Added language to allow for the participation in Study AZA-MDS-003 if a subject has abnormal coagulation parameters with the condition that they are being treated with a stable dose of anticoagulants for thrombotic prophylaxis.**

The patients enrolled in study AZA-MDS-003 to date have a median age of 73 years, with 43% being ≥ 75 years old or greater. The opportunity to include patients who have abnormal coagulation parameters due to anticoagulant therapy used for thrombotic prophylaxis reflects the real life occurrence of this combination of disorders (ie, atrial fibrillation, a previous thromboembolic event, mechanical heart valves, lupus or anti- phospholipid antibodies) in the population under study. The acceptance of such patients into the study would be only after consultation with the medical monitor so that reasonable precautions for the combination of thrombocytopenia and anticoagulant use can be discussed with the investigator.

Revised Section: 7.3

6. **Modification of Exclusion Criterion #17**

   - **Added language to allow for the participation of subjects with > 2.5 x ULN of the ALT and/or AST values if accompanied by a serum transferrin saturation of > 65% and a serum ferritin level > 1000 µg/L.**

This population of low/intermediate-1 risk MDS patients is required to be RBC transfusion dependent in order to meet eligibility criteria for enrollment into Study AZA-MDS-003. As a consequence, transfusional iron overload is a very common complication. In addition to transfusional iron loading, MDS patients have increased intestinal absorption of iron, similar to patients with hemoglobinopathies and genetic hemaochromatosis. Hence, MDS patients may show evidence of iron loading even prior to initiation of transfusion therapy. In the presence of iron overload, the liver may be damaged which could result in increased AST, ALT, and/or serum bilirubin values.

Up to the present time, there is limited evidence to indicate that azacitidine is metabolized by liver-derived pathways [redacted]. It does not appear to be a substrate, an inducer, nor an inhibitor of cytochrome P450 isoenzymes (1A2, 2C19, 3A4/5) (Vidaza/CC-486 Investigator Brochure, v. 11, 2014).

For these reasons the inclusion of patients with liver enzyme abnormalities secondary to iron overload with AST and/or ALT > 2.5 times ULN that is accompanied by a serum transferrin saturation of > 65%, and a serum ferritin of > 1000 µg/L, after consultation with the medical monitor, will be allowed. The addition of oral azacitidine would not have further deleterious effects on their liver, and could potentially result in a decrease of iron overload by decreasing RBC transfusion requirements.

- **Added language to allow for the participation of subjects with > 1.5 ULN serum bilirubin if in the presence of diagnosed or known Gilbert syndrome.**

Gilbert syndrome, also known as Gilbert-Meulengracht syndrome, is a benign hereditary condition characterized by intermittent unconjugated hyperbilirubinemia in the absence of hepatocellular disease or hemolysis (Fretzayaz, 2012). Patients with Gilbert syndrome are asymptomatic and typically have otherwise normal liver serum chemistries (VanWagner, 2015). This is a benign condition that does not otherwise affect normal liver function and should not exclude subjects from the trial.

Revised Section: 7.3

7. **Addition of secondary endpoints for RBC transfusion independence with duration of ≥ 56 days (8 weeks) and time to RBC transfusion independence.**

The following secondary endpoints were added:

- Proportion of subjects in the overall population achieving RBC transfusion independence with duration of ≥ 56 days (8 weeks);
- Duration of RBC transfusion independence of ≥ 56 days (8 weeks);
- Time to RBC transfusion independence of ≥ 56 days (8 weeks);

Adding secondary endpoints according to the definition of RBC transfusion independence by IWG criteria (i.e., a duration of 56 days) will allow for comparison of oral azacitidine efficacy within comparable study populations and MDS subsets. The secondary endpoint definition for duration of RBC transfusion independence and time to RBC transfusion independence based on a duration of 84 days will not be changed.

