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| **Official Title:** | A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis- Stimulating Agent (ESA) Treatment |
| **NCT Number:** | NCT02598661 |
| **Document Date:** | Protocol Version 8.0: 13 December 2022 |

**Geron Corporation***

**Clinical Protocol**

# A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis- Stimulating Agent (ESA) Treatment

**Protocol 63935937MDS3001 Amendment 8/USA-1; Phase 2/3**

**GRN163L (imetelstat)**

*As of protocol amendment 3, the term "sponsor", as used throughout this protocol, refers to Geron Corporation. Prior to protocol amendment 3, this study was sponsored by Janssen Research & Development or its related legal entities.

This compound is being investigated in Phase 2/3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

**EudraCT NUMBER:** 2015-002874-19

**Status:** Final
**Date:** 13 December 2022
**Prepared by:** Geron Corporation

Local Amendment to: Protocol 63935937MDS3001 Global Amendment 8, 30 November 2022

**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## LIST OF ATTACHMENTS



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### TABLES



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## PROTOCOL AMENDMENTS

| Protocol Version | Issue Date |
|---|---|
| Original Protocol | 29 July 2015 |
| Amendment 1 | 31 May 2016 |
| Amendment 2 | 31 Aug 2017 |
| Amendment 3 | 18 April 2019 |
| Amendment 4 | 23 March 2020 |
| Amendment 5 | 29 June 2020 |
| Amendment USA-1 | 03 September 2020 |
| Amendment 6 USA-1 | 01 April 2021 |
| Amendment 7 USA-1 | 02 September 2021 |
| Amendment 8 USA-1 | 13 December 2022 |

Amendments are listed beginning with the most recent amendment.

**Amendment 8** (13 December 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:**

- To add an extension phase to allow continued treatment for those subjects who are benefitting from imetelstat, and to continue long-term monitoring of safety, overall survival, and disease progression for all subjects who remain in follow-up
- Revise unblinding language and End of Study definition.
- To revise exclusion criteria for the Ventricular Repolarization (QTc) substudy.
- Additional changes were made to provide clarifications and other minor edits.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Synopsis (Objectives and Hypotheses), (Overview of Study Design), (Dosage and Administration), Section 3.1 (Overview of Study Design) | • Added primary objective for the Extension Phase evaluating the long-term safety, OS, and disease progression, including progression to AML in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment receiving imetelstat.<br>• Added Extension Phase information for drug administration, evaluations, timeframe, and analysis<br>• Text was updated to the QTc substudy text to say 45 evaluable subjects will be enrolled and that subjects who are not evaluable may be replaced, indicating that > 45 subjects may be enrolled if subjects need to be replaced.<br>• Revised End of Study definition to account for addition of Extension Phase<br>• Added text that, with Protocol Amendment 8, subjects in Part 1 will complete participation in the study as Part 1 will have already met the duration of follow-up defined for the Extension Phase |

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| Table 3 (Time and Events Schedule for Part 2, Main Study) | The following updates were included:<br>• Chemistry panel for LFT investigations (local laboratory): Comments edited to add text in alignment with Section 9.8.<br>• Medical Resource Utilization: Comments edited to add text in alignment with Section 9.7 and updated to no longer require Long-term Survival Follow-up. |
| Table 5 (Time and Events Schedule-Extension Phase) | Added Table for Extension Phase Time and Events Schedule |
| Synopsis (Overview of Study Design), Section 3.1 (Overview of Study Design), Section 9.1.6 (Extension Phase), Section 11.12 (Independent Hepatic Expert Committee) | Added text to clarify that Hepatic Expert Committee review of AEs and LFT abnormalities will continue in the Extension Phase. |
| Section 2.1 (Objectives) | Added primary objective for the Extension Phase evaluating the long-term safety, OS, and disease progression, including progression to AML in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment receiving imetelstat. |
| Section 3.1 (Overview of Study Design-Schematic) | Added Figure 3 depicting Extension Phase |
| Section 3.2 (Study Design Rationale), Section 5.2 (Blinding) | • Clarified study blinding and added 'Unblinding' to section title.<br>• Added text to clarify that subjects, investigators, and study team members will be unblinded after primary efficacy analysis. |
| Section 3.3 (Rationale for the Extension Phase) | Section added to describe rationale for adding Extension Phase |
| Synopsis (Dosage and Administration), Section 6 (Dosage and Administration), Section 7 (Treatment Compliance) | Text regarding guidelines for drug administration and dose modification in Extension Phase was added |
| Section 7 (Treatment Compliance) | Text that the guidelines for study drug administration and data collection continue in the Extension Phase |
| Section 8.3 (Concomitant Medication) | Text that recommendations for concomitant therapy continues in the Extension Phase |
| Section 9.1.1 (Overview) | • Text was added with Amendment 8 to add the Extension Phase<br>• Blood volume table for Extension Phase added |
| Section 9.1.6 (Extension Phase) | Section added explaining Extension Phase procedures |
| Table 3 (Time and Events for Part 2 Main Study); Section 9.7 (Medical Resource Utilization) | Duration of collection of medical resource utilization data was updated to start from time of first dose and end at the End of Treatment visit. As the analysis will focus on the treatment emergent MRU, the duration of data collection has been changed from ending at start of subsequent therapy to end at EOT or 30 days after the last dose of study drug, whichever occurs later. |

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| Section 9.8 (Safety Evaluations) | Clarified that monthly laboratory assessments for Grade 1 and 2 elevations of LFTs only need to be collected until resolution to at least baseline or until the start of subsequent therapy, whichever comes first. |
| Section 11 (Statistical Methods) | Added text regarding final analysis for Extension Phase |
| Section 11.4 (Efficacy Analyses) | Text revised describing when the final analysis for the main study will be completed. |
| Section 12.3.1 (All Adverse Events) | Text added for continued collection of adverse event and pregnancy reporting in the Extension Phase |
| Section 14.2 (Packaging) | Text was added for drug packaging after the study is unblinded |
| Section 15 (Study-Specific Materials) | Bullet for Sample ICFs updated to include text that an updated ICF signature is needed for Extension Phase |
| Section 17.3 (Subject Identification, Enrollment, and Screening Logs) | Removed Enrollment and Screening Logs from section title to reflect the contents of the section |
| Section 17.9.1 (Study Completion) | Text revised to describe completion including Extension Phase |
| Attachment 11 Ventricular Repolarization (QTc) substudy | The following updates were included:<br>• After consultation with an external expert cardiologist and discussion with the study steering committee, exclusion criteria #17 was updated to exclude subjects with a QTcF>490 msec in the presence of a right bundle branch block or ventricular conduction delay (QRS >119 msec) in order to avoid unnecessary exclusion of elderly subjects with MDS who have modest QRS prolongation. In these subjects with modest QRS prolongation due to right bundle branch block or ventricular conduction delay, QTc variability is not increased and QTc remains a valid indicator of increased risk of Torsades de pointes arrhythmia (TdP). All complete left bundle branch blocks remain excluded.<br>• Text was updated to say 45 evaluable subjects will be enrolled and that subjects who are not evaluable may be replaced, indicating that > 45 subjects may be enrolled if subjects need to be replaced.<br>• Text added that subjects in the QTc substudy may enter the Extension Phase after the primary analysis for the QTc substudy is reached and that subjects would be unblinded prior to entrance into Extension Phase.<br>• Clarified the timepoint when the exposure-response analysis (ie, the primary analysis) for the QTc substudy will take place.<br>• Table 14: Chemistry panel for LFT investigations (local laboratory): comments |

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| | edited to add text in alignment with Section 9.8.<br>• Removed “Note” at the bottom of the attachment. |

**Amendment 7** (02 September 2021)

**The overall reason for the amendment:**

- To modify the current Ventricular Repolarization (QTc) substudy in Part 2 to separate it from the main MDS3001 study. In Part 2, the main study will enroll 170 subjects, and the separate Ventricular Repolarization (QTc) substudy will enroll an additional 45 subjects. The substudy will have broader eligibility criteria and fewer efficacy study evaluations in order to focus on the assessment of the relationship between the plasma concentrations of imetelstat and QTc interval changes. Data from this Ventricular Repolarization (QTc) substudy will not be included as part of the primary analysis of the efficacy and safety data from the main MDS3001 study.

- Due to the extended recruitment period for the main study in Part 2, the primary efficacy and safety analysis from the main MDS3001 study is planned for 12 months (instead of 15 months) after the last subject is randomized in Part 2, as sufficient follow up information will be collected by that time to determine the benefit/risk of imetelstat in low risk, transfusion dependent MDS subjects.

- Additional changes were made to provide clarifications on assessments, in particular for post-treatment assessments and for other minor clarifications

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Synopsis (Overview of Study Design); Synopsis (Statistical Methods); Section 3.1 (Overview of Study Design) | Updated the number of subjects in the study from 225 to 270. Revised text to state that there is a main study of Part 2 and a Ventricular Repolarization substudy in Part 2. Revisions were made to include details pertaining to the Ventricular Repolarization substudy. |
| Time and Events Schedule (Part 1) (Table 1) | The following updates were included:<br>• Transfusion history and status, myeloid growth factor treatment: Updated to clarify that transfusion collection is needed until first transfusion in Posttreatment Follow-up.<br>• BM aspirate, biopsy: Updated to no longer require in Posttreatment Follow-up<br>• Response assessment: Updated to specify that assessment is only required at time of suspected PD in Posttreatment Follow-up.<br>• INR (or PT) and aPTT: Routine monitoring at Day 1 of each cycle was removed and guidance was provided to state that assessment is to be repeated during the study if subject has a Grade ≥3 bleeding event. |

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| Time and Events Schedule (Part 2) (Table 3) | The following key updates were included:<br>• Table Title was updated to specify it is applicable to the Main Study of Part 2<br>• 12-lead ECG; Pharmacokinetic/ Immunogenicity samples: Comments edited to remove Ventricular Repolarization study (QTc) substudy language.<br>• Transfusion history and status, myeloid growth factor treatment: Revised text to specify that transfusion and growth factor follow-up will continue until the first transfusion in post-treatment follow-up.<br>• Text was added to clarify that the following assessments must be completed at each DE visit, specifically when the timing does not align with a Cycle Day 1 visit: Hematology (local laboratory), Hematology (central laboratory), Transfusion history and status, myeloid growth factor treatment.<br>• BM aspirate, biopsy: Clarified text regarding requirements for BM assessment. Updated to no longer require in Posttreatment Follow-up<br>• Response assessment: Updated to specify that assessment is only required at time of suspected PD in Posttreatment Follow-up. Included text to specify that CR, PR or mCR only to be assessed in subjects with >5% baseline bone marrow aspirate blasts.<br>• INR (or PT) and aPTT (local laboratory): Modified assessment schedule because clinically significant changes to coagulation laboratory parameters in imetelstat treated subjects have not been found in Part 1 and in other recent studies. Schedule modified to require assessments at Cycle 1 Day 1 and repeat during study if subject has a Grade ≥3 bleeding event (instead of at each cycle).<br>• BM aspirate for cytogenetics (central laboratory): Clarified text regarding requirements for cytogenetic assessments.<br>• BM aspirate for RNA Seq or CyTOF (if feasible); Mutation Analysis: The timing of the assessment was clarified to include RNA Seq or Cytof at the time of mCR was added.<br>• Text was added to state that the following assessments in post-treatment follow-up will only be required until the start of subsequent therapy: MRU, FACT-An, EQ-5D-5L, QUALMS, PGIC |

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| Table 4: Time and Events for Part 2, Main Study Pharmacokinetic / Immunogenicity Sampling | The following updates were included:<br>• Table Title was updated to specify it is applicable to the Main Study of Part 2.<br>• Footnote edited to remove Ventricular Repolarization study (QTc) substudy language. |
| Section 2.1 (Objectives) | For Secondary Objectives add clarifying text for the Qtc interval objective to state it will be reported separately from Part 2. |
| Section 3.1 (Overview of Study Design);<br>Figure 2: Schematic Overview of the Study<br>Section 5.2 (Blinding) | Updated text and figure to reflect modified Ventricular Repolarization substudy and to reflect clarification for required assessments as per Time and Events Table. |
| Section 4.1 (Inclusion Criteria) | The following updates were included:<br>• Inclusion Criteria no. 8.1 removed the text "(ie, ≥1500/$mm^3$)"<br>• Inclusion Criteria no. 8.2 removed the text "(ie, ≥75,000/$mm^3$)" |
| Section 6.1.1. (Dose Modifications for Hematologic Toxicities) | Updated to delete repetition and added clarifying text explaining that for Grade 3 or Grade 4 hematologic toxicities that are not considered related to imetelstat, the dose should still be held until recovery to ANC 1 x $10^9$/L and platelets 50 x $10^9$/L. |
| 6.1.4. (Dose Modifications for COVID-19 Symptoms or Positivity (any Grade)) | Modified COVID-19 language to include following local standard of care, local recommendations for quarantine, vaccination and/or potential dosing delays, and when it is acceptable to begin/resume study treatment after positive COVID-19 test or infection based on updated knowledge and guidance. |
| Section 6.2 (Infusion-Related Reactions)<br>Section 8.2 (Premedication) | Added text to clarify premedication requirements, including guidance that specify premedications may be administered 1 hour prior to study drug infusion per local standard of care. |
| Section 8.3 (Concomitant Medications) | Added text that concomitant medication collection includes any vaccines including COVID-19 vaccination.<br>Modified text to explain that subjects receiving iron chelating agents should be assessed regularly for the need for dose reductions and/or continued use of iron chelating agents according to local prescribing information (eg, hold dose for ferritin levels <500 mcg/L) in order to reduce the potential risk of hepatic toxicity. |
| Section 9 (Study Evaluation and all subsections) | Updated to reflect modified Ventricular Repolarization substudy, clarification added for required assessments |

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| | as per Table of Events, and modification to the dose modifications for COVID-19. |
| Sections 10.2 (Discontinuation of Study Treatment) | Added and modified text to provide guidance regarding continuing treatment in exceptional cases when the subject is experiencing clinical benefit, and guidance to continue the subject in post-treatment follow-up if treatment is withdrawn. |
| Section 10.3 (Withdrawal from the Study) | Due to the modifications to the Ventricular Repolarization substudy, deleted the following text: A subject may withdraw from the Ventricular Repolarization substudy but continue participation in the main study (see Attachment 11). |
| Section 11 (Statistical Methods) | Added text to clarify that the analysis of ECG and concentration-QTc, as well as safety and limited efficacy in the Ventricular Repolarization substudy will be performed separately from the primary analysis of 170 subjects in the main study of Part 2. |
| Section 11.3 (Sample Size Determination) | Number of subjects updated and approximate number of subjects for the Ventricular repolarization substudy in Part 2 was added. |
| Section 11.4 (Efficacy Analyses) | Clarified that the primary efficacy analysis is planned 12 months (and no longer 15 months) after the last subject is randomized in Part 2. |
| Section 11.13 (Independent Review Committee) | Text added to clarify adjudicated investigator-assessed disease response and response for subjects with >5% baseline bone marrow aspirate blasts based on the central pathology reviewer's assessment. |
| Section 12.3.1 (All Adverse Events)<br>Section 12.3.2 (Serious Adverse Events)<br>Section 12.3.4 (Pregnancy) | Clarified that the form for reporting adverse events, adverse events of interest, serious adverse events and pregnancies is called the "Serious Adverse Event/Adverse Event of Interest Form". |
| Section 16.1 (Study-Specific Design Considerations) | • Updated the total blood volume to be collected from each subject from 629 mL to 569 mL for Part 2 due to the removal of the collection of coagulation factors at Day 1 of each cycle after Cycle 1.<br>• Added in total blood volume to be collected from each subject from the modified Ventricular Repolarization substudy of Part 2 as 361 mL. |

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| Section 17.8 Monitoring | Added that home healthcare visits may also occur if the subject is unable to be seen at the study site. |
| Attachment 11 (Ventricular Repolarization (QTc) Substudy | Attachment 11 was replaced with the modified Ventricular Repolarization substudy of Part 2 as agreed with the agency. Key modifications include adjustments to the inclusion / exclusion criteria, time and events table, schedule of ECG and PK assessments, and unblinding activities. |

**Amendment 6 USA-1 (01 April 2021)**

**The overall reason for the amendment:** To modify dose modification criteria for Liver Function Test Elevations and Hepatic Adverse Events to clarify the need to hold study drug, investigate the cause, and when to restart, stop, or dose reduce depending on the cause.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To modify dose modification criteria for Liver Function Test Elevations and Hepatic Adverse Events | |
| 6.1.3 Dose Modifications for Liver Function Test Elevations and Hepatic Adverse Event | Renamed section "Dose Modifications for Liver Function Test Elevations and Hepatic Adverse Events" to clarify the items that fall under this category.<br><br>Dose modifications were updated to clarify the criteria for holding study drug, and the actions that should be taken in these events. Modifications were made to Table 9 that decrease the number of times subjects are permitted to dose reduce due to Grade 3 or 4 ALT, AST, or bilirubin elevations, and Grade 3 or 4 hepatic adverse events prior to discontinuing treatment. Added modification and stopping criteria for Grade 2 ALT or AST with concomitant Grade 2 bilirubin elevations. Provided guidance on investigations into possible causes of liver function test elevations and hepatic adverse events and subsequent monitoring. |
| **Rationale:** To add ALT or AST >3.0 x ULN WITH Bilirubin >2.0 x ULN as adverse event of interest | |
| 9.8 Safety Evaluations | Added ALT or AST >3.0 x ULN **WITH** Bilirubin >2.0 x ULN as adverse event of interest and added abbreviation (AEI). Updated language for liver function test monitoring to align with new language in section 6.1.3. |
| 12.3.3.1 Elevated Liver Function Tests (LFTs) | Added ALT or AST >3.0 x ULN **WITH** Bilirubin >2.0 x ULN as adverse event of interest |
| **Rationale:** Updated section to recommend monitoring of concomitant medications while on study. | |
| 8.3. Concomitant Medications | Added language to adjust concomitant medications over the course of the study based on clinical status. |

**Amendment USA-1** (03 September 2020)

**The overall reason for the amendment:** The country-specific amendment is based on feedback from the US Food and Drug Administration (FDA).