Revised Sections: 1.3, 3.2, 10.6.2.2

8. **Addition of language to section the titled "MDS Diagnosis, WHO Classification and IPSS Risk classification" that could expand some of the allowable criteria used to determine the diagnosis and classification of MDS at screening.**

- Language has been added to allow for the use of historical cytomorphologic, histologic and/or cytogenetic bone marrow samples to support the screening central laboratory results, which may be samples that were obtained outside of the 56 day screening window, but must be from within 3 months of the first screening bone marrow procedure.
- Language has also been added to allow for the use of fewer than than 20 analyzable metaphases in standard G-banding cytogenetic analysis at screening.

- Language has been added to allow for the use of FISH analysis to rule out common chromosomal aberrations that occur in MDS if, after two bone marrow aspirate procedures as part of screening for this study, only few (<10), or no, metaphases are able to be rendered with which the karyotype can be characterized via standard G-banding.

The to-date experience in AZA-MDS-003 has shown that 14% of subjects screened have an insufficient number of metaphase cells with which to analyze their cytogenetic status. Despite undergoing repeat bone marrow aspirates, and sometimes repeat biopsies, many patients do not have sufficient cells for adequate cytogenetic analysis in order to be evaluated for inclusion by IPSS criteria.

In addition, while bone marrow chromosome banding analyses remain the gold standard of cytogenetics in MDS patients, in the case of repeated failure of standard G-banding (absent or poor quality metaphases) FISH analysis is recommended to detect targeted chromosomal abnormalities in interphase nuclei according to the European LeukemiaNet consensus regarding diagnostic procedures for MDS (Malcovati, 2013).

Similar to the challenges in performing standard G-banding chromosomal analysis from patient samples with hypocellular /fibrotic bone marrow, clear confirmation of diagnosis of MDS by cytomorphological analysis is also limited due to the fact that MDS progresses; issues of hypocellularity and reticulin fibrosis of the marrow can occur or increase in amount. In this circumstance, confirmation of a definitive MDS diagnosis on prior marrows could enable the central pathologist to have a clearer understanding for the presence of MDS in the screening samples for this study. The 3 month window during which the historical bone marrow samples must have been obtained has been proposed to minimize the chance that the evolution of the MDS has occurred in this time period.

Revised section: 6.1.1

9. **The exploratory efficacy analyses has been amended to include a question of whether or not a subject was enrolled under Protocol Amendment #2.**

This change has been made in order to carry out sensitivity analyses to compare the results obtained before versus after implementation of the protocol amendments.

Revised Section: 10.6.2.3

**Minor changes included in this amendment are summarized below:**

1. **An administrative update was made to reflect the change of** [redacted]

Revised Section: signature page (pg. 2)

2. **Added language to emphasize the need for accurate and thorough documentation of platelet transfusion status since this information is used in the efficacy analysis.**

This has been modified to provide clarity to the existing protocol language.

Revised Section: 4.1.1

3. **Language has been added to the protocol that would enable the implementation of a roll-over protocol.**

This language has been added to allow for the closing of the study if the primary analysis has been completed (and been unblinded) in order to reconsent any remaining subjects into a roll-over protocol without amending the original protocol. This roll-over protocol will provide subjects who continue to benefit from treatment continuation via post-study treatment with this compound.

Revised Sections: 4.1.4, 14.8

4. **Added language to clarify the existing language regarding the study windows and 7-day drug holiday.**

This has been modified to provide emphasis on the necessity of a study drug holiday.

Revised Sections: 6.0, Table 1 (footnote a)

5. **Removed the time frame of "within 14 days of randomization" from the performance of a reticulocyte count in screening.**

This has been modified to reflect the fact that analyzing the reticulocyte count earlier during the screening period allows for earlier testing for the presence of autoimmune hemolytic anemia in the case of a patient with an elevated indirect bilirubin level. This would thus give the investigator the opportunity to avoid invasive bone marrow assessments for a patient who would ultimately be ineligible due to autoimmune hemolytic anemia.

Revised Sections: Table 1 (footnote n), 6.1.13

6. **Added language to clarify when the HRQoL questionnaire should be completed by the subjects.**

This has been modified due to the scheduling by some sites of laboratory draws prior to the actual visit date, and the fact that laboratory personnel are not study specific and do not have access to the devices on which the subjects answer the questionnaire.

Revised Sections: Table 1 (footnote x)

7. **Language was added to account for an in-home nursing service which may be utilized at the investigators discretion (if applicable in the respective country) to obtain hematology and serum chemistry laboratory samples on Days 8, 15, and 22.**

This language has been added to the protocol as in-home nursing service will be rolled-out in some countries as applicable (depending on local regulations and demand) in the near future. This service is being initiated to address the concerns of some investigators regarding subjects who live a great distance from an investigative site and who may not be able to enter the study because the travel time for the frequency of visits would be prohibitive.

Revised Sections: 6.6.5

**Supportive Literature Used in the SOC**

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.

Fretzayaz et al. Gilbert syndrome. Eur J Pediatric, 2012 Jan;171(1):11-5.

Garcia-Manero G, Shan J, Faderl S, Cortes J, Ravandi F, Borthakur G, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia 2008a;22(3):538-43.

Malcovati, L, Cazzola, M. Refractory anemia with ring sideroblasts. Best Practice & Research Clinical Haematology 26 (2013) 377–385.

VanWagner, L, Green, R. Evaluating elevated bilirubin levels in asymptomatic adults. JAMA 2015 February 3; 313(5): 516-517.

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

1. [redacted]

One main purpose of this protocol amendment is to extend the targeted patient population by increasing the platelet count limit at screening from the current platelet counts of [redacted] as entry criteria for enrollment into the protocol (Inclusion Criterion #4, Section 7.2). [redacted] As this increase is not considered to be significant enough to warrant any change to the current sample size calculation, the samples size of 386 subjects (193 in each group) remains the same as in the original AZA-MDS-003 protocol.

2. **Extension of targeted patient population to allow subjects who had prior treatment with lenalidomide**

An additional reason for this protocol amendment is to allow subjects who had prior treatment with lenalidomide entering the study, provided that subjects had their last lenalidomide treatment ≥ 24 weeks prior to randomization (Exclusion Criterion #5, Section 7.3). Lenalidomide (Revlimid®) is an immunomodulating agent with activity demonstrated in patients with lower risk MDS, particularly in lower risk transfusion dependent MDS patients with chromosome 5q deletion [del(5q)] who are RBC transfusion-dependent. The majority of these patients achieve transfusion independence with lenalidomide, however, patients frequently relapse and become dependent on transfusions again despite taking lenalidomide. It is currently recommended that patients discontinue lenalidomide therapy at that point (NCCN Guidelines MDS, 2014), however, only very limited alternative treatment options are available for these patients to date.

Based on publications by List (2006) and Raza (2008) lenalidomide shows significant activity in subjects with deletion of 5q as well as subjects without 5q deletion, respectively. Currently there is no evidence that no response or relapse to a prior response to lenalidomide treatment has any negative impact on subsequent azacitidine response. Komrokji et al. reported response to treatment with azacitidine in del(5q) MDS subjects after lenalidomide treatment failure (Komrokji, 2012). Overall response rates (CR and PR) in these del(5q) patients previously treated with lenalidomide appear to be similar to those observed in the azacitidine registration trials for MDS (Vidaza® Prescribing Information), indicating that

azacitidine may be an effective option for salvage treatment in patients previously failing lenalidomide.

The mandated window of at least 24 weeks between the last dose of lenalidomide administered and randomization in the AZA-MDS-003 study, will account for potential late-responders to lenalidomide and also rule out any potential synergistic effects lenalidomide and azacitidine might have. In addition, this 24-week window allows subjects to recover from possible myelosuppression such as worsening of thrombocytopenia, that may be related to lenalidomide therapy before entering the AZA-MDS-003 study, thereby avoiding that a late hematologic recovery could be mistaken as a response to study treatment (CC-486 or placebo).