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Biochemical laboratory test values of bilirubin were clarified at the request of the FDA. | |
| 4.1 Inclusion Criteria (Criterion 9.4.1) | Added an upper limit for direct bilirubin for patients with Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion. |
| **Rationale:** Actions to be taken for Grade 3 or 4 LFT elevations and hepatic events were clarified at the request of the FDA. | |
| 6.1.3 Dose Modifications for Hepatic Toxicities | Added additional language to the dose modification language for hepatic toxicity to allow continuing treatment if another cause of transaminase or bilirubin elevation is clearly identified. |

**Amendment 5** (29 June 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** To clarify eligibility criteria/assessments and study procedures pertaining to Part 2 of the study.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To clarify eligibility criteria/assessments | |
| 4.1 Inclusion Criteria (Criterion 5.2.1) | Added text to Inclusion Criteria no. 5 to further clarify the definition of MDS relapsed to ESA treatment (ie. to clarify that subjects must receive at least 8 weeks of ESA treatment at the protocol specified dose before meeting the definition of relapsed). |
| 4.1 Inclusion Criteria;<br>9.8.1 Clinical Laboratory Tests | • Added text to Inclusion Criteria no. 9.4 to allow bilirubin (total/direct) outside the specified range due to Gilbert's syndrome, ineffective erythropoiesis due to MDS or in case of hemolysis due to RBC transfusions.<br>• Added text to the serum chemistry panel to allow for additional testing to demonstrate eligibility if a subject with elevated bilirubin levels meets the revised criterion. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 4.2 Exclusion Criteria | • Added text to Exclusion Criteria no. 2 to clarify that subjects who received an experimental or investigational drug within 30 days prior to Randomization will be excluded from participation.<br>• Added text to Exclusion Criteria no. 5.2 to add thalidomide and thalidomide analogues to the list of prohibited prior treatment.<br>• Added text to Exclusion Criteria no. 5.3 to specify receiving anti-MDS therapy within 4 weeks prior to Randomization as an exclusion criterion. |
| **Rationale:** To clarify the study procedures | |
| Time and Events Schedule for Part 2 (Table 3) | • Informed consent: Added text regarding further clarification of screening procedures.<br>• Hematology (local laboratory); hematology (central laboratory): Added text to clarify that tests should also be conducted pre-transfusion to ensure availability of pre-transfusion Hb and platelet count data.<br>• BM aspirate, biopsy:<br>- Central cytogenetics results are required for eligibility confirmation, aligned with Inclusion Criteria no. 2.3. Clarified that local cytogenetic analysis may be performed per local standard of care.<br>- Added text to clarify that a confirmatory BM should be performed 4 to 8 weeks after investigator-assessed CR, PR, or mCR, if clinically feasible.<br>- Added cross-references to Section 9.3.1.3, Section 9.1.4, and Section 11.13.<br>- Bone marrow assessments at the time of suspected HI-E (Hb) were removed. This is no longer required for study purposes and is not required for the confirmation of HI-E (HI-E evaluation is based upon Hb results and transfusion requirements per modified IWG 2006). Bone marrow will continue to be assessed at all other study time points as planned. Section 9.1.4 was revised accordingly.<br>• Response assessment; hematology (central laboratory): Adjusted text to clarify that central hematology results will be used for calculation of hematologic improvement-erythroid (HI-E) and local laboratory results should be used for investigator-assessed response evaluations.<br>• Survival status and subsequent therapy: Adjusted text to clarify the time point of follow-up as at least every 12 to 16 weeks; more frequently if needed.<br>• Serum ferritin, transferrin saturation (local laboratory): Added text to clarify that total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site. |

| Applicable Section(s) | Description of Change(s) |
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| | • Hepatitis serologies: Added text to clarify that hepatitis testing is to establish a baseline, but subjects with positive results will not be excluded from study treatment unless the subject meets Exclusion Criteria no. 12 (active systemic hepatitis infection requiring treatment) (Section 4.2). The change here is to minimize the need for retesting if the screening period lasts >28 days (see Section 9.1.3 about the screening period).<br>• Pharmacokinetic/Immunogenicity samples: Added cross-references to Table 4 and Attachment 11 to clarify sample collection time points.<br>• TA, TL and hTERT: Moved the row of information previously listed under Bone Marrow, to reflect that blood samples will be assessed.<br>• Bone marrow (BM aspirate for cytogenetics [central laboratory]): Added text to align the screening cytogenetics timeframe with the remaining screening bone marrow assessments. |
| Synopsis (Efficacy Evaluations);<br>3.1 Overview of Study Design;<br>9.1.4 Treatment Phase;<br>9.3.1.3 Bone Marrow Assessment | Adjusted and added text on BM assessments in alignment with other protocol sections. |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations);<br>Table 4 Time and Events for Part 2 Pharmacokinetic/Immunogenicity Sampling;<br>3.2 Study Design Rationale (Endpoints [Pharmacokinetic and Immunogenicity Evaluations]);<br>9.4.1 Sample Collection and Handling;<br>9.4.3 Pharmacokinetic Parameters | Adjusted and added text on PK sample collection and PK evaluations in alignment with other protocol sections. |
| 6 Dosage and Administration (Study Drug [Imetelstat or Placebo]) | Added text to clarify that site does not necessarily need to wait until the weight changes by 10% to recalculate the total dose. The total dose may be recalculated more frequently (eg, at each study visit) depending on local practice. |
| 6.1.3 Dose Modifications for Hepatic Toxicities | Added text to allow for events that are not related to study drug and the underlying origin is known, and the subject may benefit from treatment with study drug. |
| 8.2 Premedication | Added text to clarify the administration time of premedication. |
| 8.3 Concomitant Medications | Added text to further clarify the allowed supportive care and medications prohibited during the study. |
| 9.1.2 Blood Volume (Table 11) | Adjusted blood volumes in alignment with Table 3 (Time and Events Schedule). |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 9.1.3 Screening Phase and Predose | • Added text to clarify that the central MDS diagnosis confirmation will primarily be based upon the central pathology review of the bone marrow sample taken within 12 weeks of Randomization. Supportive historic bone marrow samples and lab data (ie. hematology) are often useful to help support this diagnosis.<br>• Added text on best practice if transfusion treatment and collection of screening labs coincide in the same subject.<br>• Added text to clarify procedures to be followed in the event the screening period extends beyond 28 days (for example, if time is required for results and/or retesting).<br>• Adjusted text in line with other sections of the protocol. |
| 9.1.4 Treatment Phase | • Added text to clarify that the modified IWG 2006 will be used to assess subject response.<br>• Added text to clarify that all disease assessments should be repeated relative to the time of initial assessment of CR and PR in order to confirm a CR or PR, if feasible, per modified IWG 2006 criteria.<br>• Added text to clarify the purpose and feasibility of confirmatory bone marrow assessments to define the response. |
| 9.1.5 Posttreatment Phase (Follow-Up) | Adjusted text to clarify the time period for the collection of transfusion data. |
| 9.3.1.2 Hemoglobin Assessment | • Adjusted text to clarify the definitions of pretreatment Hb and HI-E response.<br>• Adjusted and added text to clarify assessment and presentation of hematology data.<br>• Adjusted text in line with other sections of the protocol. |
| 9.5 Biomarkers | Adjusted text to clarify the collection of biomarker assessments. |
| 9.8.1 Clinical Laboratory Tests;<br>Table 3 (Time and Events Schedule for Part 2);<br>Table 11 (Volume of Blood to be Collected from Each Subject) | • Added text to clarify if a site's local laboratory does not assess the laboratory tests noted in Section 9.8.1, other laboratory tests may be performed to calculate the values to be assessed, for example:<br>- Added total iron binding capacity and serum iron to calculate transferrin saturation if transferrin saturation is not available at the site.<br>• Added urea to the serum chemistry panel as an alternative assessment if a site is unable to assess blood urea nitrogen.<br>• Added text to clarify that hepatitis serologies may be performed by local or central laboratory. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 14.5 Drug Accountability | Adjusted text to clarify that study drug administration, return of unused study drug, and study drug destruction on-site must be documented in the IWRS. |
| 15 Study-specific Materials | Adjusted text to reflect that investigational product preparation instructions are presented in the Site Investigational Product Manual. |
| 17.3 Subject Identification, Enrollment, and Screening Logs | Adjusted text in alignment with data protection requirements. |
| **Rationale:** To clarify the secondary objectives and endpoints | |
| Synopsis (Objectives, Endpoints, Statistical Methods)<br>2.1 Objectives (Secondary Objectives)<br>3.2 Study Design Rationale (Endpoints)<br>9.2.2 Secondary Endpoints<br>11.4 Efficacy Analysis | • Added text to clarify that mCR is being assessed as part of the secondary endpoints for disease response.<br>• Updated Section 11.4 in alignment with objectives and endpoints. |
| 9.2.2 Secondary Endpoints | Added text to clarify the time to 8-week RBC TI and the duration of the RBC TI. |
| **Rationale:** To clarify adjudication of investigator-assessed disease response assessments | |
| 11.13 Independent Review Committee | Added text to establish an Independent Review Committee (IRC) to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) based on the modified IWG 2006 criteria. Responsibilities, authorities and procedures will be detailed in a separate charter. |
| Table 3 (Time and Events Schedule for Part 2 );<br>9.1.4 Treatment Phase<br>9.3.1.2 Hemoglobin Assessment<br>16.1 Ethical Aspects, Study-specific Design Considerations | Added text in alignment with and/or cross-references to Section 11.13. |
| **Rationale:** To clarify adverse event reporting | |
| 12.1.1 Adverse Event Definitions and Classifications (Unlisted [Unexpected] Adverse Event/Reference Safety Information | Added text to clarify responsibility for determination of expectedness/listedness of adverse events. |
| 12.2 Special Reporting Situations | Added text to clarify reporting of special reporting situations that meet the criteria of a SAE. |
| 12.3.2 Serious Adverse Events | Adjusted text in alignment of the current procedure for reporting of SAEs. |
| **Rationale:** To provide clarifications on the Ventricular Repolarization substudy | |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Attachment 11 (Ventricular Repolarization Substudy at Selected Sites [Study Design and Subject Population]) | Adjusted text to clarify the expected numbers of subjects (approximately 30 and 15 subjects in the imetelstat and placebo groups, respectively) to account for the fact that the study is blinded. |
| **Rationale:** To further clarify considerations regarding the COVID-19 pandemic | |
| 1.3 Benefit-risk Assessment: COVID-19 | Added section to describe risk/benefit for COVID-19 instruction that was included as part of Protocol Amendment 4. |
| 6.1.4 Dose Modifications for COVID-19 Symptoms or Positivity (any Grade) | Added text to clarify recording of cases of confirmed, suspected, or exposed COVID-19 infection. |
| 17.8 Monitoring | Added text to allow for remote monitoring. |
| **Rationale:** To provide clarification of future research | |
| 16.2.5 Long-term Retention of Samples and Use of Data for Additional Future Research | Added text to outline the use of samples and data for future research. |
| **Rationale:** Administrative changes and minor corrections were made | |
| Attachment 5 International Working Group (IWG) Response Criteria 2006 | Corrected wording under Erythroid response in alignment with protocol text. |
| Attachment 10 Anticipated Events | Wording updated in alignment with sponsor regulatory reporting procedures. |
| Throughout the protocol | • Changed "QTc" substudy to "Ventricular Repolarization" substudy for consistency.<br>• Minor grammatical, formatting, or spelling changes were made. In addition, minor rewording or clarifications were added to improve the understanding of the content of the protocol. |

**Amendment 4** (23 March 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, and healthy authority guidance on the COVID-19 pandemic.

**The overall reasons for the amendment:** Amendment 4 is issued in consideration of the COVID-19 pandemic and includes guidelines for the management of subjects who have confirmed COVID-19 infection, have clinical signs and symptoms consistent with COVID-19 infection, or have been exposed to a person with confirmed COVID-19 infection.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To include guidance for subjects with symptoms or confirmed cases COVID-19 infection | |
| 6.1.4 Dose Modifications for COVID-19 symptoms or positivity (any Grade) | Added subsection to the protocol to include dose modification guidance regarding COVID-19 for subjects on treatment. |
| **Rationale:** To clarify evaluation at screening | |
| 9.1.3 Screening Phase and Predose | Added text to elucidate COVID-19 screening procedures and enrollment decisions as they pertain to COVID-19. |
| **Rationale:** To clarify evaluation of physical examination | |
| 9.8.4 Physical Examination;<br>Table 3 Time and Events Schedule for Part 2 | Added text to elucidate monitoring, follow-up and reporting of clinical signs and symptoms of COVID-19 infection.<br>Cross-reference to Section 9.8.4 was added in Table 3. |
| **Rationale:** Administrative change | |
| Throughout the protocol | Following recent move in location, the sponsor's contact details were updated to Geron Corporation, 919 E. Hillsdale Blvd., Suite 250, Foster City, CA 94404. |

**Amendment 3** (18 April 2019)

This amendment is considered to be substantial based on the on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reasons for the amendment:** To update sponsorship change to Geron Corporation, to include efficacy and safety data from Part 1 of the study as a basis for starting Part 2 of the study, and to clarify study procedures and conduct.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To reflect change of sponsorship as of protocol amendment 3 | |
| Cover page, Synopsis, 6. Dosage and Administration, Investigator Agreement | Change of sponsor name from Janssen Research & Development to Geron Corporation, including change of product designation. |
| **Rationale:** To clarify the definitions of study entry for Part 1 and Part 2, Treatment Phase, and End of Study | |
| Throughout the protocol | Clarified that study entry referred to Cycle 1 Day 1 for Part 1 (C1D1) and Randomization for Part 2.<br>Clarified that the Treatment Phase will extend from C1D1 (Part 1) or Randomization (Part 2) until disease progression, or unacceptable toxicity, or withdrawal of consent (ie, deleted the mention of lack of response).<br>Clarified that the End of Study is defined as 24 months after randomization of the last subject in Part 2 or anytime the sponsor terminates the study, whichever comes first. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To provide Part 1 data of the current study that support continuing with Part 2 | |
| Synopsis (Overview of Study Design, Statistical Methods), 1.2. Overall Rationale for the Study, 3.1. Overview of Study Design, 3.2. Study Design Rationale, 11.3. Sample Size Determination | Added information on the actual number of subjects evaluated in the completed Part 1 and clarified that data from Part 1 support continuing with Part 2. |
| 1.1.5. Clinical Experience with Imetelstat in Myeloproliferative Neoplasms and MDS | Added a statement to mention that a comprehensive summary of the clinical data is provided in the Investigator's Brochure (Edition 14).<br>Added a summary of results from Part 1. |
| **Rationale:** To clarify the study objectives and study endpoints | |
| Synopsis (Secondary Objectives, Exploratory Objectives, Endpoints), 2.1. Objectives, 9.2.2. Secondary Endpoints, 9.2.3. Exploratory Endpoints, 9.5. Biomarkers | Clarified that the following secondary objectives (and associated endpoints) are only applicable to Part 2:<br>• To assess the rate and amount of supportive care, including transfusion and myeloid growth factors.<br>• To assess the effect of treatment on medical resource utilization.<br>• To assess the effect of imetelstat on corrected QT (QTc) interval in a subset of subjects).<br>Clarified that the following exploratory objective (and associated endpoint) is only applicable to Part 1:<br>• To explore the effects of imetelstat on immune profiles through immunophenotyping.<br>Clarified that TL samples are only collected at baseline. |
| **Rationale:** To clarify the study procedures | |
| Time and Events Schedule (Table 3) | • Added a row to clarify when the randomization is to occur.<br>• Clarified that for subjects who stop treatment before 15 months (instead of 12 months originally), the collection of transfusion data must be continued for a minimum of 15 months (instead of 12 months originally) from Randomization. Added the mention that pre-transfusion Hb must be documented.<br>• Clarified that for hematology performed at a local laboratory, hematology panel includes hemoglobin, platelet count, white blood cell count, ANC) and added that manual absolute peripheral blast count should be done prior to randomization and on D1 of each cycle only).<br>• Added a row with hematology assessments performed at the central laboratory (with same timing of assessments as those performed in a local laboratory) and clarified that central laboratory will be used for HI-E assessments Hematology panel assessed in central laboratory will be hemoglobin, platelet count, white blood cell count and ANC. Manual |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| | absolute peripheral blast count for the central lab should be done prior to randomization and on C1 of each cycle only.<br>• Clarified the procedure for the bone marrow aspirate and biopsy and the response assessment (central review).<br>• Clarified that all other clinical laboratory assessments (chemistry, chemistry panel for LFT investigations, INR and aPTT, serum EPO level, serum ferritin, transferrin saturation, and B12/folic acid/reticulocytes) will be done at a local laboratory.<br>• Added that serum or urine pregnancy test will be done on Day 1 of every cycle and at end of study.<br>• Added that for the Ventricular Repolarization substudy, blood for PK samples will be collected on C1D1 prior to study drug administration through 24 hours after start of infusion.<br>• Modified the timing of assessment for TA, TL, and hTERT: instead of having them assessed at CID1 predose only, TA and hTERT will be done at C1D1 predose, 24h post-dose, C1D8, C2D1, C2D8; TL will be done at baseline only.<br>• Clarified the procedure for the BM aspirate for cytogenetics (central laboratory): Baseline aspirate should be obtained during screening and must be submitted to the central laboratory to confirm eligibility. Aspirate is required for all subjects with baseline abnormalities every 24 weeks after C1D1 at the time of suspected HI-E (Hb), PR, or CR and every 24 weeks thereafter up to and including suspected PD. Sample should be obtained at the time of suspected PD for all subjects irrespective of baseline status.<br>• Modified the timing of assessment for mutation analysis to every 12 weeks after C1D1, at time of suspected response HI-E (Hb), PR or CR and at time of PD (instead of "at time of suspected HI-E [Hb], PR, CR, and PD").<br>• Deleted the assessment of immunophenotyping as it is no longer applicable to Part 2. |
| Time and Events Schedule (Table 3), Figure 2, 9.1.4. Treatment Phase | Clarified the time frame of the EOT visit (ie, 30 days ±3 days after the last dose). |
| 3.1. Overview of Study Design | Added that subjects in Part 1 are not eligible to enroll in Part 2.<br>Clarified that robust transfusion data will be collected for a minimum of 15 months from Randomization in Part 2 (instead of 12 months).<br>Added that, for Part 2, central laboratory will be used for assessment of the HI-E response. |
| 3.1. Overview of Study Design, Figure 2, 6. Dosage and Administration | Deleted statement mentioning that, for Part 1 and Part 2, if after 6 months of treatment, a subject has not achieved hematologic |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| | improvement-erythroid (HI-E) or RBC TI for ≥8 weeks, further continuation of treatment should be discussed with the sponsor. |
| 3.2. Study Design Rationale (Pharmacokinetic and Immunogenicity Evaluations) | Added that anti-drug antibodies will be assessed during the study. |
| 4.1. Inclusion Criteria (no. 2), 9.1.3 Screening Phase and Predose | Deleted that a copy of the local pathology report may suffice for central pathology review prior to randomization, with baseline bone marrow samples submitted as soon as possible during screening or after randomization. Replaced with a statement that central laboratory review is required to confirm diagnosis of MDS prior to randomization in Part 2. |
| 4.1. Inclusion Criteria (no. 10.2); 12.1.1. Adverse Events Definitions and Classifications; 12.2. Special Reporting Situations | Added that women of childbearing potential must agree to be tested on Day 1 of every cycle and at end of study (30 days post last dose) as part of the inclusion criteria.<br>Added that female subjects who become pregnant during the course of the study up to 30 day after the last dose or a female partner of a male subject who becomes pregnant up to 90 days of the last dose for the male subject. constitutes a medically important event to be reported as a serious adverse event. |
| 6. Dosage and Administration | Deleted the statement that the sponsor may permit an extension to the hold of study drug to allow for further subject assessment with the possibility for restarting treatment. |
| 6.1.1, Dose modifications for Hematologic Toxicities, 6.1.2. Dose Modifications for Non-hematologic Toxicities, Excluding Hepatic Toxicities, 6.1.3. Dose Modifications for Hepatic Toxicities | Clarified that actions should be taken for all Grade 3 or 4 events regardless of the relationship to study drug (ie, deleted the part mentioning “drug-related”) |
| 9.1.2. Blood Volume | Clarified that immunophenotyping is only applicable to Part 1.<br>Added an additional 5 mL blood sample for the central laboratory hematology (Part 2).<br>Clarified that additional serum or urine pregnancy tests may be performed at the local laboratory. |
| 9.1.3 Screening Phase and Predose | Clarified that the bone marrow aspirate or biopsy at screening must be of adequate quality for central review. |
| 9.1.5. Posttreatment Phase | Deleted that follow up samples of bone marrow aspirate/biopsy must be submitted for central review at the time of suspected response, including HI-E (Hb), PR, CR, and at the time of suspected PD; however, local assessment will be used for treatment decisions.<br>Changed the time period for the collection of transfusion data regardless of study drug discontinuation, progressive disease, or subsequent therapy (from a minimum of 12months to a minimum of 15 months). |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 9.6. Patient Reported Outcomes | Clarified the process to be followed when questionnaires are conducted over a telephone call during the posttreatment period. |
| 9.7. Medical Resource Utilization | Added that frequency of hospitalization will also be collected. |
| **Rationale:** To clarify the use of central laboratory | |
| 9.3 Efficacy, 9.3.1.2 Hemoglobin assessment, 9.3.1.3 Bone Marrow Assessment | Added that, in Part 2, in addition to the local laboratory, a central laboratory will be used for all planned Hb assessments. Treatment decision may be based on the local laboratory; however, efficacy assessments will be based on the central laboratory.<br><br>Deleted that local disease evaluations will be used for treatment decisions and clarified that bone marrow aspirate and biopsy must be available for submission for central pathology review prior to the Randomization in Part 2 to confirm diagnosis and eligibility for study.<br><br>Deleted that a copy of the local pathology report (in English) must be submitted for diagnosis confirmation. |
| 9.8.1. Clinical Laboratory Tests | Added the following text: “In addition, central laboratory will be utilized for hematology panel (hemoglobin, platelet count, white blood cell count, ANC and manual absolute peripheral blast count) and will be used for HI-E assessment. Local hematology panel may be used for treatment decision.”<br><br>Added the following text: “In addition, the following hematology tests will be performed at the central laboratory: hemoglobin, platelet count, white blood cell count and ANC; and manual absolute peripheral blast count.” |
| **Rationale:** To clarify the statistical section | |
| 11.4. Efficacy Analyses | Clarified that the primary efficacy analysis is planned 15 months (and no longer 12 months) after the last subject is randomized in Part 2. |
| 11.5. Pharmacokinetic Analyses | Added that detailed pharmacokinetic analysis will be provided in a specific PK-statistical analysis plan. |
| 11.9. Medical Resource Utilization Analyses | Clarified that this subsection is applicable to Part 2 only. |
| **Rationale:** To align with new sponsor policies | |
| 13. Product Quality Complaint Handling | Deleted the statement mentioning that the sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of product quality complaint information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures. |
| 16.2.4. Privacy of Personal Data | Clarified that personal data collected during the study will be processed in compliance with the patient information and informed consent form and agreements with the sponsor. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| | Clarified that the transfer of data to other entities or other countries will be done in compliance with applicable data privacy laws and regulations.<br><br>Clarified how subjects can submit data privacy requests. |
| 17.11. Use of Information and Publication | Deleted the statement mentioning that recruitment performance or specific expertise related to the nature and key assessment parameters of the study will be used to determine a coordinating investigator.<br><br>Modified the duration during which investigators must withhold publications from 60 days to 90 days.<br><br>Added that if an investigator wishes to publish information from the study, the confidentiality of sponsor's information must be respected.<br><br>Modified the duration during which the investigators must not submit for publication data derived from the individual study site from within 12 months to within 18 months of the availability of the final data. |
| **Rationale:** To provide clarifications on the Ventricular Repolarization substudy | |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations), Time and Events Schedule (Table 3) | Clarified that in Part 2, for subjects participating in the Ventricular Repolarization substudy, serial blood samples for pharmacokinetic evaluation will be collected at C1D1 at prespecified time points over 24 hours, prior to and after start of infusion. |
| 3.2. Study Design Rationale (Pharmacokinetic and Immunogenicity Evaluations) | Added that pharmacokinetic sampling will be performed in 30 subjects in the Ventricular Repolarization substudy (Part 2). |
| 16.1. Study-Specific Design Considerations | Added that subjects participating in the Ventricular Repolarization substudy are expected to have an additional 8 mL of blood draws due to increased intensity of sampling. |
| Attachment 11 (Ventricular Repolarization Substudy at Selected Sites) | Clarifications added on the approximate number of subjects that will be enrolled in the Ventricular Repolarization substudy.<br><br>Added that efficacy, pharmacodynamic, biomarker and immunogenicity evaluations will be assessed in the main study and that cardiac-related adverse events will be reviewed by the Data Monitoring Committee on an ongoing basis.<br><br>Clarified the activities specific to the Ventricular Repolarization substudy. |
| **Rationale:** To add new references supported adding data from Part 1 | |
| References | Added references from Fenaux et al (2018), Steensma (abstract 2018), and Williams (2017). |
| **Rationale:** To provide a more recent WHO classification | |
| Attachment 1 (World Health Organization (WHO) 2008 Classification) | To update with 2008 classification. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Minor corrections were made | |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. In addition, minor rewording or clarifications were added to improve the understanding of the content of the protocol. |