3. **Inclusion of subjects with secondary MDS**

An additional reason for this protocol amendment is to allow subjects with secondary MDS (ie, MDS that is known to have arisen as the result of chemical injury or treatment with chemotherapy and/or radiation for other diseases) if subjects have been off-treatment from prior antineoplastic therapy ≥ 24 weeks prior to randomization.

Generally secondary MDS has a worse prognosis than primary (de novo) MDS and this is thought for the most part, to be related to the fact that the karyotypic abnormalities are more complex in secondary MDS (Heim, 1992; Vanleeuwen, 1996; Larson, 1996; West, 2000).

As complex karyotypes are frequent in secondary MDS the majority of patients are classified as higher risk disease according to the IPSS risk classification. However, a smaller fraction of secondary MDS with no chromosomal abnormalities, or better karyotypes, are classified as INT-1 according to IPSS displaying similar features as de novo MDS. It is thought that the prognostic differences that are seen in these two patient groups (de novo MDS versus secondary MDS) relate primarily to the occurrence of their underlying cytogenetic changes and that survival is similar in de novo versus secondary MDS for equivalent chromosomal abnormalities (Estey, 1998; Tong, 2012).

Based on the above observation, that karyotypic abnormalities appear to be one of the primary contributors on prognosis in both de novo MDS and secondary MDS, it is not expected that the inclusion of patients with secondary Int-1-risk MDS in the AZA-MDS-003 study would affect the overall study population significantly with regards to the expected OS. However, azacitidine could potentially offer clinical benefit in this population with otherwise limited treatment options.

4. **Further clarification on the inclusion of subjects with hypoplastic MDS or other subtypes**

The original protocol allows for inclusion of subjects with hypoplastic MDS or other subtype who are not eligible for treatment with immunotherapy. The addition of "based on investigator's judgment" further clarifies that it is solely at the treating investigator's discretion to judge the patients' suitability for treatment with immunotherapy.

Based on several studies evaluating the use of immunosuppressive therapy with ATG with or without cyclosporine, it has been established that immunosuppressive therapy is most efficacious in MDS patients with a HLA-DR15 histocompatibility type (Jonasova, 1998; Molldrem, 1997; Sauntharajah, 2003). Responses may also occur in subjects who have

alternate HLA-DR typing, but responses occur less frequently (Saunthararajah, 2003). However, subjects with a higher age are at significant increased risk of developing serious life-threatening infections with this form of therapy, and this mode of treatment is not frequently prescribed for this older age group due to serious side effects that can transpire (Sloand, 2009). Furthermore, from a global perspective, immunosuppressive therapy is not necessarily routinely used or available for this subtype of MDS.

Due to the fact that several patient specific parameters need to be considered when evaluating whether immunosuppressive therapy may be an adequate treatment option for an individual patient, Celgene has included the clarification "based on investigator's judgment" to indicate that it is solely at the discretion of the treating investigator to determine whether immunosuppressive therapy may be a suitable treatment option for the patient.

Furthermore, new emerging data specifically assessing response to azacitidine in patients with hypoplastic MDS indicates clinical efficacy in this specific patient population (Seymour, 2013). Additionally, safety related to azacitidine treatment does not appear to be compromised in this hypoplastic MDS population in comparison to that seen with alternative therapies including best supportive care, low dose Ara-C or more aggressive chemotherapy combinations including Ara-C plus anthracyclines (Seymour, 2013). This new data further supports that patients with hypoplastic MDS should not be excluded from participation in this study unless considered suitable for immunosuppressive therapy by the investigator.

5. **Modification to study procedure at screening - addition of a mandatory bone marrow biopsy at screening**

Although the classification of MDS according to the WHO 2008 classification is primarily based on cytomorphologic and quantitative criteria derived from bone marrow aspirate and peripheral blood smear, the value of the bone marrow biopsy in MDS is well established and regarded mandatory by widely acknowledged diagnostic guidelines (Swerdlow, 2008; Malcovati, 2013; NCCN Guidelines MDS, 2014).

A bone marrow biopsy exam may aid in confirming a suspected diagnosis of MDS by excluding reactive and non-reactive conditions in which cytopenia and dyshematopoietic changes may also be observed. A biopsy provides information on marrow cellularity, megakaryocyte component, blast compartment, bone marrow fibrosis, bone marrow tissue architecture such as granulomas and the presence of non-hematological cells, such as metastases. The bone marrow in MDS is usually hyper- or normocellular, but in a minority of cases (approximately 10%), the bone marrow is hypocellular (hypoplastic MDS). This group needs to be distinguished from both aplastic anemia and hypocellular AML. The separation between these entities can be problematic as morphological differences may be subtle (Maschek, 1993; Huang, 2008; Sloand, 2009) and a bone marrow biopsy has been shown to be useful in distinguishing hypoplastic MDS from cases of aplastic anemia (Bennett, 2009).

In 10% to 20% of cases of MDS there is moderate to severe bone marrow fibrosis in which bone marrow aspiration often fails or delivers smears of inferior quality. MDS with bone marrow fibrosis identifies a distinct subgroup of MDS with multilineage dysplasia and high transfusion requirement. These cases need to be differentiated from other myeloid neoplasms with bone marrow fibrosis, such as chronic myelomonocytic leukemia, primary

myelofibrosis, acute megakaryoblastic leukemia and acute panmyelosis with myelofibrosis. Most cases of MDS with fibrosis have an excess of blasts and an aggressive clinical course. Such cases may erroneously be considered low-grade MDS if only the blast count is determined from the BM aspirate, which in the presence of fibrosis is often diluted with peripheral blood. In the fibrotic group, as in other cases of MDS with inadequate aspirates, an accurate blast determination requires a bone marrow biopsy and immunohistochemical studies for CD34. Immunohistochemistry with anti-CD34 allows the identification and enumeration of CD34+ blast cells. This is particularly useful in the case of an aspirate of suboptimal quality because of bone marrow fibrosis or hypocellularity (Buesche, 2008; Della Porta, 2009; Thiele, 2005).

On the basis of these findings and given the target patient population for the AZA-MDS-003 study with significant marrow dysfunction related to thrombocytopenia plus red blood cell transfusion dependency, it is possible that a proportion of the eligible subjects have hypoplastic marrows or marrows that have features of fibrosis. In fact, it appears that bone marrow aspirates drawn from a considerable fraction of the patients screened for the AZA-MDS-003 study thus far, presented with reduced marrow particles and cellularity. Thus performing a bone marrow biopsy for central confirmation of the diagnosis of MDS at screening provides addition valuable information on the condition of the bone marrow and also helps to distinguish the fraction of hypoplastic MDS patients from patients with aplastic anemia.

6. **Oral azacitidine may be taken on an empty stomach or with food**

Currently Celgene is evaluating the pharmacokinetics and effect of food of a new tablet formulation of oral azacitidine (CC-486) in the ongoing Phase 1 study AZA-MDS-004 "A Phase 1, Multicenter, Open-label Study to Evaluate The Pharmacokinetics and Effect of Food of A New Tablet Formulation of Oral Azacitidine, and to Evaluate The Safety and Efficacy of Oral Azacitidine in Subjects with Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia or Acute Myeloid Leukemia". Part 1 of the AZA-MDS-004 study assessed the PK of oral azacitidine administered once daily as two 150-mg tablets (F8 formulation, the formulation being assessed in the AZA-MDS-003 study) and three 100-mg tablets (F6 formulation) and evaluated the effect of food (600 calories) on oral azacitidine absorption from the two 150-mg tablets (F8). Preliminary results showed that under fasted condition, the F6 and F8 PK profiles are comparable (N=17). Compared to fasted condition, the F8 PK profile under fed condition shifted ~1.0 hour to the right. Under fasted conditions, the PK parameters ($AUC_{inf}$, $C_{max}$, $T_{max}$, terminal half-life elimination, apparent clearance, apparent volume of distribution) obtained following F6 and F8 administration are similar. Following F8 administration under fed and fasted conditions, the PK parameters are similar with the exception of the median $T_{max}$, which is delayed by ~1.0 hour under fed condition.