**Amendment 2** (31 Aug 2017)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** This amendment revised some aspects of study design and conduct following an analysis of Part 1, Week-24 data.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** In Part 1, no subject who received prior treatment with lenalidomide or a hypomethylating agent achieved transfusion independence, and a trend toward higher incidence of cytopenia was observed for these subjects. | |
| Synopsis (Overview of Study Design);<br>3.1. Overview of Study Design;<br>3.2. Study Design Rationale;<br>5.1. Treatment Allocation | Prior lenalidomide use was removed as a stratification factor for Part 2. |
| Synopsis (Subject Population) | Clarification was added that beginning with this amendment, enrolled subjects will have non-del(5q) MDS and no prior exposure to either a hypomethylating agent or lenalidomide. |
| 3.2. Study Design Rationale | Part 1 findings for 8-week TI were described for subjects with prior exposure to lenalidomide or a hypomethylating agent and for subjects with non-del(5q) MDS without prior exposure to either a hypomethylating agent or lenalidomide. |
| 4.2. Exclusion Criteria (no. 5) | Exclusion criterion 5 was separated into 3 parts to exclude prior use of hypomethylating agents (Part 5.1), lenalidomide (Part 5.2), and to specify the minimum allowable interval following prior use of an ESA or any chemotherapy, immunomodulatory, or immunosuppressive therapy (Part 5.3). |
| 4.1. Inclusion Criteria (no. 13) | Inclusion Criterion 13 was deleted. Previously, subjects with the del(5q) karyotype are eligible if they failed treatment with lenalidomide. |
| 4.2. Exclusion Criteria (no. 17) | Inclusion Criterion 17 was added. Subjects with the del(5q) karyotype are excluded from the study. |
| **Rationale:** Review of safety and efficacy data from the initial Part 1 cohort of 32 subjects showed better efficacy among subjects with non-del(5q) MDS without prior exposure to either a hypomethylating agent or lenalidomide. Part 1 of the study is expanded to include additional subjects with non-del(5q) MDS who have not received prior treatment with lenalidomide or a hypomethylating agent to further confirm the 7.5 mg/kg dose of imetelstat in this patient population. | |
| Synopsis (Overview of Study Design, Statistical Methods);<br>3.1. Overview of Study Design; | Enrollment in Part 1 will be expanded to include approximately 22 additional subjects in the target population meeting the revised entry criteria. Total enrollment in Part 1 (initial cohort plus expanded |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Figure 2 (Schematic Overview of the Study);<br>11.3. Sample Size Determination | cohort) will increase from up to 30 subjects to approximately 55 subjects. Total study enrollment will increase from approximately 200 subjects to approximately 225 subjects. If data from Part 1 for the target population continue to be supportive of a satisfactory benefit/risk profile, Part 2 of the study will be initiated. |
| **Rationale:** In Part 1, dose escalation from 7.5 mg/kg to 9.4 mg/kg was not associated with improved transfusion independence. | |
| Synopsis (Dosage and Administration);<br>Time and Events Table 1 and Table 3 (Hematology);<br>3.1. Overview of Study Design;<br>Figure 2 (Schematic Overview of the Study);<br>6. Dosage and Administration;<br>6.1. Dose Modifications;<br>9.3.1.2. Hemoglobin Assessment | Dose escalation to 9.4 mg/kg and dose re-escalation following dose reduction is not permitted in Part 2. Text associated with dose escalation and re-escalation was deleted. |
| Synopsis (Dosage and Administration);<br>3.1. Overview of Study Design;<br>Figure 2 (Schematic Overview of the Study);<br>6. Dosage and Administration;<br>6.1. Dose Modifications | Clarification added that subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose. |
| **Rationale:** Investigation of the potential effects of imetelstat on ventricular repolarization was added with a Ventricular Repolarization substudy to be performed in Part 2. | |
| Synopsis (Overview of Study Design);<br>Time and Events Table 3 (12-lead ECG);<br>3.1. Overview of Study Design;<br>Figure 2 (Schematic Overview of the Study);<br>4. Subject Population;<br>9.1.2. Blood Volume;<br>9.8.2. Electrocardiogram<br>11.10. Safety Analyses (Electrocardiogram);<br>Attachment 11 | Newly added Attachment 11 describes the Ventricular Repolarization substudy that will be performed at selected sites to characterize the effects of imetelstat treatment on QTc interval in Part 2. |
| 10.3. Withdrawal from the Study | Text was added to indicate that subjects may withdraw from the Ventricular Repolarization substudy but continue participation in the main study. |
| **Rationale:** In Part 1, the median prior RBC transfusion burden was approximately 6 units. Revising the stratification criteria is expected to allow the 2 treatment groups to be balanced for this variable. | |
| Synopsis (Overview of Study Design);<br>3.1. Overview of Study Design;<br>3.2. Study Design Rationale;<br>5.1. Treatment Allocation | The stratification factor prior RBC transfusion burden was changed from 4 or >4 units to ≤6 or >6 units RBC. |
| **Rationale:** In Part 1, the study population was fairly well-balanced between the IPSS low (approximately 60%) and intermediate-1 risk (approximately 40%) subgroups. Response rates differed by IPSS subgroup, so stratification using IPSS criteria is expected to ensure balance for these subgroups within the 2 treatment groups. | |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Synopsis (Overview of Study Design);<br>3.1. Overview of Study Design;<br>3.2. Study Design Rationale;<br>5.1. Treatment Allocation | IPSS risk group (low versus intermediate-1 risk) was added as a stratification factor. |
| **Rationale:** Additional sampling is required to further characterize the pharmacokinetic profile for imetelstat. | |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations);<br>Time and Events Table 2 | Beginning with Amendment 2, serial PK sampling was removed for Part 1, as data have been collected from adequate number of subjects. PK sampling time points for Cycle 1 Day 1 for all subjects in Part 1 were updated to better characterize kinetics after the end of infusion. An end-of-infusion PK sample was added for all cycles after Cycle 1 to assess potential longitudinal changes in exposure during treatment. Time points for immunogenicity evaluation were revised. |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations);<br>Time and Events Table 3 (Pharmacokinetic/ Immunogenicity samples);<br>Time and Events Table 4 (Part 2 Pharmacokinetic / Immunogenicity Sampling) | PK and immunogenicity sampling in Part 2 is described in newly added Table 4. In Part 2, end-of-infusion blood samples will be collected for PK evaluation on Day 1 of all cycles. Pre-dose blood samples for immunogenicity evaluation will be collected on Day 1 of Cycle 1 and then every 3 cycles thereafter (Day 1 of Cycles 4, 7, 10, etc.). |
| 9.4.3. Pharmacokinetic Parameters | Clarification was added that pharmacokinetic parameters based on serial sampling will be derived <u>in Part 1</u>. Descriptive statistics (geometric and arithmetic means, standard deviation, coefficient of variation [%]) will be provided to summarize imetelstat plasma concentrations at each sampling time point <u>for both Part 1 and Part 2.</u> |
| **Rationale:** Addition of an Independent Central Pathology Review provides an impartial confirmation of disease status at baseline and following disease response. | |
| Synopsis (Efficacy Evaluations);<br>Time and Events Table 3 (BM aspirate biopsy);<br>3.1. Overview of Study Design;<br>4.1. Inclusion Criteria (no. 2);<br>9.1.3. Screening Phase and Predose;<br>9.1.4. Treatment Phase;<br>9.1.5. Posttreatment Phase;<br>9.3.1.3. Bone Marrow Assessment | Centralized review of bone marrow aspirate/biopsies is required in Part 2 for all subjects at screening, at the time of suspected response (ie, HI-E [Hb], CR, PR), and at the time of suspected PD. Treatment decisions will continue to be made based on the investigator's assessment of local pathology review. |
| **Rationale:** Study endpoints and objectives have been expanded following examination of Part 1 data and changes to the scope of study procedures. | |
| Synopsis (Secondary Objectives);<br>Synopsis (Endpoints);<br>2.1. Objectives;<br>9.2.2. Secondary Endpoints;<br>11.4. Efficacy Analyses | Assessment of progression free survival (PFS) was added as a secondary objective. |
| Synopsis (Secondary Objectives);<br>Synopsis (Endpoints);<br>2.1. Objectives;<br>9.2.2. Secondary Endpoints | Assessment of the effect of imetelstat on QTc interval in a subset of subjects was added as a secondary objective. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 11.5. Pharmacokinetic Analyses | Text was revised: Descriptive statistics will be provided to summarize imetelstat plasma concentrations at each sampling time point for subjects undergoing serial pharmacokinetic sampling <u>in Part 1 and the Ventricular Repolarization substudy in Part 2</u>. |
| Synopsis (Exploratory Objectives);<br>Synopsis (Endpoints);<br>Synopsis (Pharmacodynamic and Biomarker Evaluations);<br>2.1. Objectives;<br>3.2. Study Design Rationale;<br>9.2.3. Exploratory;<br>9.5. Biomarkers | Evaluation of mutation changes during treatment was added to evaluation of baseline mutation status for the purpose of exploring the association with clinical response was added as an exploratory objective. |
| **Rationale:** Clarification was added for document consistency, to aid interpretation of procedures, reflect experience gained in Part 1, and improve study quality. | |
| Title Page | Janssen Pharmaceuticals NV was added to the sponsorship statement as a legal entity. |
| Synopsis (Overview of Study Design);<br>3.1. Overview of Study Design | The following text was added: Enrollment into the study may be temporarily held between Part 1 and Part 2 while safety and efficacy data are analyzed. |
| Synopsis (Endpoints);<br>Synopsis (Pharmacodynamic and Biomarker Evaluations);<br>9.2.3. Exploratory;<br>9.5. Biomarkers (Cytogenetic Response) | Clarification was added that cytogenetic assessment will include cytogenetic changes including response. |
| Synopsis (Efficacy Evaluations) | Clarification was added that symptom assessments will be based on patient-reported outcomes. |
| Synopsis (Safety Evaluations) | Unnecessary text was deleted: Additionally, an Independent Data Monitoring Committee will be commissioned to monitor safety data during ~~Part 1 and Part 2 of~~ the study. |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations) | Part 1 and Part 2 pharmacokinetic and immunogenicity evaluations were presented separately. |
| Synopsis (Pharmacokinetic and Immunogenicity Evaluations; Pharmacodynamic and Biomarker Evaluations) | Text addressing exposure-response relationships was simplified and moved from the Pharmacokinetic and Immunogenicity Evaluations section of the Synopsis to the Pharmacodynamic and Biomarker Evaluations section of the Synopsis. |
| Time and Events Table 1, Table 3 | The window for survival follow-up during the Posttreatment Follow-up Phase was changed from “every 16 weeks (±7 days)” to “every 12-16 weeks”. |
| Time and Events Schedule Table 1 (BM aspirate, biopsy; BM aspirate for RNA Seq or CyTOF | Clarification was added that in addition to previous time points, bone marrow aspirate should be obtained at the time of suspected HI-E (Hb). |
| Time and Events Table 1 and Table 3 (Chemistry) | Additional cross-reference to Section 9.8 was added. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Time and Events Table 1 and Table 3 | "BM aspirate for cytogenetics", "BM aspirate for RNA Seq or CyTOF", "Immunophenotyping" will not be performed after the End-of-Treatment Visit. |
| Time and Events Table 1, Table 3 (BM aspirate for cytogenetics);<br>9.5. Biomarkers | In Part 1, BM aspirate for cytogenetics is required for all subjects at the time of PD. Subjects with baseline abnormalities will also have BM aspirate at the time of suspected PR, CR, or HI-E (Hb) and every 24 weeks thereafter up to and including the time of PD. |
| Time and Events Table 1, Table 3 (Mutation analysis) | Mutation analysis is required at the time of suspected response (CR, PR, HI-E [Hb]) or PD. |
| Time and Events Table 3 | Post-screening assessments will occur at the time of suspected HI-E (Hb), PR, CR, PD, and as otherwise specified. |
| Time and Events Table 1 and Table 3 (Hematology);<br>9.8.1. Clinical Laboratory Tests | Clarification was added to the comment that if hematology tests are repeated on the day of the visit, the most recent results should be reviewed before dosing. |
| Time and Events Table and Table 3 (Response assessment) | Bone marrow analysis is required at the time of suspected response or progression in addition to the analysis required every 24 weeks. |
| Time and Events Table 1 and Table 3 (Serum EPO level) | An additional measurement of serum erythropoietin level is required at the first occurrence of suspected HI-E (Hb), PR, or CR. Subsequent measurement is not required if response further improves. |
| Time and Events Table 1 and Table 3 (serum ferritin, transferrin saturation) | Serum ferritin and transferrin saturation were separated from other laboratory assessments and given a separate line in the Time and Events Schedules. In addition to screening assessments, serum ferritin and transferrin saturation will be measured on Day 1 of all cycles and at the EOT visit. |
| Time and Events Table 1, Table 3 (TA, TL and hTERT);<br>9.5. Biomarkers | All subjects in Part 1 will have blood samples for TA, TL, and hTERT evaluation. Only predose Day 1 Cycle 1 blood samples will be collected in Part 2. |
| Time and Events Table 2 | Clarification was added that the table only applies to Part 1. |
| 3.1. Overview of Study Design | Clarification was added that 170 eligible subjects will be randomized in Part 2. |
| 3.1. Overview of Study Design;<br>6. Dosage and Administration (Study Drug);<br>6.1. Dose Modifications | Text describing conditions under which dose re-escalation may occur was deleted, as re-escalation is not permitted in Part 2. |
| 3.2. Study Design Rationale | "The time to AML progression" was rephrased as "the time to progression to AML". |
| 4. Subject Population;<br>4.2. Exclusion Criteria | A NOTE stressing the importance of compliance with enrollment criteria was made more prominent by repositioned the text from the bottom of Section 4.2 to the bottom of Section 4. |
| 4.2 Exclusion Criteria (no. 4) | Exclusion criterion 4 was revised to address prestudy restrictions on corticosteroid and growth factor treatment only. |
| 4.2. Exclusion Criteria (no. 16) | A new exclusion criterion was added: Individuals previously diagnosed with IPSS intermediate-2 or high risk MDS are excluded from the study. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 4.2. Exclusion Criteria (no. 18) | A new exclusion criterion was added: Subject with MDS/ myeloproliferative neoplasm (MPN) Overlap Syndrome. |
| 6. Dosage and Administration | Clarification was added that the sponsor should be contacted before study drug is discontinued for subjects with study drug being held more than 28 days due to toxicity, if the subject is otherwise responding to treatment and the toxicity appears to be manageable. |
| 6.1.1 Dose Modifications for Hematologic Toxicities; Table 6; Table 7 | Text was added recommending contact with the sponsor before discontinuing treatment for Grade 3 or Grade 4 hematologic toxicity, particularly when the hematologic toxicity is asymptomatic. The following text was added as a footnote to the Dose Modification tables: "Note: Contact the sponsor to discuss the specific case before study drug is discontinued for hematologic toxicity". |
| 8.3. Concomitant Medications | Clarification was added that chemotherapy, including anticancer or hypomethylating agents, is prohibited during the study. |
| 9.1.2. Total Blood Volume (Table 11); 16.1. Study-Specific Design Considerations | The blood volume to be collected was updated to reflect revised study procedures. The total blood volume to be collected was changed from 486 mL to 555 mL. |
| 9.1.3. Screening Phase and Predose | Text was updated to emphasize that only limited retesting of abnormal screening values is permitted. |
| 9.1.4. Treatment Phase | Clarification was added that disease assessments should be performed for subjects with suspected disease progression or suspected response (eg, HI-E (Hb) in conjunction with recovery from cytopenias) |
| 9.2.2. Secondary Endpoints | The definition of time to progression to AML was clarified as the interval from Study Day 1 to the date of AML diagnosis. |
| 9.3.1.2. Hemoglobin Assessment | Part "i" of the definition of HI-E was revised as follows: Hematologic improvement-erythroid (HI-E) response is defined as i) a Hb rise of at least 1.5 g/dL above pretreatment level ~~baseline, measured 28 days or more following the last RBC transfusion.~~ A definition of pretreatment Hb level was added. |
| 9.8.1. Clinical Laboratory Tests | An Anemia Panel (including B12, folic acid, reticulocytes) was separated from Screening testing, as some or all of these tests may be repeated after screening. Serum erythropoietin, serum ferritin, and transferrin saturation were separated from other anemia tests to match the Time and Events Schedules. "Screening testing" was revised to "Pregnancy testing" and the pregnancy test was clarified as β-hCG. |
| 11.4. Efficacy Analyses | Reference to the Hochberg procedure was deleted. |
| 11.7. Pharmacokinetic/ Pharmacodynamic Analyses | Clarification was made that a population pharmacokinetic/pharmacodynamic analysis may be performed using nonlinear mixed-effects modeling if required, and that data may be combined with relevant Phase 1 and Phase 2 studies for the analyses. Exposure-response analysis for the Ventricular Repolarization substudy in Part 2 may be provided in a separate report. |
| 12.3.1. All Adverse Events | Adverse event information will be collected until 30 days after the last dose of study drug (changed from completion of last study- |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| | related procedure), for consistency with the Time and Events Schedule. The following text was added: Any adverse event thought to be potentially related to study drug must be reported to the sponsor irrespective of timing from the last dose of study drug. |
| 12.3.1. All Adverse Events; Attachment 10 | Text related to anticipated events was moved to Attachment 10, which identifies anticipated events associated with MDS and describes reporting and analysis procedures. Progressive disease of MDS was deleted as an Anticipated Event. |
| 14.5. Drug Accountability | Text not applicable to the study was deleted. |
| **Rationale:** Minor errors were noted | |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. |