In summary, following oral administration, azacitidine is rapidly absorbed. Little or no effect of food on azacitidine PK was observed with the F8 formulation, except $T_{max}$ delay of ~1.0 hour under fed condition. Based on these results, oral azacitidine can be taken without regard to food (up to 600 calories) (Investigator's Brochure) and this was reflected in the protocol.

7. **Granulocyte colony stimulating factors may be administered as secondary prophylaxis during the study**

The current protocol allows the administration of granulocyte colony stimulating factors (G-CSF and granulocyte macrophage colony-stimulating factor [GM-CSF]) for the treatment of neutropenic infections. Celgene plans to amend the protocol to also allow administration of granulocyte colony stimulating factors as secondary prophylaxis as per the investigator's discretion.

Febrile neutropenia is a serious and potentially life-threatening complication in patients undergoing systemic chemotherapy and an increase in frequency of febrile neutropenia may occur related to both the severity and duration of neutropenia. Patients with MDS frequently succumb to infection, partly due to neutropenia and partly due to neutrophil dysfunction (Komrokji, 2003). The use of secondary prophylaxis with Colony Stimulating Factors (CSF) in patients with a previous episode/episodes of severe febrile neutropenia may reduce the risk of developing recurrent febrile neutropenia/ neutropenia Grade 4 and in some cases may help sustain treatment intensity by enabling subsequent treatment cycles to occur on time. Currently there is no evidence to support the use of CSF as sole treatment in MDS patients, but it has been demonstrated that CSF can raise neutrophil counts in MDS patients receiving GM-CSF and G-CSF (Ganser, 1996). However, in a randomized trial, G-CSF had no effect on survival, transformation to AML, or hemoglobin levels (Greenberg, 1993; Komrokji, 2004).

Based on the above background data, no impact on the primary and key secondary objective of the study (ie, RBC transfusion independence and Overall survival, respectively) is expected by allowing the administration of granulocyte colony stimulating factors as secondary prophylaxis. Allowing a CSF depending on the discretion of the treating physician, is made primarily on a patient safety basis.

8. **Modification of the wording concerning the involvement of the medical monitor in the unblinding and discontinuation of trial subjects**

The reason for the modification is to provide clearer wording, in accordance with the Declaration of Helsinki 3§ and ICH GCP (4.3, 5.13.4, and 4.7), in the respective sections of the protocol to clarify that the investigator is not required to discuss emergency unblinding or discontinuation if he/she feels that emergency unblinding or discontinuation of the subject is necessary.

**The amendment also includes several other minor clarifications and corrections:**

- Addition of the EudraCT number to the cover page
- Change of Medical Monitor / Emergency Contact Information
- Change of Therapeutic Area Head
- [redacted]