**Amendment 1** (31 May 2016)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** 1) To modify the eligibility criteria (MDS criteria, biochemistry inclusion and hepatitis exclusion criterion) for alignment across the imetelstat clinical program, based on advice from the Hepatic Expert Committee, consultations with Health Authorities, and MDS experts; 2) To add the QUALMS instrument, which is a newly validated MDS-specific measure of PRO; 3) To make clarifications throughout protocol based on questions received during execution of Part 1.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Protocol changes were requested following consultation with Health Authorities. | |
| Synopsis (Overview of Study Design); 3.1. Study Design; 3.2. Study Design Rationale (Randomization); 5.1. Treatment Allocation | The definition of "prior RBC transfusion burden" was revised to the maximum number of RBC units transfused over an 8-week period during the 16 weeks (changed from 12 weeks) prior to Study Entry. |
| Synopsis (Population); 4.1. Inclusion Criteria (no. 2) | Eligible subjects must have a diagnosis of MDS based on WHO criteria. An MDS diagnosis based only on FAB classification (Attachment 2) is not permitted. |
| Time and Events Schedule (Table 1, Table 2; Transfusion history); 8.1. Prestudy Therapy; 9.1.3. Screening Phase and Predose | RBC transfusion history is required for the 16-week period before Study Entry (changed from 12 weeks). |
| Time and Events Schedule (Table 1, Table 2; Transfusion history); 3.1. Overview of Study Design; 9.1.5. Posttreatment Phase; 9.3.1.1. Transfusions | Text was added to help ensure collection of robust transfusion data until treatment is stopped. For subjects who receive less than 12 months of treatment, transfusion data will be collected for a minimum of 12 months from Study Entry. Text was added to Section 9.3.1.1 describing transfusion data collection methods, including enhanced monitoring and continuous medical review. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Time and Events Schedule (Table 1, Table 2; Transfusion history);<br>9.1.5. Posttreatment Phase;<br>9.3.1.1. Transfusions | Clarification was added that during the Posttreatment Phase, transfusion information should be collected every 4 to 6 weeks. |
| 4.1. Inclusion Criteria (no. 4); | The definition of "transfusion dependent" for determining study eligibility was revised to having received at least 4 RBC units over an 8-week period during the 16 weeks (changed from 12 weeks) prior to Study Entry. |
| 4.1. Inclusion Criteria (no. 6) | To ensure subjects have adequate iron stores they must have transferrin saturation greater than 20% and (changed from either) serum ferritin greater than 400 ng/mL. |
| 4.1. Inclusion Criteria | Inclusion criterion no. 13 was added. Subjects with the del(5q) karyotype are eligible if they have failed treatment with lenalidomide. |
| 11.4. Efficacy Analyses (Part 2) | Clarification was added that subjects will not be considered transfusion independent in the absence of robust, continuous assessment of transfusion requirements during the observation period. |
| **Rationale:** Eligibility criteria or study procedures were aligned with expert advisor recommendations and across the imetelstat clinical program. | |
| Time and Events Schedule (Table 2, BM aspirate, biopsy);<br>9.3.1.3. Bone Marrow Assessment | Requirement added that a sample of the bone marrow used for diagnostic confirmation must be available to submit for central pathology review, if requested. |
| Time and Events (Table 1, Table 2; Hepatitis serologies)<br>9.8.1. Clinical Laboratory (Viral hepatitis) | Requirements for screening hepatitis serology were clarified. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg). |
| 4.1. Inclusion Criteria (no. 9.4) | Requirement added that total bilirubin must be ≤3 x ULN. Requirement for direct bilirubin was changed from ≤1.5 x ULN to ≤2 x ULN. Patients with elevated bilirubin due to Gilbert's syndrome may be eligible to participate in the study. |
| 4.2. Exclusion Criteria (no. 12) | History of prior hepatitis infection was deleted as part of the exclusion criterion. Subjects with active systemic hepatitis infection requiring treatment are excluded (carriers of hepatitis virus are permitted to enter the study). |
| **Rationale:** Additional PRO instruments have been identified for use in the study. | |
| Synopsis (Endpoints);<br>9.2.2. Secondary Endpoints | "Change from baseline in scores from FACT-An and EQ-5D-5L" was changed to "Assessment of QUALMS, FACT-An and EQ-5D-5L." |
| Time and Events Schedule (Table 2, Efficacy Assessments);<br>3.2. Study Design Rationale (Patient-Reported Outcomes);<br>9.1.3. Screening;<br>9.1.5. Posttreatment Phase;<br>9.6. Patient–Reported Outcomes | QUALMS and PGIC were added to FACT-An and EQ-5D-5L for use in Part 2. When applicable, these are referred to collectively as PRO measures or PRO questionnaires. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 11.4. Efficacy Analyses (Part 2) | A description of efficacy analyses related to QUALMS was added. |
| Attachment 7; Attachment 8; Attachment 9 | Attachment 7 (EQ-5D-5L) was updated. Attachments for QUALMS (Attachment 8) and PGIC (Attachment 9) were added. |
| **Rationale:** The flexibility to use peripheral blood instead of bone marrow aspirate for cytogenetic testing will allow cytogenetic testing to occur when bone marrow aspiration is clinically unfeasible. Bone marrow aspirate is preferred to peripheral blood for cytogenetic assessment. The same sample type should be collected at screening and subsequent time points, if possible, because changes in cytogenetic findings may result for a given subject when different sample types are used. | |
| Time and Events Schedule (Table 1, Table 2; BM aspirate for cytogenetics); 9.5 Biomarkers (Cytogenetic Analysis) | Guidance was provided for when bone marrow aspiration yields a dry tap. Peripheral blood can be submitted if bone marrow aspirate cannot be collected. A consistent type of sample (peripheral blood or bone marrow aspirate) should be used throughout the study. |
| **Rationale:** Clarification was added to aid interpretation of procedures, for consistency with other parts of the protocol, and to reflect experience gained during conduct of Part 1. | |
| Synopsis (Exploratory Objectives) | The list of exploratory objectives was aligned with Section 2.1, Objectives. |
| Synopsis (Overview of Study Design); 3.1. Overview of Study Design; 11.2. Subject Information | The definition of "Study Entry" was clarified for Part 1 and Part 2 of the study. Study Day 1 is equivalent to Study Entry and is defined as the day of the first dose for subjects enrolled in Part 1 and the day of randomization for subjects enrolled in Part 2. In Section 3.1, specific reference to Study Entry as the day of the first dose was deleted, as the text is not specific to Part 1. |
| Synopsis (Endpoints); 9.2.2. Secondary Endpoints | Secondary endpoints were revised as follows: "Rate and amount of transfusions" was revised to "amount and relative change in RBC transfusions," and "dose of myeloid growth factors usage" was revised to "duration of myeloid growth factors usage." |
| Synopsis (Safety Evaluations); 3.1. Overview of Study Design; 11.11. Independent DMC; 16.1. Study Design Considerations | The independent DMC's involvement in the study was extended to Part 1 in addition to Part 2. |
| Synopsis (Pharmacokinetics); Time and Events Schedule (Table 1, Table 2; Pharmacokinetics) | Pharmacokinetic sampling scheduled for Cycle 3 was moved to Cycle 4. Subsequent sampling was shifted accordingly. |
| Time and Events Schedule (Table 1, Table 2; Study Entry) | The row for Study Entry was deleted. |
| Time and Events Schedule (Table 1, Table 2; Dispense/administer study drug); 6. Dosage and Administration (Study Drug) | Clarification was added that the body weight measurement collected at Screening is used for the initial dose calculation. Clarification was added that dosing should begin within 72 hours of enrollment (Part 1) or randomization (Part 2) in IWRS. |
| Time and Events Schedule (Table 1, Table 2; Hematology, BM aspirate, biopsy) | Rows for "Hematology" and "BM aspirate, biopsy" were repositioned as Efficacy Assessments to keep together all evaluations required for response assessment. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Time and Events Schedule (Table 1, Table 2: BM aspirate, biopsy; Response assessment; TA, TL, hTERT; BM aspirate for cytogenetics; Immunophenotyping) | Clarification was added that samples are collected at the time of suspected PR, CR, and PD. |
| Time and Events Schedule (Table 1, Table 2; Hematology, Chemistry) | Screening hematology and chemistry tests should (changed from must) be performed within 14 days before Study Entry. |
| Time and Events Schedule (Table 1, Table 2; Hematology);<br>6.1.1. Dose Modification;<br>9.1.4. Treatment Phase<br>9.8.1. Clinical Laboratory Tests | Text was added to emphasize that laboratory testing beyond required assessments in the Time and Events Schedules should be performed as clinically indicated. Weekly hematology follow-up is required after any Grade ≥3 thrombocytopenia or neutropenia that occurs during the treatment phase until values return to baseline. |
| Time and Events Schedule (Table 1, Table 2; Hematology);<br>6.1. Dose Modification;<br>9.3.1.2. Hemoglobin Assessment | Clarification added that "dose escalation" means "dose escalation to 9.4 mg/kg." |
| Time and Events Schedule (Table 2; Hematology) | Hematology assessments were added for the first visit of the Posttreatment Follow-up Phase. |
| Time and Events Schedule (Table 1, Table 2; BM aspirate, biopsy) | After baseline, BM assessments can be performed with a window of ±7 days. Clarification was added that the every-24-week interval for BM aspirate assessment begins from C1D1 and that BM biopsy occurs annually (every 48 weeks) after C1D1. A cross-reference to additional BM sampling procedures was added. |
| Time and Events Schedule (Table 1, Table 2; Response Assessment) | Required evaluations for response assessment were added to the Comments column (peripheral blood and RBC transfusion requirements at all assessments; bone marrow analysis every 24 weeks). A cross-reference to Section 9.1.5 was added for subjects who discontinue treatment for any reason other than disease progression. Clarification was added that the every-12-week interval for response assessment begins from C1D1 ±1 week. |
| Time and Events Schedule (Table 1, Table 2; Chemistry) | A cross-reference to Section 9.8.1 was added for additional detail on required clinical laboratory testing. |
| Time and Events Schedule (Table 1, Table 2; Chemistry Panel for LFT investigations) | Both the routine chemistry panel and LFT investigations chemistry panel are repeated weekly as required. Subjects with Grade 1 or Grade 2 elevations in AST, ALT, ALP, or bilirubin at the time of treatment discontinuation will continue to be tested monthly until resolution to at least baseline. |
| Time and Events Schedule (Table 1, Table 2; INR (or PT) and aPTT;<br>9.1.4. Treatment Phase;<br>9.8.1. Clinical Laboratory Tests | Text was added to clarify the requirement for additional coagulation assessments for subjects who experience a hemorrhagic event during the treatment phase. |
| Time and Events Schedule (Table 1, Table 2; TA, TL, and hTERT) | Clarification was added that blood samples are collected. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| Time and Events Schedule (Table 1, Table 2; BM aspirate for cytogenetics) | Clarification was added that local cytogenetic analysis of BM aspirate is recommended for Screening (a sample must still also be submitted to the central laboratory). The baseline sample for the central laboratory may be collected either during Screening or before dosing on C1D1. Bone marrow aspirate is required "at time of suspected PR/CR and every 24 weeks thereafter up to and including PD" (changed from until PD). |
| Time and Events Schedule (Table 1, Table 2; BM aspirate for RNA Seq or CyTOF) | Text was added to allow collection of the baseline aspirate sample either during Screening or before dosing on C1D1. After baseline, BM assessments can be performed with a window of ±7 days. |
| Time and Events Schedule (Table 3) | Clarification was added to the first column that the Cycle 1, 22h – 26h postdose time point may occur on Day 1 or Day 2. All Cycle 3 sampling was changed to Cycle 4, with subsequent sampling revised from "Day 1 of Cycles 6, 9, etc." to "Day 1 of Cycles 7, 10, etc." Additional Serial Pharmacokinetic samples were added for Cycle 4, Day 1 at 2 hours and 3 to 6 hours. Additional Serial Pharmacokinetic and Sparse Pharmacokinetic samples were added for subjects who have a dose escalation to 9.4 mg/kg. Footnote "c" was added for the "Sparse Pharmacokinetic Blood Sampling" column. Footnote "d" clarified to indicate that the 2 h time points should correspond to a time point immediately before the end of infusion, including cases where infusion time extends beyond 2 hours. Footnote "f" was revised to reflect changes to sample collecting. |
| 3.1. Study Design;<br>Figure 2 (Study Schematic);<br>6. Dosage and Administration | Guidance for discontinuation of study treatment for subjects with inadequate response after 6 months of treatment was aligned for Part 1 and Part 2. |
| 3.1. Overview of Study Design;<br>6. Dosage and Administration (Study Drug);<br>6.1 Dose Modifications | Clarification was added that dose re-escalation may (changed from will) be considered for subjects with improved tolerability after the dose had been reduced due to toxicity. |
| 4.1. Inclusion Criteria;<br>4.2. Exclusion Criteria | Bulleted sub-criteria for inclusion no. 5, inclusion no. 8, inclusion no. 9, and exclusion no. 9, were assigned numbers. The bulleted inclusion criterion regarding acceptable methods of birth control was assigned the number 10.1. The subsequent inclusion criterion regarding pregnancy testing was renumbered 10.2 (previously no. 10). |
| 4.1. Inclusion Criteria (no. 5.4) | "Serum EPO level" was clarified as "Endogenous serum EPO level". |
| 4.2. Exclusion Criteria | The following text was added to the "Note:" below the list of exclusion criteria: "The last laboratory result obtained prior to enrollment/randomization will be used to determine eligibility." |
| 5.1. Treatment Allocation | Clarification was added that that pre-transfusion Hb should be ≤9.0 g/dL to count towards the 4-unit total, unless there is clinical rationale for transfusing at a higher Hb level. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| 6. Dosage and Administration (Study Drug);<br>6.1.1. Dose Modifications (Hematologic);<br>6.1.2 Dose Modifications (Non-hematologic);<br>6.1.3. Dose Modifications (Hepatic) | Clarification was added that the dose modification instructions provided in Tables 5 to 9 are applicable only when Grade 3 or Grade 4 toxicities are present at the planned time of study drug administration on Day 1 of a dosing cycle. |
| 6.1. Dose Modifications | Additional guidance was added to the Table 4 footnote. Subjects must receive 3 cycles of treatment at 7.5 mg/kg before escalation to 9.4 mg/kg can be considered. Guidance was added to perform additional pharmacokinetic sampling per Table 3 when dose escalation to 9.4 mg/kg occurs. |
| 6.2. Infusion-Related Reactions (Table 9) | Revised guidance was provided for management of Grade 2 infusion-related reactions. |
| 9.1.1. Overview;<br>9.8.2. Electrocardiogram | The detailed recommendation for the order of study procedures was deleted. |
| 9.1.2. Total Blood Volume (Table 10);<br>16.1. Study Design Considerations | The total blood volume to be collected was increased by 16 mL due to additional pharmacokinetic sampling and expanded hepatitis testing. |
| 9.1.4. Treatment Phase | Clarification was added that a window of ±3 days is allowed for visits to the clinic. |
| 9.1.5. Posttreatment Phase | Clarification was added regarding continuation of response assessments when study drug is discontinued for reasons other than disease progression. Response assessment visits should continue per timing in the Time and Events Schedule or according to site standard practice through the time of disease progression or until the start of subsequent therapy, whichever comes first. Redundant reference to the Time and Events Schedule was deleted. |
| 9.3.1.2. Hemoglobin Assessment | Clarification was added to the definition of HI-E that reduction in transfusion burden is a comparison to "prior RBC transfusion burden." |
| 9.5. Biomarkers | Text describing immunophenotype analysis was repositioned within the section. The subheading "Additional analysis" was changed to "BM aspirate for RNA Seq or CyTOF." |
| 9.8.1. Clinical Laboratory Tests | Clarification was added to the Serum Chemistry Panel (Routine) that total bilirubin with fractionation is required at screening. Fractionation is required post-screening if total bilirubin is abnormal. |
| 10.2. Discontinuation of Study Treatment | Inadequate response after 6 months of treatment was deleted as a reason for study drug discontinuation. |
| 11.4. Efficacy Analyses (Part 1 and Part 2) | Additional detail was added to the description of planned efficacy analyses for Part 1 and Part 2. |
| 12.3.3. Adverse Events of Interest | Adverse events of interest must be reported to the sponsor with 24 hours of awareness (changed from will). Adverse events of interest must be reported irrespective of seriousness. |
| References | References 1 and 46 were added. Unused references were deleted. Citation numbering was revised accordingly. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Additional information regarding Study CP14B019 has become available. | |
| 1.1.5. Clinical Experience;<br>1.1.5.2.1. Hematologic Toxicities;<br>1.1.5.2.3. Hepatotoxicity | Information related to the MDS cohort in CP14B019 was added or updated based on currently available published literature. |
| **Rationale:** Janssen Research & Development standard protocol text has been updated. | |
| Title Page | Janssen Infectious Diseases BVBA has been deleted as one of the legal entities comprising Janssen Research & Development. |
| 4. Subject Population | Clarification was added that waivers to required entry criteria are not permitted. |
| 12.2. Special Reporting Situations | Exposure to a sponsor study drug from breastfeeding was added as an event that may require expedited reporting and safety evaluation. |
| 12.3.1. All Adverse Events | Additional text was added describing Anticipated Events and the reporting process for serious Anticipated Events. |
| 16.2.2. IEC or IEB | Clarification was made that IEC/IRB annual approval of the protocol will be obtained, where required. |
| **Rationale:** Minor errors were noted | |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. |

# SYNOPSIS

A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment.

Imetelstat (GRN163L) is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. Telomerase inhibition leads to loss of a cancer cell's ability to maintain telomere length (TL), resulting in cell-cycle arrest, apoptosis, or senescence. Imetelstat binds with high affinity to the template region of the ribonucleic acid (RNA) component of human telomerase reverse transcriptase (hTERT) and is a competitive inhibitor of telomerase enzymatic activity.[2,24] Treatment of various cancer cells with imetelstat in vitro increases their sensitivity to radiation, decreases their clonogenic potential, and results in altered expression of stem-cell related genes. Clinical data in a small number of MDS subjects further indicate that treatment with imetelstat resulted in transfusion independence and other measures of hematologic improvement.

## OBJECTIVES AND HYPOTHESES

### Primary Objective

Part 1: To evaluate the efficacy and safety of imetelstat in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

Part 2: To compare the efficacy, in terms of red blood cell (RBC) transfusion independence (TI), of imetelstat to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

Extension Phase: To evaluate the long-term safety, OS, and disease progression, including progression to AML in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment receiving imetelstat.

### Secondary Objectives (Part 1 and Part 2)

- To assess the safety of imetelstat in subjects with MDS
- To assess the time to RBC TI and duration of RBC TI
- To assess the rate of hematologic improvement
- To assess the rates of complete remission (CR), partial remission (PR), or marrow complete remission (mCR)
- To assess overall survival (OS)
- To assess progression free survival (PFS)
- To assess time to progression to acute myeloid leukemia (AML)
- To assess the rate and amount of supportive care, including transfusions and myeloid growth factors (Part 2 only)
- To evaluate the pharmacokinetics and immunogenicity of imetelstat in subjects with MDS
- To assess the effect of imetelstat treatment on patient-reported outcomes (PROs)
- To assess the effect of treatment on medical resource utilization (Part 2 only)
- To assess the effect of imetelstat on corrected QT (QTc) interval in subjects in the Ventricular Repolarization substudy (to be reported separately from Part 2)

**Exploratory Objectives (Part 1 and Part 2)**

- To evaluate pharmacodynamic biomarkers such as telomerase activity (TA), TL and hTERT and to explore the association between baseline results and clinical response
- To evaluate change of cytogenetic abnormalities and explore the association between baseline cytogenetic status and clinical response
- To evaluate baseline mutational status and mutation changes during treatment for exploring the association with clinical response
- To explore the effects of imetelstat on immune profiles through immunophenotyping (Part 1 only)
- To evaluate the exposure-response relationship between pharmacokinetics and pharmacodynamic biomarkers, efficacy and safety

**Hypothesis**

The primary hypothesis is that imetelstat will improve the rate of RBC TI as compared to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

## OVERVIEW OF STUDY DESIGN

This is a multicenter study of imetelstat in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment (as per inclusion criteria). The study will consist of 2 parts, and approximately 270 subjects will be enrolled. Part 1 was an open-label, single-arm design to assess the efficacy and safety of imetelstat, which enrolled 57 subjects. Part 2 is a double-blind, randomized, placebo-controlled design to compare the efficacy of imetelstat with placebo. In addition to the approximately 170 subjects to be enrolled in the main study in Part 2, approximately 45 subjects will be enrolled in a separate Ventricular Repolarization substudy. Subjects should be enrolled in the main study of Part 2 until enrollment is complete unless a subject is known to meet criteria that would make the subject ineligible for the main study (eg, del 5 q, prior HMA therapy). The sponsor has reviewed and assessed all available data in Part 1, including blood counts, transfusion requirement, tolerability, pharmacokinetic, and pharmacodynamic biomarker data.

The futility criteria before Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (eg, transfusion reduction, erythroid improvement). Upon review of the efficacy and safety data observed with the 7.5 mg/kg dose among 32 subjects in Part 1, a subset of 13 subjects was identified with higher hematologic response rates. These were subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. As of Amendment 2, Part 1 was expanded to include only subjects who meet these criteria, with the goal to confirm the safety and efficacy data seen in this subset and to re-confirm the dose. Twenty-five additional subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide, so called target population, were enrolled for a total of 38 (from 57 enrolled in Part 1).

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat (see Section 3.2 for a summary of data from the 38 subjects in the target population), Part 2 of the study will be initiated in subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. Enrollment into the study was temporarily held between Part 1 and Part 2 while safety and efficacy data were analyzed. Subjects in Part 2 will be randomized in a 2:1 ratio to receive either imetelstat or placebo, respectively. Randomization will be stratified by prior RBC transfusion burden (≤6 or >6 units RBC) and by International Prognostic Scoring System (IPSS) risk group (low versus intermediate-1). Prior

RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to Cycle1 Day 1 (C1D1) for subjects enrolled in Part 1 or the day of randomization for subjects enrolled in Part 2. Each part of the study will consist of 3 phases:

- a Screening Phase of up to 28 days during which subject eligibility will be reviewed and approved by the sponsor prior to C1D1 (Part 1) or Randomization (Part 2);
- a Treatment Phase that will extend from C1D1 (Part 1) or Randomization (Part 2) until disease progression, or unacceptable toxicity, or withdrawal of consent; and
- a Posttreatment Follow-up Phase which will continue until death, loss to follow-up, withdrawal of consent, or the end of the study (whichever occurs first). The end of the main study is defined as 24 months after the randomization of the last subject in the main study of Part 2.
- An Extension Phase will begin after the end of the main study (24 months after the last subject was randomized in the main study of Part 2) and continue until subjects who entered from Part 2 of the main study participate in the study for at least 5 years from the first dose of imetelstat (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up.

In Part 2, approximately 45 evaluable subjects (in addition to the approximately 170 subjects who will be enrolled in the main study) will be enrolled in a separate Ventricular Repolarization (QTc) substudy investigating the effects of imetelstat exposure on ventricular repolarization. Subjects who are not evaluable for the QTc substudy primary electrocardiograms (ECG) endpoint may be replaced with new subjects. Serial ECGs will be obtained with PK samples on Day 1 of Cycle 1 as indicated in Attachment 11. The cardiac safety analysis in regard to ECG and concentration QTc analysis in the substudy based on the additional 45 subjects will be performed separately from the primary analysis of 170 subjects in the main study (refer to Attachment 11 for further details). Subjects who have enrolled into the Ventricular Repolarization substudy of Part 2 prior to Protocol Amendment 7 will continue with the assessments as required for the main study.

Subjects benefiting from imetelstat at the end of the main study (ie, 24 months after last subject randomized in the main study of Part 2) per investigator assessment may continue to receive imetelstat during the Extension Phase. Subjects in the Posttreatment Follow-up Phase of the main study will also continue in the Extension Phase for assessment of survival status, subsequent anticancer therapy, and monitoring of disease progression. Subjects will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up. During the Extension Phase, the Independent Hepatic Expert Committee (HEC) will be available to review all hepatic adverse events and liver function test abnormalities at least on a quarterly basis, or more frequently if needed.

Subjects who are receiving imetelstat in the QTc substudy may also enter the Extension Phase after the clinical cut off for the primary analysis is reached for the QTc substudy (ie, after approximately 45 evaluable subjects have completed Cycle 2). Once the end of the Extension Phase is reached for subjects participating in the main study (as described above), the study will also end for the QTc substudy subjects who enter the Extension Phase.

With Protocol Amendment 8, Part 1 of the study will close as all subjects in Part 1 have already discontinued treatment and the study will have already met the duration of follow-up defined for the Extension Phase (ie, at least 5 years from the first dose of imetelstat treatment, or 3 years of post-treatment follow-up from

the last dose of study treatment, whichever occurs later). Any Part 1 subjects remaining in follow-up will be discontinued from the study. Therefore, the Extension Phase does not apply to Part 1 subjects.

**SUBJECT POPULATION**

Key eligibility criteria include the following: ≥18 years of age; diagnosis of MDS according to World Health Organization criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to C1D1 (Part 1) or Randomization (Part 2); IPSS low or intermediate-1 risk non-del(5q) MDS that is relapsed/refractory to ESA treatment; RBC transfusion dependent; an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2; and no prior treatment with either a hypomethylating agent or lenalidomide. Eligibility criteria for the additional 45 subjects enrolled in the Ventricular Repolarization substudy of Part 2 are outlined in Attachment 11.

**DOSAGE AND ADMINISTRATION**

All subjects in Part 1 will receive imetelstat. Subjects in Part 2 will receive either imetelstat or placebo. The term 'Study Drug', as used in this protocol, refers to either imetelstat or placebo.

The study drug is administered as an intravenous (IV) infusion. The starting dose of the study drug is 7.5 mg/kg every 4 weeks. Subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose (Part 1 only).

Guidelines for imetelstat dosage and administration for subjects who continue treatment during the Extension Phase will follow those described in the Treatment Phase.

**ENDPOINTS**

The primary efficacy endpoint of this study is the rate of RBC TI lasting at least 8 weeks. The 8-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks starting from Study Day 1.

The secondary endpoints of this study are: the safety of imetelstat in subjects with MDS; the rate of RBC TI lasting at least 24 weeks; the time to and duration of RBC TI; the rate of hematologic improvement, including hematologic improvement-erythroid; the rates of CR, PR, or mCR; OS; PFS; time to progression to AML; amount and relative change in RBC transfusions; rate and duration of myeloid growth factors usage; assessment of Quality of Life in Myelodysplasia Scale (QUALMS), Functional Assessment of Cancer Therapy-Anemia-Related Effects (FACT-An), and EuroQol-EQ-5D-5L (EQ-5D-5L); pharmacokinetic parameters (eg, $C_{max}$, $AUC_{0-t}$), and immunogenicity of imetelstat (eg, antibodies to imetelstat); and the medical resource utilization data including hospitalization, emergency room visits, hematology specialist visits, and ECG parameters including change in QTc interval for subjects enrolled in the Ventricular Repolarization substudy (Part 2 only).

The exploratory endpoints of this study are: TA, and hTERT at baseline and the change from baseline, TL at baseline; the cytogenetic status at baseline and cytogenetic changes, including response; the mutation status at baseline; mutation changes during treatment; and the immune profiles at baseline and change from baseline (Part 1 only).

**EFFICACY EVALUATIONS**

Efficacy evaluations will include transfusion data, blood count assessments, limited physical examinations, bone marrow biopsy and aspirate for disease and cytogenetic assessments, and symptom assessment via PRO. In addition to local disease evaluations, which will be used for treatment decisions, in Part 2, an Independent Central Pathology Reviewer will review bone marrow assessments performed at baseline to confirm diagnosis throughout the duration of the main study. An Independent Review Committee will be established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response).

Patient-reported outcome questionnaires will be collected to provide an assessment of the subject's functional status, well-being, and MDS symptoms over time and to provide estimates of utility to include in future cost effectiveness models.

**SAFETY EVALUATIONS**

Safety will be assessed by adverse events (AEs), physical examinations, clinical laboratory parameters, electrocardiograms, vital sign measurements, ECOG performance status, and concomitant medication usage. The sponsor will review the safety data on an ongoing basis. Additionally, an Independent Data Monitoring Committee (DMC) will be commissioned to monitor safety data during the study. All hepatic adverse events and liver function test abnormalities will also be reviewed at least on a quarterly basis, or more frequently if needed, by an Independent HEC throughout the study.

**PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS**

Samples to assess both the plasma concentration (pharmacokinetics) of imetelstat and the generation of antibodies to imetelstat (immunogenicity) will be obtained.

In Part 1, serial PK sampling on Cycle 1 Day 1 was completed before implementation of Amendment 2. Subjects will have an end-of-infusion blood sample collected on Day 1 of each cycle. Pre-dose blood samples for immunogenicity evaluation will be collected on Day 1 of Cycle 1 and then every 3 cycles thereafter (Day 1 of Cycles 4, 7, 10, etc.).

In Part 2, blood samples will be collected for PK evaluation on Day 1 of Cycle 1 and then at prespecified time points thereafter as indicated in Table 4. Pre-dose blood samples for immunogenicity evaluation will be collected on Day 1 of Cycle 1 and then every 3 cycles thereafter (Day 1 of Cycles 4, 7, 10, etc.).

In Part 2, for subjects participating in the Ventricular Repolarization substudy, serial blood samples for PK evaluation will be collected at C1D1 at prespecified time points, prior to and after start of infusion (SOI) as indicated in the schedule of events in Attachment 11.

**PHARMACODYNAMIC AND BIOMARKER EVALUATIONS**

The exposure-response relationship for key efficacy and safety parameters will be evaluated.

Blood and bone marrow samples will be collected to evaluate the mechanism of action of imetelstat and to determine cytogenetic and mutation changes, including response. Other markers may be assessed to evaluate potential inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to treatment with imetelstat.

## STATISTICAL METHODS

A total of approximately 270 subjects will be enrolled in the study (a total of 57 subjects were enrolled in Part 1, approximately 170 subjects are planned for the main study of Part 2, and approximately 45 subjects are planned for the Ventricular Repolarization substudy of Part 2 with Protocol Amendment 7). The initial cohort of 32 subjects enrolled into Part 1 was expanded with Protocol Amendment 2 to include 25 additional subjects who meet the revised entrance criteria, for 57 subjects in total for Part 1.

On the basis of historical data, RBC TI rate is expected to be approximately 7.5% in subjects with low or intermediate-1 risk MDS without any active treatment. The RBC TI rate with imetelstat treatment is expected to be approximately 30% based on preliminary data from Study CP14B019. The futility criteria before Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (eg, transfusion reduction, erythroid improvement). The assumption was that if the RBC TI rate of 30% with imetelstat treatment is true, the probability of passing the futility criterion would be 97%.

Upon review of the efficacy and safety data observed with the 7.5 mg/kg dose among 32 subjects in the initial cohort of Part 1, a subset of 13 subjects was identified with higher hematologic response rates. These were subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. As of Amendment 2, Part 1 was expanded to include only subjects who meet these criteria, with the goal to confirm the safety and efficacy data seen in this subset and to re-confirm the dose. Twenty-five additional subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide were enrolled for a total of 38 (from 57 enrolled in Part 1) that met these criteria.

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat (Section 1.1.5), Part 2 of the main study will be initiated in subjects with non-del(5q) MDS without prior exposure to either hypomethylating agents or lenalidomide.

In the main study of Part 2, approximately 170 subjects will be randomized in a 2:1 ratio to receive either imetelstat or placebo. Using a 2:1 ratio randomization and a 2-group continuity corrected Chi-square test with 0.05 (2-sided) significance level, 150 subjects are needed to achieve a power of approximately 88% to detect the difference between a RBC TI rate of 30% in the imetelstat group and a RBC TI rate of 7.5% in the placebo group. After correction for a 10% drop-out rate, a total of approximately 170 subjects (115 subjects in the imetelstat group and 55 subjects in the placebo group) will be needed. The overall study power from Part 1 and Part 2 is approximately 85%.

Efficacy data in Part 1 will be descriptively summarized based on the treated population. The proportion of subjects with 8-week RBC TI, 24-week RBC TI, CR, PR, mCR, hematologic improvement, and other binary endpoints will be summarized with percentage along with its 95% 2-sided exact confidence interval. Efficacy data in the main study of Part 2 will be compared between the imetelstat group and the placebo group based on the intent to treat population. Transfusion independence rates will be summarized with frequency and percentage along with a 2-sided 95% confidence interval for each treatment group. The comparison will be based on stratified Cochran-Mantel-Haenszel test adjusting for the stratification factors at a two-sided significance level of 0.05.

Safety variables are to be tabulated by descriptive statistics.

The ECG and concentration-QTc in the Ventricular Repolarization substudy as well as safety and limited efficacy based on the additional 45 evaluable subjects enrolled, will be performed separately from the primary analysis of 170 subjects in the main study of Part 2 (see Attachment 11). These data may only be available after the primary analysis of the main study of Part 2 has already been completed.