- Clarification and implementation throughout the protocol that an Interactive Response Technology (IRT) system is used for central randomization which includes both an Interactive Voice and Web Response System(IVRS/IWRS)
- Further clarification on the disease status assessment at the end of Cycle 6, to emphasize that it is sufficient that any one of the criteria listed is met, in order for subjects to proceed to Cycle 7
- Clarification that not a maximum of, but approximately 150 sites will be opened to enroll approximately 386 subjects
- Clarification and consistent implementation throughout the protocol, that the EQ-5D-3L (3 level version) of the EQ-5D questionnaire from the EuroQoL Group is used for the study
- Clarification that immunophenotyping of bone marrow precursor cells at baseline will be performed centrally and not at a subset of centers
- Clarification and consistent implementation throughout the protocol, that vital signs cover blood pressure, pulse, temperature and the respiratory rate
- Clarification and implementation throughout the protocol that serum pregnancy testing in female subjects of childbearing potential is mandatory at screening while both serum or urine pregnancy test (investigator's discretion; sensitivity of at least 25 mIU/mL) is acceptable during treatment phase and at the Treatment Discontinuation visit
- Clarification and consistent implementation of time points for the completion of the FACT-An and EQ-5D-3L questionnaires
- Clarification that (prophylactic) antiemetic medication may be administered at the investigator´s discretion
- Revision to remove the referenced "Study reference manual" as this document is not being used in the study
- Clarification that it is the investigator´s accountability to verify all eligibility criteria, while the sponsor will only review key eligibility criteria including selected central lab results as well as central pathology and cytogenetic reports required as per protocol
- Modification of Section 6.6.5 to implement that Day 8, 15, and 22 hematology and serum chemistry draws may be performed at the subject's local/primary physician office and shipped to the central laboratory for analysis on a case-by-case basis (at the investigator's discretion and in consultation with Celgene)
- Modification of Section 6.7.2 to implement that the investigative site may inquire about signs and symptoms of bleeding events via a phone call made to the subject
- Revision of Section 6.7.7 to provide further guidance on the timing of the serum EPO sample scheduled for Day 1 of Cycle 6, in order to accommodate that serum EPO level should not be collected within 1 week after any RBC transfusion (if applicable) due to possible reduction of the serum level related to the hemoglobin level achieved after the last transfusion

- Minor clarification on Inclusion/Exclusion criteria (Section 7)
  - Inclusion criterion #3: clarification that the required RBC transfusion history of at least 84 days (with an average of ≥ 2 units** per 28 days) immediately preceding randomization overlaps with the screening phase
  - Inclusion criterion #4: clarification that both platelet counts required to prove thrombocytopenia (≤ 75 x $10^9$/L and ≥ 21 days apart) must be analyzed by the central lab
  - Exclusion criterion #10: clarification that only ongoing medically significant adverse events from previous treatments would exclude a subject from participation in the study
  - Exclusion criterion #11: revision to allow for stable or decreasing doses of iron-chelating agents for at least 8 weeks (56 days) prior to randomization
- Additions to the dose modification guidelines (Section 8.2.4)
  - Dose modification guidelines for neutropenia Grade 4 (if deemed necessary by the investigator) have been added to account for the very low neutrophil counts frequently seen in the targeted patient population in the absence of fever and/or infection
  - Dose modification guidelines for hematologic or non-hematologic adverse events that would put a subject at unacceptable risk in the investigator´s opinion (independent of IP relationship)
  - The possibility to use G-CSF as secondary prophylaxis has been added to the dose modification guidelines for neutropenic fever and neutropenia Grade 4 to match the modifications in Section 9.1 (Permitted Concomitant Medications and Procedures)
  - Additional editorial revisions have been made to clarify that this is a guidance only and that it is at the investigator´s discretion to modify the IP dose to ensure the safety of the patient
- Modification of the wording on the use of prophylactic fluoroquinolone antibiotics for subjects who develop very low ANC was modified to provide guidance that the use of prophylactic fluoroquinolone antibiotics may be considered with an ANC Grade 4 (ie, ANC < 0.5 x $10^9$/L)
- Revision of Section 10.6.2.3 on additional exploratory subgroup analyses to allow for assessment of additional factors that may have a potential impact on the treatment outcome, such as the baseline platelet count, whether a subject received prior lenalidomide treatment and whether a subject has been diagnosed with secondary MDS or not
- Revision of Section 11 to clarify that there is no requirement to report progressive disease (PD) as a Serious Adverse Event (SAE) as this is part of the natural course of

** As is consistent with medical practice in Japan, 1 unit RBC referenced in this protocol is equivalent to 2 units RBC in Japan.

the disease and does not warrant by itself criteria for seriousness (eg, PD from Int-1 MDS to Int-2 or high risk MDS).

- Revision of Appendix F (EQ-5D Health Questionnaires) to delete the third page referenced as EQ-5D by mistake. This page is not part of the EQ-5D-3L questionnaire and is not used in the study