# TIME AND EVENTS SCHEDULES

**Table 1: Time and Events Schedule for Part 1 (Open-label, Imetelstat Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before first dose** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit within 30 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| ***Screening*** | | | | | | | | |
| Informed consent | | X | | | | | | |
| Inclusion/exclusion criteria | | X | | | | | | |
| Medical history and demographics | | X | | | | | | |
| ***Study Medication Administration*** | | | | | | | | |
| Dispense/administer study drug | Refers to imetelstat (see Section 6) The screening weight is considered baseline for dose calculation. Recalculate dose if ≥10% weight change from baseline. Dosing should begin within 72 hours of enrollment in IWRS. | | X | | X (D1 only) | X | | |
| ***Safety Assessments*** | | | | | | | | |
| Physical exam (including weight) | Full PE at screening; limited symptom-directed PE thereafter. | X | X | | X (D1 only) | X | X | |
| Vital signs | Includes temperature, HR, SBP and DBP (preferably in a seated position). Measure and record prior to infusion. | X | X | | X (D1 only) | X | X | |
| 12-lead ECG | At screening, at C2D1 and as clinically indicated. | X | | | X (D1 only) | | | |
| ***Efficacy Assessments*** | | | | | | | | |
| Transfusion history and status, myeloid growth factor treatment | Assessment of RBC transfusion requirement 16 weeks prior to C1D1 and at each clinic visit until end of treatment. For subjects who stop treatment before 12 months, continue to collect transfusion data for a minimum of 12 months from C1D1. Sites should make every attempt to obtain complete information, including both in-patient and out-patient transfusions (see Section 9.3.1.1 for additional information). | X | X | | X (D1 only) | X | X | X (every 4-6 weeks) until first transfusion in Posttreatment Follow-up |
| Hematology | Screening tests should be within 14 days prior to C1D1. For C1D1, no need to repeat if the screening tests were performed within 5 days. Refer to the Inclusion Criteria (Section 4.1) for further details. After C1D1, tests must be performed within 48h before the scheduled visit. For all cycles, if tests are repeated on the day of the visit, the most recent results should be reviewed before dosing. Perform unscheduled weekly follow-up after any Grade ≥3 thrombocytopenia or neutropenia until values return to baseline. | X | X | X | X | X | X | X (first visit if feasible) |

**Table 1 Continued: Time and Events Schedule for Part 1 (Open-label, Imetelstat Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before first dose** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit within 30 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| BM aspirate, biopsy | All BM biopsies must be assessed for presence of fibrosis. A BM aspirate and biopsy with iron stain completed up to 12 weeks prior to C1D1 may be used for sponsor confirmation of eligibility; otherwise BM biopsy and aspirate must be done at screening (within 28 days of C1D1). After baseline, BM assessments can be performed with a window of ±7 days. Following PR or CR, aspirate should be repeated 4 to 8 weeks later for confirmatory purposes. If assessment occurred within 8 weeks of EOT a repeat is not required. See below for additional required BM sampling for biomarkers. | X | Aspirate: Every 24 weeks after C1D1, at time of suspected HI-E (Hb), PR, or CR, and every 24 weeks thereafter up to and including suspected PD<br>Biopsy: annually (every 48 weeks after C1D1 in conjunction with BM aspirate) and at suspected PD | | | | | |
| Response assessment | Per IWG 2006; see Attachment 5. Each response assessment requires assessment of peripheral blood and RBC transfusion requirements. Bone marrow analysis is required every 24 weeks, with additional assessments at the time of suspected response or progression. If study drug is discontinued for any reason other than disease progression, refer to Section 9.1.5 | | Every 12 weeks from C1D1 (±1 week) up to week 72, then every 24 weeks until suspected PD | | | | | At suspected PD |
| ECOG performance status | See Attachment 4 | X | X | | X (D1 only) | X | X | |
| Survival status and subsequent therapy | Subsequent therapy collected throughout survival follow-up period. | | | | | | X | X |
| ***Clinical Laboratory Assessments*** | | | | | | | | |
| Chemistry | Screening tests should be performed within 14 days prior to C1D1. For C1D1, no need to repeat if Screening tests performed within 5 days. After C1D1, tests must be performed within 48h before the scheduled visit. Refer to Inclusion Criteria (Section 4.1) for further details. Refer to Sections 9.8 and 9.8.1 for additional detail on required clinical laboratory testing. | X | X | X | X (D1 only) | X | X | |
| Chemistry panel for LFT investigations | Includes GGT, chloride, bicarbonate, magnesium, and fractionated bilirubin. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, repeat chemistry panel and LFT investigations panel weekly until bilirubin with fractionation is <3x ULN, and AST, ALT and ALP is <5x ULN. Subjects with Grade 1 or Grade 2 elevations in AST, ALT, ALP, or bilirubin at time of treatment discontinuation, continue to test monthly until resolution to at least baseline. | | If an adverse event of interest occurs | | | | | |
| INR (or PT) and aPTT | With additional assessments performed during treatment phase if subject has a hemorrhagic event. | X | Repeat during study if subject has a Grade ≥3 bleeding event | | | | | |

**Table 1 Continued: Time and Events Schedule for Part 1 (Open-label, Imetelstat Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before first dose** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit within 30 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| Serum EPO level | Only required during treatment at first suspected response. Repeat assessment is not required if response further improves. | X | At time of suspected HI-E (Hb), PR, CR | | | | | |
| Serum ferritin, transferrin saturation | | X | X | | X (D1 only) | X | X | |
| B12 / folic acid / reticulocytes | | X | | | | | | |
| Hepatitis serologies | Comprehensive hepatitis serology panel A through E. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg). | X | | | | | | |
| Serum or urine pregnancy test | | X | | | | | | |
| ***Pharmacokinetics, Pharmacodynamics and Immunogenicity*** | | | | | | | | |
| Pharmacokinetic / immunogenicity samples | See Table 2, Part 1 PK Time and Events Schedule. If possible, anytime an IRR is observed, a blood sample should be drawn as soon as possible after the IRR for potential immune response and pharmacokinetic analysis. | | X | | X (D1 only) | X (Cycle 4 then every 3 cycles) | X | X (first visit if feasible) |
| TA, TL and hTERT | All subjects in Part 1 will have predose and on treatment samples collected. | | X (predose and 24h postdose) | X (D8 only) | X (D8 only) | At time of suspected PR, CR, and PD | | |
| ***Bone Marrow*** | | | | | | | | |
| BM aspirate for cytogenetics | Local cytogenetics results should be obtained for screening; samples must also be submitted to the central lab. The baseline aspirate sample for the central laboratory may be collected during Screening or before dosing on C1D1. After baseline, BM assessments can be performed with a window of ±7 days. If BM aspiration yields a dry tap, see Section 9.5. | X | At the time of suspected PD for all subjects. For subjects with baseline abnormalities, also at the time of suspected PR, CR, or HI-E (Hb) and every 24 weeks thereafter up to and including suspected PD. Information will be provided to the sites on which subjects will need to have repeat BM aspirate samples. | | | | | |
| BM aspirate for RNA Seq or CyTOF | Samples must be submitted to the central lab for all subjects if collection of the sample is feasible. The baseline aspirate sample may be collected during Screening or before dosing on C1D1. After baseline, BM assessments can be performed with a window of ±7 days. | X | At time of suspected HI-E (Hb), PR, CR, and PD | | | | | |
| ***Biomarkers*** | | | | | | | | |
| Mutation analysis | | | X | At the time of suspected response (CR, PR, HI-E [Hb] or PD | | | | |
| Immunophenotyping | | X | | X (D8 only) | X (D8 only) | At time of suspected PR, CR and PD | | |
| ***Ongoing Subject Review*** | | | | | | | | |
| Concomitant therapy | | X | Continuous | | | | X | |
| Adverse events | | X | Continuous | | | | X | |

Abbreviations: BM=Bone Marrow; C=Cycle; CR=complete remission; CyTOF= cytometry by time of flight ; D=Day; DBP=diastolic blood pressure; EOT=end of treatment; EPO=erythropoietin; GGT=gamma-glutamyl transpeptidase; HI-E (Hb)=hematologic improvement-erythroid (hemoglobin); hTERT=human telomerase reverse transcriptase; HR=heart rate; INR=international normalized ratio; IRR=infusion-related reaction; IWRS=interactive web response system; PD=disease progression; PE=physical exam; PK=pharmacokinetic; PR=partial remission; PT=prothrombin time; SBP=systolic blood pressure; TA=telomerase activity; TL=telomere length; ULN=upper limit of normal

**Table 2: Time and Events for Part 1 Pharmacokinetic / Immunogenicity Sampling (Amendment 2)**

| Study Day | Pharmacokinetic Blood Sampling Time [a] | Pharmacokinetic Blood Sampling | Immunogenicity Evaluation [c,d] |
|---|---|---|---|
| **Cycle 1 Day 1** | 0 (before start of infusion) | | X |
| **Cycle 1 Day 1** | 2h [b] | X | |
| **Cycle 1 Day 1** | 4-5h | X | |
| **Cycle 1 Day 1** | 6h-7h | X | |
| **Day 1 of all subsequent cycles** | 2h [b] | X | |
| **Day 1 of Cycles 4, 7, 10, etc.** | 0 (before the start of the infusion) | | X [d] |
| **End of Treatment** | during the visit | X | X [d] |
| **First Posttreatment Follow-up** | during the first visit | X | X [d] |

Abbreviations: h=hour; PK=pharmacokinetic

a. All samples are collected at the time point relative to the START of the infusion.
b. For the 2-hour time points (relative to the start of the infusion), the pharmacokinetic sample should be taken immediately before the end of the infusion (ie, this includes cases where infusion time is extended beyond 2 hours).
c. An aliquot from the pharmacokinetic sample will be used to assess immunogenicity (separate blood draw not needed). If possible, anytime an IRR is observed, a blood sample should be drawn as soon as possible after the IRR for potential immune response and pharmacokinetic analysis.
d. Beginning at Cycle 4, collect a sample at predose Day 1 and then predose every 3 cycles (Cycles 7, 10, etc.); at the EOT visit, and at the first posttreatment visit.

Note: Ten subjects enrolled in Part 1 completed serial pharmacokinetic sampling before implementation of Amendment 2. The time points for serial PK sampling are provided in Amendment 1.

**Table 3: Time and Events Schedule for Part 2 Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| ***Screening*** | | | | | | | | |
| Informed consent | Refer to Section 9.1.3 for guidance regarding COVID-19 and further clarification of screening procedures. | X | | | | | | |
| Inclusion/exclusion criteria | | X | X | | | | | |
| Medical history and demographics | | X | | | | | | |
| ***Study Medication Administration*** | | | | | | | | |
| Randomization | Randomization will occur on C1D1 or up to 72h prior to study drug administration | | X | | | | | |
| Dispense/administer study drug | Refers to Imetelstat or placebo (see Section 6). The screening weight is considered baseline for dose calculation. Recalculate dose if ≥10% weight change from baseline. Dosing should begin within 72 hours of randomization in IWRS. | | X | | X (D1 only) | X | | |
| ***Safety Assessments*** | | | | | | | | |
| Physical exam (including weight) | Full PE at Screening; limited symptom-directed PE thereafter. Refer to Section 9.8.4 for guidance regarding COVID-19. | X | X | | X (D1 only) | X | X | |
| Vital signs | Includes temperature, HR, SBP and DBP (preferably in a seated position). Measured and recorded prior to infusion. | X | X | | X (D1 only) | X | X | |
| 12-lead ECG | At screening, at C2D1 and as clinically indicated. | X | | | X (D1 only) | | | |
| ***Efficacy Assessments*** | | | | | | | | |
| Transfusion history and status; myeloid growth factor treatment | Assessment of RBC transfusion requirement 16 weeks prior to Randomization and at each clinic visit until the end of treatment. Sites should make every attempt to obtain complete information, including both in-patient and out-patient transfusions (see Section 9.3.1.1 for additional information). Pre-transfusion Hb must be documented.<br>Note: if DE Visit does not align with a Cycle Day 1 visit, then transfusion data must be collected at the DE Visit. | X | X | | X (D1 only) | X | X | X (every 4-6 weeks) until first transfusion in Posttreatment follow-up |

**Table 3 Continued: Time and Events Schedule for Part 2 Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| Hematology (local laboratory) | Screening tests should be within 14 days prior to Randomization. For C1D1, no need to repeat if Screening tests performed within 5 days. Refer to Inclusion Criteria (Section 4.1) for further details. After C1D1, tests must be performed within 48h before the scheduled visit. For all cycles, if tests are repeated on the day of the visit, the most recent results should be reviewed before dosing. Perform unscheduled weekly follow-up after any Grade ≥3 thrombocytopenia or neutropenia until values return to baseline. Testing should be conducted pre-transfusion, if feasible. Hematology panel includes hemoglobin, platelet count, white blood cell count, ANC. Absolute peripheral blast count should be done prior to randomization and on D1 of each cycle only.<br>Note: if DE Visit does not align with a Cycle Day 1 visit, then hematology (local) is required at the DE Visit. | X | X | X | X | X | X | X (first visit if feasible) |
| Hematology (central laboratory) | Hematology panel assessed in central laboratory will be hemoglobin, platelet count, white blood cell count and ANC. Central hematology sample should also be collected pre-transfusion, if feasible.<br><br>Manual absolute peripheral blast count for the central lab should be done prior to randomization and on D1 of each cycle only.<br><br>Note: if DE Visit does not align with a Cycle Day 1 visit, then hematology (central) is required at the DE Visit. | X | X | X | X | X | X | X (first visit if feasible) |

**Table 3 Continued: Time and Events Schedule for Part 2 Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| Study Procedures | Comments | Up to 28 days before Randomization | Cycle 1 Day 1 (predose) | Cycle 1 Day 8, 15, 22 | Cycle 2 Day 1, 8, 15, 22 | Cycle 3 until EOT Day 1 | EOT Visit 30 ±3 days after last dose | Survival Follow-up Every 12-16 weeks |
| BM aspirate, biopsy | A BM aspirate and biopsy with iron stain completed up to 12 weeks prior to Randomization may be used for confirmation of eligibility (assessed both locally and centrally); otherwise BM biopsy and aspirate assessment must be done during screening. After baseline, BM assessments may be performed with a window of ±7 days. Following investigator-assessed CR, PR, or mCR, in subjects with >5% baseline bone marrow aspirate blasts, repeat aspirate 4 to 8 weeks later for confirmatory purposes, if clinically feasible (also see Section 9.1.4).<br>Central Pathology Review: Timely submission of all bone marrow samples (aspirate smear and bone marrow biopsy) to the Independent Central Pathology Reviewer is required for diagnostic confirmation. Local pathology assessments are used for treatment decisions. See below for additional required BM sampling for cytogenics and biomarkers. | X | Aspirate: Every 24 weeks after C1D1, at time of suspected PR, CR, or mCR and every 24 weeks thereafter up to and including suspected PD<br><br>Biopsy: annually (every 48 weeks after C1D1 in conjunction with BM aspirate) and at suspected PD | | | | | |
| Response assessment | Per modified IWG 2006; see Attachment 5 (see Section 11.13 for adjudication of assessments by independent review). Each response assessment every 12 weeks requires review of peripheral blood and RBC transfusion requirements. In addition, bone marrow analysis (including central review) is required every 24 weeks with additional assessments at the time of suspected response or progression. Investigators will use local laboratory and bone marrow results for response evaluations. If study drug is discontinued for any reason other than disease progression, refer to Section 9.1.5. See under Hematology (central laboratory) for hematology panel and peripheral blast count to be used for response assessment.<br>Note: CR, PR or mCR only to be assessed in subjects with >5% baseline bone marrow aspirate blasts. | | Every 12 weeks from C1D1 (±1 week) up to week 72, then every 24 weeks until suspected PD | | | | | At suspected PD |
| ECOG performance status | See Attachment 4 | X | X | | X (D1 only) | X | X | |

**Table 3 Continued: Time and Events Schedule for Part 2 Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| FACT-An | See Attachment 6; At all visits, complete before any tests, procedures, dosing or other consultations are performed and before the subject is informed of any assessment results (eg, hemoglobin values), when possible. | | X | | X (D1 only) | X | X | X (until start of subsequent therapy) |
| EQ-5D-5L | See Attachment 7; At all visits, complete before any tests, procedures, dosing or other consultations are performed and before the subject is informed of any assessment results (eg, hemoglobin values), when possible. | | X | | X (D1 only) | X | X | X (until start of subsequent therapy) |
| QUALMS | See Attachment 8. At all visits, complete before any tests, procedures, dosing or other consultations are performed and before the subject is informed of any assessment results (eg, hemoglobin values), when possible. | | X | | X (D1 only) | X | X | X (until start of subsequent therapy) |
| PGIC | See Attachment 9. At all visits, complete before any tests, procedures, dosing or other consultations are performed and before the subject is informed of any assessment results (eg, hemoglobin values), when possible. | | | | X (D1 only) | X | X | X (until start of subsequent therapy) |
| Survival status and subsequent anti MDS/AML therapy | Survival status and subsequent therapy are planned to be collected at the EOT visit and throughout survival follow-up period at least every 12 to 16 weeks (data may be collected more frequently, if needed). | | | | | | X | X |
| ***Clinical Laboratory Assessments*** | | | | | | | | |
| Chemistry (local laboratory) | Screening tests should be performed within 14 days prior to Randomization. For C1D1, no need to repeat if Screening tests performed within 5 days. After C1D1, tests must be performed within 48h before the scheduled visit. Refer to Inclusion Criteria (Section 4.1) for further details. Refer to Sections 9.8 and 9.8.1 for additional detail on required clinical laboratory testing. | X | X | X | X (D1 only) | X | X | |
| Chemistry panel for LFT investigations (local laboratory) | Includes GGT, chloride, bicarbonate, magnesium, and fractionated bilirubin. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, repeat chemistry panel and LFT investigations panel weekly until bilirubin with fractionation is <3x ULN, and AST, ALT and ALP is <5x ULN. Subjects with Grade 1 or Grade 2 elevations in AST, ALT, ALP or bilirubin at time of treatment discontinuation should continue to have tests monthly until resolution to at least baseline grade or until the start of subsequent therapy, whichever comes first. | | If an adverse event of interest occurs | | | | | |
| INR (or PT) and aPTT (local laboratory) | With additional assessments performed during treatment phase if subject has a hemorrhagic event. | X | Repeat during study if subject has a Grade ≥3 bleeding event | | | | | |
| Serum EPO level (local laboratory) | Only required during treatment at first suspected response. Repeat assessment is not required if response further improves. | X | At time of suspected HI-E (Hb), PR, CR | | | | | |

**Table 3 Continued: Time and Events Schedule for Part 2, Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 until EOT Day 1** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| Serum ferritin, transferrin saturation (local laboratory) | Total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site. | X | X | | X (D1 only) | X | X | |
| B12 / folic acid / reticulocytes (local laboratory) | | X | | | | | | |
| Hepatitis serologies | Comprehensive hepatitis serology panel A through E. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg). If the subject screening window is >28 days (Section 9.1.3), hepatitis screening results may still be used to determine eligibility outside of the initial 28-day screening period provided the subject is asymptomatic and does not meet Exclusion Criteria no. 12 (Section 4.2). | X | | | | | | |
| Serum or urine pregnancy test | | X | | | X (D1 only) | X | X | |
| ***Pharmacokinetics, Pharmacodynamics and Immunogenicity*** | | | | | | | | |
| Pharmacokinetic/ Immunogenicity samples | See Table 4, Part 2 PK Time and Events Schedule. | | Refer to Table 4. | | | | | |
| TL | Collection of samples for TL assessments will be done at baseline (C1D1) only. | | X (predose) | | | | | |
| TA, and hTERT | Collection of samples for TA and hTERT assessments will be done at C1D1 predose, 24h post-dose, C1D8, C2D1, C2D8. | | X (predose and 24h post-dose) | X (at D8 only) | X (at D1 [predose] and D8 only) | | | |
| ***Bone Marrow*** | | | | | | | | |
| BM aspirate for cytogenetics (central laboratory) | Baseline aspirate for cytogenetics should be obtained during screening and must be submitted to the central laboratory to confirm eligibility.<br>If results are available from cytogenetic assessment within 12 weeks prior to Randomization, or if aspiration yields a dry tap, peripheral blood sample (instead of a bone marrow sample) may be submitted for central cytogenetic assessment at screening.<br>Central or local cytogenetics may be used for eligibility and stratification purposes. After baseline, BM assessments may be performed with a window of ±7 days. | X | | Aspirate is required for all subjects with baseline abnormalities every 24 weeks after C1D1, at the time of suspected PR, or CR and every 24 weeks thereafter up to and including suspected PD. Sample should be obtained at the time of suspected PD for all subjects irrespective of baseline status. Information will be provided to the sites on which subjects will need to have repeat BM aspirate samples. | | | | |
| BM aspirate for RNA Seq or CyTOF (if feasible) | Samples must be submitted to the central lab for all subjects if collection of the sample is feasible. The baseline aspirate sample may be collected during Screening or before dosing on C1D1. After baseline, BM assessments can be performed with a window of ±7 days. | X | | At time of suspected PR, CR, mCR, and PD | | | | |

**Table 3 Continued: Time and Events Schedule for Part 2, Main Study (Double-blind, Randomized 2:1, Imetelstat or Placebo Treatment)**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | Posttreatment Follow-up Phase | |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose)** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 Day 1 until EOT** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| ***Biomarkers*** | | | | | | | | |
| Mutation analysis | | | X | Every 12 weeks after C1D1, at time of suspected response HI-E(Hb), PR, mCR or CR and at time of PD | | | | |
| ***Ongoing Subject Review*** | | | | | | | | |
| Concomitant therapy | | X | | Continuous | | | X | |
| Adverse events | | X | | Continuous | | | X | |
| Medical Resource Utilization | Data associated with medical encounters (not protocol specified), will be collected for all subjects throughout the study from the time of first dose until the EOT or 30 days after the last dose of study drug, whichever occurs later. | | | Continuous | | | X | |

Abbreviations: AML = acute myeloid leukemia; BM=Bone Marrow; C=Cycle; CR=complete remission; CyTOF=cytometry by time of flight ; D=Day; DBP=diastolic blood pressure; EOT=end of treatment; EPO=erythropoietin; EQ-5D-5L=EuroQol-EQ-5D-5L; FACT-An= Functional Assessment of Cancer Therapy - Anemia-Related Effects; HI-E (Hb)=hematologic improvement-erythroid (hemoglobin); HR=heart rate; GGT= gamma-glutamyl transpeptidase; hTERT = human telomerase reverse transcriptase; INR=international normalized ratio; IRR=infusion-related reaction; IWRS=interactive web response system; mCR=marrow complete remission; MDS = myelodysplastic syndrome; PD=disease progression; PE=physical exam; PGIC= Patient Global Impression of Change; PK=pharmacokinetic; PR=partial remission; PT=prothrombin time; QUALMS= Quality of Life in Myelodysplasia Scale; SBP=systolic blood pressure; TA=telomerase activity; TL=telomere length; ULN=upper limit of normal

**Table 4: Time and Events for Part 2, Main Study Pharmacokinetic / Immunogenicity Sampling**

| Study Day | Pharmacokinetic Blood Sampling Time [a] | Pharmacokinetic Blood Sampling | Immunogenicity Evaluation |
|---|---|---|---|
| Cycle 1 Day 1 | 0 (before start of infusion) | | X |
| Cycle 1 Day 1 | 2h[b] (end of infusion) | X | |
| Cycle 1 Day 1 | 4-5 h | X | |
| Cycle 1 Day 1 | 6-7 h | X | |
| Day 1 of all subsequent cycles | 2h [b] (end of infusion) | X | |
| Day 1 of Cycles 4, 7, 10, etc. | 0 (before the start of the infusion) | | X |
| If IRR is observed | As soon as possible after IRR is observed | X | X [c] |
| End of Treatment | During the visit | | X |
| First Posttreatment Follow-up, if feasible | During the first visit | | X |

a. All samples are collected at the time point relative to the START of the infusion.
b. For the 2-hour time points (relative to the start of the infusion), the pharmacokinetic sample should be taken immediately before the end of the infusion (ie, this includes cases where infusion time is extended beyond 2 hours).
c. An aliquot from the pharmacokinetic sample will be used to assess immunogenicity (separate blood draw not needed).

**Table 5 Time and Events Schedule for Extension Phase**

| Study Procedures | Comments | All Subjects | Extended Treatment (4-week cycles ± 3 days) | EOT Visit 30 ± 3 days after last dose | Extended Follow-up (Every 16 weeks ± 7 days from EOT Visit) |
|---|---|---|---|---|---|
| Informed Consent | All subjects must provide informed consent to enter the Extension Phase. This must occur before the first dose of imetelstat for subjects continuing treatment in the Extension Phase, or before the first extended follow-up assessment for subjects continuing in the Extended Follow-up Phase. | X | | | |
| Dispense/administer study drug | Refer to imetelstat Section 6 for dose modification requirements. Investigator should assess chemistry and hematology results prior to dosing. | | X (Day 1) | | |
| Directed physical exam (including weight) | Limited symptom-directed physical exam. Refer to Section 9.8.4 for guidance regarding COVID-19. | | X | X | |
| Vital signs | Includes temperature, heart rate, SBP, and DBP (preferably in a seated position). Measured and recorded prior to infusion. | | X | X | |
| Transfusion status; myeloid growth factor treatment | Sites should make every attempt to obtain complete information, including both in-patient and out-patient transfusions (see Section 9.3.1.1 for additional information). Pre-transfusion Hb must be documented. | | X | X | X (until first transfusion in Extended Follow-up) |
| Chemistry (local laboratory) | Tests must be performed within 48 hours before the scheduled visit. Refer to Inclusion Criteria (Section 4.1) for further details. Refer to Sections 9.8 and 9.8.1 for additional detail on required clinical laboratory testing. | | X | X | |
| Hematology (local laboratory) | Tests must be performed within 48 hours before the scheduled visit. For all cycles, if tests are repeated on the day of the visit, the most recent results should be reviewed before dosing. Perform unscheduled weekly follow-up after any Grade ≥3 thrombocytopenia or neutropenia until values return to baseline. Testing should be conducted pre-transfusion, if feasible. Hematology panel includes hemoglobin, platelet count, white blood cell count, ANC. Absolute peripheral blast count should be done on D1 of each cycle. | | X | X | |

| Study Procedures | Comments | All Subjects | Extended Treatment (4-week cycles ± 3 days) | EOT Visit 30 ± 3 days after last dose | Extended Follow-up (Every 16 weeks ± 7 days from EOT Visit) |
|---|---|---|---|---|---|
| Chemistry panel for LFT investigations (local laboratory) | Includes GGT, chloride, bicarbonate, magnesium, and fractionated bilirubin. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, repeat chemistry panel and LFT investigations panel weekly until bilirubin with fractionation is <3x ULN, and AST, ALT and ALP is <5x ULN. Subjects with Grade 1 or Grade 2 elevations in AST, ALT, ALP or bilirubin at time of treatment discontinuation should continue to have tests monthly until resolution to at least baseline grade or until the start of subsequent therapy, whichever comes first. | | If an adverse event of interest occurs | | |
| INR (or PT) and aPTT (local laboratory) | Additional assessments performed during treatment phase if subject has a hemorrhagic event. | | Repeat during study if subject has a Grade ≥3 bleeding event | | |
| Serum or urine pregnancy test | | | X | X | |
| Concomitant Therapy | | | X | X | |
| Adverse Events | Adverse events, including SAE, pregnancy, and AEI monitoring, will continue in the Extension Phase | | X | X | |
| Survival Status and Subsequent Anti-MDS/AML Therapy | Survival status and subsequent therapy are planned to be collected throughout the survival follow-up approximately 16 weeks (data may be collected more frequently, if needed). | | | X | X |
| Disease Progression Follow-up | Per modified IWG 2006; see Attachment 5. Data to be collected includes date of disease progression to AML, and any available supporting bone marrow, peripheral blast, and laboratory results. | | Continuous | | Until progression to AML |

AE = adverse event; AEI = adverse event of interest; AML = acute myeloid leukemia; DBP = diastolic blood pressure; EOT = end of treatment; IWG = International Working Group; MDS = myelodysplastic syndrome; q = every; SAE = serious adverse event; SBP = systolic blood pressure

## ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AEI | adverse events of interest |
| aPTT | activated partial thromboplastin time |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BM | bone marrow |
| CFU-MK | colony-forming unit-megakaryocyte |
| $C_{max}$ | maximum plasma concentration |
| CMML | chronic myelomonocytic leukemia |
| CR | complete remission |
| CRF | case report form |
| CSC | circulating stem cells |
| CyTOF | cytometry by time of flight |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOT | end of treatment |
| EPO | erythropoietin |
| EQ-5D-5L | EuroQol-EQ-5D-5L |
| ESA | erythropoiesis-stimulating agent |
| ET | essential thrombocythemia |
| FAB | French-American-British |
| FACT-An | Functional Assessment of Cancer Therapy - Anemia-Related Effects |
| FACT-G | Functional Assessment of Cancer Therapy - General |
| FDA | Food and Drug Administration |
| G-CSF | granulocyte-colony stimulating factor |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| β-hCG | beta human chorionic gonadotropin |
| Hb | hemoglobin |
| HEC | Hepatic Expert Committee |
| HI-E | hematologic improvement-erythroid |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| hTERT | human telomerase reverse transcriptase |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| INR | international normalized ratio |
| IP | investigational product |
| IPSS | International Prognostic Scoring System |
| IPSS-R | Revised International Prognostic Scoring System |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee (see Section 11.13) |
| IRR | infusion-related reaction |
| ITT | intent to treat |
| IV | intravenous |
| IWG | International Working Group |
| IWG 2006 | International Working Group Response Criteria 2006 |
| IWG-MRT | International Working Group – Myeloproliferative Neoplasms Research and Treatment |
| IWRS | interactive web response system |
| LFT | liver function tests |
| mCR | Marrow complete remission |
| MDS | myelodysplastic syndrome(s) |

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | myelofibrosis |
| Modified IWG 2006 | Proposed modification of IWG 2006 response criteria in myelodysplasia |
| NASH | nonalcoholic steatohepatitis |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| OS | overall survival |
| PD | progressive disease / disease progression |
| PE | physical exam |
| PFS | progression free survival |
| PGIC | Patient Global Impression of Change |
| PK | pharmacokinetics |
| PQC | product quality complaint |
| PR | partial remission |
| pRBC | packed red blood cell |
| PRO | patient-reported outcome(s) |
| PT | prothrombin time |
| qRT-PCR | quantitative real-time polymerase chain reaction |
| QTcB | QT interval by Bazett's correction method |
| QTcF | QT interval by Fridericia's correction method |
| QUALMS | Quality of Life in Myelodysplasia Scale |
| RBC | red blood cell |
| RNA | ribonucleic acid |
| SAP | statistical analysis plan |
| SIPM | Site Investigational Product Manual |
| TA | telomerase activity |
| TI | transfusion independence |
| TIC | tumor inducing cell |
| TL | telomere length |
| TQT | Thorough QT study |
| ULN | upper limit of normal |
| WHO | World Health Organization |
| WPSS | WHO Classification-Based Prognostic Scoring System |

# 1. INTRODUCTION

For the most current comprehensive nonclinical and clinical information regarding imetelstat, including information on adverse drug reactions, refer to the latest version of the Investigator's Brochure (IB) and IB Addenda for imetelstat.[25]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

## 1.1. Background

### 1.1.1. Telomeres and Telomerase

Telomeres consist of tandem repeats of the deoxyribonucleic acid (DNA) sequence TTAGGG, forming a T-loop structure to cap the ends of all mammalian chromosomes. Capping prevents chromosomal fusion and prevents their ends from being misinterpreted as DNA double-strand breaks.[36] Normal somatic cells have relatively long telomeres (approximately 9 to 12 kilobases) and typically do not express detectable levels of telomerase. Telomeres shorten approximately 50 to 120 nucleotides at each cell division.[21,18] When telomeres get critically short, they can no longer cap the chromosome ends, thus destabilizing the T-loop and exposing a 3' overhang which triggers a DNA damage signal, ultimately resulting in senescence, terminal differentiation, or apoptosis. Telomere loss is prevented by the presence of the enzyme telomerase, which consists of 2 essential components: the human telomerase ribonucleic acid (RNA) template (hTR) and the human telomerase reverse transcriptase (hTERT) catalytic subunit. Telomerase counters telomere loss by the addition of TTAGGG repeats to the chromosome ends.[19]

### 1.1.2. Imetelstat

Imetelstat (GRN163L) is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. Telomerase inhibition leads to loss of a cancer cell's ability to maintain telomere length (TL), resulting in cell-cycle arrest, apoptosis, or senescence. Imetelstat binds with high affinity to the template region of the RNA component of hTERT and is a competitive inhibitor of telomerase enzymatic activity.[2,23] Treatment of various cancer cells with imetelstat in vitro increases their sensitivity to radiation, decreases their clonogenic potential, and results in altered expression of stem-cell related genes.[12,20]

#### 1.1.2.1. Rationale for use of Imetelstat in Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is characterized by clonal myeloproliferation that arises from malignant progenitor cell clones that have shorter telomeres and multiple clonal genetic abnormalities. Telomerase is highly activated and continually upregulated in malignant progenitor clones enabling continued and uncontrolled proliferation. While telomerase activity (TA) is generally undetectable in normal somatic cells, it is expressed in approximately 85% of human cancers as well as in cancer progenitor cells, which are believed to play a critical role in dysregulated cell growth and tumor metastasis.[20] In MDS, TA and expression of hTERT, a key catalytic subunit of telomerase, are significantly increased as compared to healthy controls.[4,5] Myelodysplastic syndrome patients with high TA have been shown to have a significantly shorter

overall survival (OS) as compared to those with lower TA.[17] In addition, the average TL has been shown to be significantly shorter in MDS patients as compared to healthy controls,[30,40] and progression of the disease and conversion of MDS to acute myeloid leukemia (AML) are connected with progressive decrease in TL.[43] Several studies showed that higher TA and hTERT, and shorter TL correlate with International Prognostic Scoring System (IPSS) risk score in MDS.[5,38,52] In low risk MDS patients, in addition to other factors, short telomeres and high TA were also reported as poor prognostic features.[37,51] Given the role of TA in preventing cell senescence and apoptotic cell death in immortalized cells such as tumor cells,[24] inhibition of TA constitutes an attractive therapeutic approach in MDS.

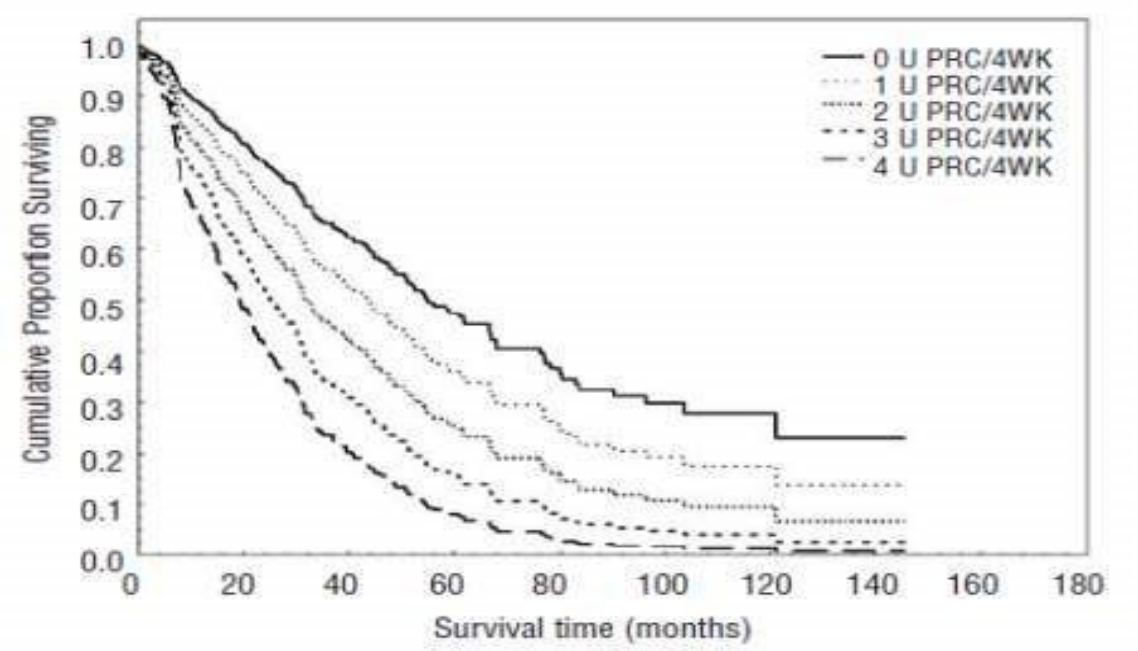
### 1.1.3. Myelodysplastic Syndromes

Myelodysplastic syndromes constitute a heterogeneous form of blood cancer that primarily affects the elderly and are characterized by anemia and other cytopenias and a high risk of leukemic transformation.[7] In routine clinical practice, MDS are suspected when an otherwise unexplained anemia is associated with other cytopenias, increased mean corpuscular volume, or increased red cell distribution width. Diagnosis requires bone marrow examination and cytogenetic studies. The bone marrow is typically hyperproliferative. The diagnosis is based on demonstration of erythroid, granulocyte, or megakaryocyte dysplasia in 10% or more of informative cells.[50] The natural history of MDS includes transformation to AML in a proportion of patients.

The standard prognostic tool in MDS is the IPSS, which classifies patients into low, intermediate-1, intermediate-2, and high risk categories on the basis of the percentage of bone marrow blasts, the karyotype, and the number of cytopenias. The median survival rates for the low, intermediate-1, intermediate-2, and high risk categories are estimated at 5.7, 3.5, 1.2, and 0.4 years, respectively. The estimated times for 25% to transform to AML by prognostic group are 9.4, 3.3, 1.1 and 0.2 years, respectively.[7,15] Other prognostic systems have also been described, namely the World Health Organization (WHO) Classification-Based Prognostic Scoring System (WPSS)[35] and the Revised International Prognostic Scoring System (IPSS-R).[16] The IPSS is more frequently referenced in clinical studies. Patients with low and intermediate-1 risk MDS are also often referred to as having “lower-risk” disease, whereas those with intermediate-2 and high risk MDS are referred to as patients with “higher-risk” disease.

Many anemic patients with MDS eventually develop dependence on packed red blood cell (pRBC) transfusions.[45] In a cohort of patients in Italy, the nonleukemic causes of death were: cardiac events, including cardiomyopathies and arrhythmias (50%); infection (30%); bleeding complications (8%); and liver cirrhosis (8%).[34,35] Examination of these cases suggests that iron overload after chronic transfusions may be a contributing factor in the overall morbidity of the disease. The development of transfusion dependence and iron overload (as measured by serum ferritin) was associated with further worsening of OS and leukemia-free survival in addition to the known risk factors associated with MDS WHO subtype and cytogenetics.[34] Further evaluations have indicated that a transfusion requirement of 2 units per month reduces the life expectancy of a patient with MDS by approximately 50% (Figure 1).[33] The use of iron chelation therapy may ameliorate some of the consequences of iron overload. However, its use in this setting is not universal.[49]

**Figure 1: Survival According to Intensity of Red Blood Cell Transfusion Requirement**




Survival of MDS patients according to the intensity of their RBC transfusion requirement, calculated as the number of packed red cell units per month (U PRC/4WK) (data obtained from 426 patients diagnosed with MDS according to WHO criteria at the IRCCS Policlinico San Matteo, Pavia, Italy, between 1992 and 2004). The between-group comparison was performed by applying a Cox proportional hazard regression model with time dependent covariates.[34]

### 1.1.4. Treatment Options for Myelodysplastic Syndromes

For most patients with IPSS low and intermediate-1 risk MDS, the initial approach to treatment remains supportive care, aimed at alleviating cytopenias. This can be accomplished through transfusions or the use of erythropoiesis-stimulating agents (ESAs) or other hematopoietic growth factors. Among anemic patients with low and intermediate-1 risk MDS and anemia treated with ESAs, approximately 40% will achieve an International Working Group (IWG) defined hematologic improvement for a median duration of 2 years. The Nordic MDS group has developed a model which identifies patients more likely to respond to ESAs. Those with low or absent transfusion requirement (<2 pRBC units/month) and a low serum erythropoietin level (<500 mU/mL) have a higher response rate than those with high transfusion needs (≥2 units/month) and elevated serum erythropoietin levels (≥500 mU/mL); 74% versus 7%, respectively.[22]

Treatment options after ESA failure (primary resistance or relapse after a response) in patients who remain with a low or intermediate-1 IPSS score for MDS are limited. Most patients eventually require long-term RBC transfusions. Early ESA failure (no response to ESA or relapse within 6 months) appears to be a marker of disease severity and is associated with frequent subsequent AML progression (12-20% over 5 years) and a median survival of approximately 3.5 years.[9,28]

Lenalidomide is approved by both the United States Food and Drug Association (FDA) and the European Medicines Agency for the treatment of lower risk (IPSS low and intermediate-1), transfusion-dependent MDS patients with the del(5q) chromosomal abnormality. In Phase 2 and

Phase 3 registration studies, approximately 60% of subjects achieved durable (>24 weeks) independence from RBC transfusions. The median duration of response was approximately 2 years. Myelosuppression (neutropenia 51-55%; thrombocytopenia 23-44%) was the most frequently reported Grade 3 or 4 toxicity.[10,31] Phase 2 and Phase 3 studies have also been conducted in transfusion-dependent MDS subjects who did not have the del(5q) abnormality. Rates and durability of transfusion independence (TI) were lower than those observed in the cohorts with the del(5q). Approximately one-quarter of subjects (27%) who received lenalidomide achieved RBC TI, with median duration of response ranging from 33 to 41 weeks.[39,41] In the placebo controlled Phase 3 study, only 3% of placebo-treated subjects achieved TI lasting at least 8 weeks.

In contrast to lower-risk MDS, poorer OS and more rapid progression to AML that characterizes higher-risk MDS warrant the initiation of disease-modifying therapy. In this setting, 2 hypomethylating agents (azacitidine or decitabine) are used as single agents. The postulated mechanism of action is the reversal of aberrant methylation of tumor suppressor genes that are common in higher-risk MDS.[26,42] In a Phase 3 study in which decitabine was compared with supportive care, 17% of patients achieved complete remission (CR) or partial remission (PR) according to IWG criteria, and another 13% showed hematologic improvement.[27] When azacitidine was evaluated in a randomized study of MDS subjects (higher-risk and lower-risk with significant cytopenias) and compared to supportive care, 14% of subjects achieved CR or PR and an additional 30% showed hematologic improvement based on IWG criteria.[44]

These hypomethylating agents are also used in lower risk MDS patients with multiple cytopenias, frequently after failure of other agents. Low-dose decitabine has been evaluated in 2 Phase 2 studies. In 1 study, decitabine was given at a dose of 20 mg/m$^2$ for 3 days per 28-day cycle to 65 subjects with lower risk MDS, of whom 22% achieved an IWG response (per modified IWG 2006).[14] In the other study, decitabine was administered at 3.5 to 7 mg/m$^2$ 1-3 times weekly to 25 subjects, of whom 47% achieved an IWG response.[32]

Oral azacitidine has been evaluated in 1 study of 41 subjects, of whom 48% had lower risk disease. Among the 32 enrolled subjects with MDS, 35% of previously treated and 60% of first-line-treated subjects had an overall response (CR, hematologic improvement, or RBC/platelet TI). This drug is being explored in the Phase 3 setting.[13]

### 1.1.5. Clinical Experience with Imetelstat in Myeloproliferative Neoplasms and MDS

Study CP14B015 (Phase 2) was the first proof of concept study in hematological malignancies. Subjects with essential thrombocythemia (ET) who were resistant to, intolerant of or had refused conventional therapies were enrolled. Imetelstat induced and maintained hematologic responses in 100% of the subjects, with 16 of 18 (89%) achieving a CR. Importantly, 7 of 8 subjects with the JAK2V617F mutation achieved partial molecular response with 72% to 96% reduction in allele burden.[3]

An open-label, Phase 2 study (CP14B019) was conducted to evaluate the safety and efficacy of single-agent imetelstat in multiple dosing cohorts in 60 subjects with myelofibrosis (MF). Additional cohorts enrolled subjects with MDS (N=9) and blast-phase MF (N=9). Among the 33 MF subjects treated with 9.4 mg/kg imetelstat every 3 weeks (Arm A) or 9.4 mg/kg imetelstat on Days 1, 8, 15, 22 and then every 3 weeks (Arm B), the median duration of treatment was 8.6 months (range 1.4 to 21.7 months) as of December 2014. Twelve of the 33 subjects (36.4%) achieved an overall response (CR, PR, or clinical improvement) as defined by the 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria. Of note, 7 subjects were in remission (defined as CR+PR) including 4 subjects with a CR. Additionally, 5 subjects (15.2%) had clinical improvement.[48] The 9 subjects in the MDS cohort were given a starting imetelstat dose of 7.5 mg/kg every 4 weeks. Median age was 70 years; 78% were male. This was lower than the dose given to the MF subjects to minimize the risk for myelosuppression in subjects with an already compromised bone marrow. All were anemic (hemoglobin [Hb]<10 g/dL) and 8 of the 9 subjects were considered to be transfusion dependent prestudy (per modified IWG 2006 criteria for MDS). Baseline IPSS scores were intermediate-1 (7 subjects) and intermediate-2 (2 subjects). Seven of these subjects had received prior treatments, including 6 who previously received ESAs. Additional treatments received by less than one-third of the cohort included lenalidomide, a Janus kinase inhibitor, hydroxyurea and hypomethylating agents.

As of 10 May 2015 (CP14B019), the median duration of treatment with imetelstat was 13.7 months (range 6.6-17.9). Three subjects who had been deemed transfusion dependent prestudy became transfusion independent during treatment, defined as not requiring transfusions for at least 8 weeks.[47] Among these 3 subjects, the transfusion independent interval started between Weeks 9 and 14, and the durations of TI were 9, 24 and 28 weeks. Hemoglobin increase of ≥1.5 g/dL above baseline following a transfusion-free period of at least 28 days was achieved by 4 subjects and occurred at Weeks 16 (in 2 subjects), 19, and 32. Hemoglobin increase of ≥1.5 g/dL after a transfusion-free period of ≥14 days was also observed in 4 subjects at Weeks 12, 16, 17, and 21. Three subjects who met both criteria went on to become transfusion independent; 2 others had only transient increases in Hb.

A comprehensive summary of the clinical data is provided in the Investigator's Brochure (Edition 14).[25]

Data from Part 1 of the current study demonstrated activity of imetelstat in subjects with MDS with higher rates of red blood cell (RBC) TI in subjects with non-del(5q).[11,46] In the initial cohort of 32 MDS subjects, RBC TI was observed in 11 (34%) subjects, with a higher rate of RBC TI in 7 of the 13 (54%) subjects with non-del(5q) MDS and no prior lenalidomide or hypomethylating agent therapy. The study was amended to include only these subjects. As of the clinical cut-off date of 26 October 2018, 38 subjects (13 original and 25 additional) who had non-del(5q) MDS and no prior lenalidomide or hypomethylating agent therapy were enrolled and dosed with imetelstat. The median follow-up for the initial 13 subjects was 29.1 months and 8.7 months for the additional 25 subjects. The median number of treatment cycles was 8 (range, 1-34) and the median dose intensity was 6.9 mg/kg/cycle. The median baseline transfusion burden was 8 units/8 weeks (range, 4-14 units). The 8-week and 24-week were 14/38 (37%) subjects, and 10/38 (26%) subjects, respectively. The median time to onset of RBC TI was 8.1 weeks (range 0.1-33.1 weeks) and the median duration of RBC TI has not been achieved (17 weeks- not estimated [NE]). The mean relative reduction of RBC transfusion burden was 68%, and 8 subjects (21%) had responses by modified IWG 2006 criteria (complete remission [CR]+ marrow CR + partial remission [PR]). The 24-week RBC TI responses were accompanied by a Hb rise of ≥3 g/dL. The HI-E rate was 71%.

#### 1.1.5.1. Clinical Pharmacology of Imetelstat

Single-dose kinetics showed dose dependent increases in exposure at the 6 mg/kg to 11.7 mg/kg range with half-life ranging from 4 to 5 hours. At the 6 mg/kg to 11.7 mg/kg range, imetelstat clearance appears to be independent of dose. The excretion and metabolism of imetelstat has not been evaluated in the clinical setting. However, it is anticipated that imetelstat is predominantly metabolized in systemic circulation and its component fragments are excreted mainly via the urinary tract, as observed for other oligonucleotides.

#### 1.1.5.2. Clinical Safety of Imetelstat

A detailed summary of safety is provided in the Investigator's Brochure (Edition 14).[25]

##### 1.1.5.2.1. Hematologic Toxicities

Cytopenias, in particular thrombocytopenia, are dose-limiting in both single-agent imetelstat studies and when imetelstat is combined with other chemotherapy. The frequency and severity of all cytopenias, particularly thrombocytopenia and neutropenia, was associated with the dose intensity (dose and frequency of dosing) of imetelstat, concomitant administration with other cytotoxic agents, the number and nature of prior chemotherapy regimens to which subjects had been exposed, and low marrow reserve.

In Study CP14B019 (as of the clinical cutoff date of 10 May 2015), among the 9 subjects with MDS, the incidence of treatment-emergent Grade 3 and Grade 4 thrombocytopenia was 22.2% and 11.1%, respectively.[47] Treatment-emergent Grade 3 and Grade 4 neutropenia occurred in 44.4% and 22.2% of the MDS subjects, respectively.[25] None of the Grade 3 or Grade 4 hematologic events lasted ≥4 weeks and all demonstrated reversibility. Despite several subjects having nadir absolute

neutrophil count (ANC) values below 1.0 x $10^9$/L, no serious infections were reported (data on file).

The incidence of treatment-emergent Grade 3 and 4 thrombocytopenia in the MF cohort (n=33) was 27.3% and 21.2%, respectively. Twelve (36.3%) subjects with MF required dose reduction, and 2 discontinued following these events. One subject died after suffering intracerebral hemorrhage in the setting of Grade 4 thrombocytopenia and febrile neutropenia. The incidence of treatment-emergent Grade 3 and 4 neutropenia in the MF cohort was 20.5% and 12.8%, respectively. Seven subjects with MF required dose reduction following Grade 3 or 4 neutropenia, but none discontinued due to this event. Grade 3 treatment-emergent anemia occurred in 52.6% of subjects with MF; no Grade 4 treatment-emergent anemia was reported.

In Part 1 of the current study, Grade 3 or higher neutropenia was observed in 34/57 enrolled subjects (59.6%). Grade 3 or higher thrombocytopenia was observed in 31/57 enrolled subjects (54.4%) and anemia in 10/57 enrolled subjects (17.5%). Most of the cytopenias were manageable with dose modifications and resolved in approximately 4 weeks. Three subjects (5.3%) had febrile neutropenia. In general, cytopenia was managed by cycle delays and dose reduction.[11,46]

#### 1.1.5.2.2. Non-Hematologic Toxicities

In Study CP14B019, the incidence of severe (Grade 3 or greater) non-hematologic adverse events was low. Grade 3 or higher events that occurred in at least 5% of all eligible subjects treated (n=78) were: fatigue (9.0%), lung infection (7.7%), hyperkalemia (6.4%), and atrial fibrillation, hypotension and heart failure (5.1% for each). Within the MDS cohort, the following ≥Grade 3 events occurred in 1 subject each: fatigue and aspiration. One subject had 3 cardiac events of Grade 3 or higher [Grade 3 heart failure, Grade 3 hypotension, and Grade 5 (fatal) cardiac arrest]; this same subject also had other Grade 3 non-hematologic adverse events of duodenal ulcer, hyperglycemia, hypoalbuminemia and hypocalcemia.[25]

In Part 1 of the study Grade 3 or higher treatment-emergent adverse events were reported in 46 of the 57 enrolled subjects (80.7%). Increased liver enzymes were reported in 3 (5.3%), back pain in 3 (5.3%), bronchitis, cellulitis, hyponatremia and iron overload in 2 (3.5%) subjects each. Other events occurred in 1 subject only and no specific trends in adverse events was noted (data on file).[25]

#### 1.1.5.2.3. Hepatotoxicity

The adverse events of concern in the clinical studies thus far have been liver function test (LFT) abnormalities or clinical hepatic adverse events.

Among the 9 subjects with MDS, no Grade 3 or 4 LFT abnormalities were reported. The frequencies of Grade 1 or 2 abnormalities were: alanine aminotransferase (ALT) 67%, aspartate aminotransferase (AST) 67%, alkaline phosphatase (ALP) 33.3% and total bilirubin 11%.[47] The CP14B019 study is ongoing and LFT monitoring continues. Reversibility of liver function test abnormalities was demonstrated. Following cessation of imetelstat in the ET/ polycythemia vera and multiple myeloma subjects, there were no new liver-related adverse events and the LFT abnormalities resolved in the majority of the subjects whose data were available. However, the

clinical significance and long-term consequences of the abnormal hepatic biochemistry findings with ongoing treatment remain unknown at this time. Severe hepatobiliary events, including acute hepatic failure and cirrhosis have been observed and relationship to imetelstat cannot be excluded.

Among the 33 subjects with MF in Study CP14B019, worsening in AST (60.6%) is the most commonly reported treatment emergent LFT parameter, followed by ALP (57.6%), total bilirubin (48.5%), and ALT (42.4%). Most LFT abnormalities were Grade 1 and Grade 2, with only 3 subjects experiencing Grade 3 events (2 subjects with ALP and 1 subject with total bilirubin). No subject had Grade 3 or higher AST or ALT elevation. No hepatic adverse events attributed to imetelstat in MF subjects were reported and no treatment discontinuations or delays were due to LFT abnormalities.

In Part 1 of the study, there were no elevation of LFTs consistent with Hy's Law in any of the enrolled subjects. Of the 38 subjects in the target population, 3 (8%) subjects had reversible Grade 3 LFT elevations and none of the LFT increases were considered to be drug-related by an Independent Hepatic Expert Committee.

## 1.2. Overall Rationale for the Study

Limited treatment options are available for RBC transfusion dependent, IPSS low or intermediate-1 risk MDS patients who are considered poor candidates for ESA treatment (due to having both high levels of endogenous erythropoietin [EPO] and transfusion dependency) or who have already received at least 1 prior treatment with an ESA without achieving or maintaining a response. The median survival for low-risk MDS patients for whom ESA treatment has failed is about 3.5 years, which is considerably shorter than predicted at the time of diagnosis. Therefore, there remains a highly unmet need for effective treatments for these patients.

Imetelstat, a first-in-class telomerase inhibitor, with its novel mechanism of action, may provide clinical benefit to MDS patients. Imetelstat has a long half-life and is preferentially distributed in the bone marrow, spleen and plasma. Imetelstat accumulates in bone marrow, has the ability to target circulating stem cells (CSCs) and tumor inducing cells (TICs), inhibits malignant megakaryocyte colony-forming unit (CFU-MK) in vitro, targets diseases with short TL, and has the ability to inhibit telomerase. All such properties are relevant to patients with MDS, as this disease state arises from malignant progenitor cell clones, is associated with short TLs and highly active telomerase. In addition, data from Study CP14B015 suggest that imetelstat can selectively inhibit neoplastic clonal proliferation in patients with ET and provide a rationale for evaluating imetelstat in patients with other myeloproliferative neoplasms and MDS. Clinical data from Study CP14B019 further indicate that treatment with imetelstat resulted in transfusion independence and other measures of hematologic improvement in subjects with MDS.

Furthermore, as summarized in Section 1.1.5, clinical data from Part 1 show that treatment with imetelstat provides clinical benefit in this patient population which warrants further investigation of imetelstat in Low/Int-1 MDS patients.

## 1.3. Benefit-risk Assessment: COVID-19

As a result of the COVID-19 pandemic, which began in Wuhan, China in December 2019 and became a global public health emergency in March 2020, changes to this MDS3001 protocol were made as an Urgent Safety Measure (USM) after careful review of regulatory guidelines and outreach to investigators and study coordinators at participating sites. These changes with respect to COVID-19 were outlined in a Dear Investigator Letter (DIL) dated 18 March 2020 and added to the protocol as part of Protocol Amendment 4 (PA4).

Given that the MDS3001 study enrolls subjects with cancer who are in need of treatment, the protocol allows subjects who are in screening or on active treatment to continue to receive potentially beneficial treatment if the investigator determines that the risk of potential exposure to COVID-19 (ie, as a result of travel to the site and considering any other co-morbidities or risk factors the subject may have) does not outweigh the potential benefit of receiving treatment. Therefore, in order to protect the safety of these subjects, PA4 includes enhanced ongoing monitoring for signs and symptoms of COVID-19 and exposure to COVID-19. In addition, there is guidance provided for withholding treatment for subjects who have tested positive, who show signs and/or symptoms of COVID-19, or who have potential exposure to COVID-19. Decisions to either initiate or continue study treatment are left to the discretion of the local investigators depending on the outcome of these COVID-19 assessments and the overall status of each individual subject.

For enrollment of new subjects on the study, given that each site and/or country may be impacted differently during the COVID-19 pandemic and changes may occur at a rapid pace, through close communication with the sites, it was determined that the sites should follow their own institutional guidelines, as well as making individual risk assessments of their sites ability to enroll new subjects and, when needed, to hold enrollment of new subjects at their site.

Therefore, the additional measures for COVID-19 monitoring and treatment management outlined in PA4 are designed to minimize the risk to subjects posed by COVID-19 while enabling them to continue to receive treatment for their cancer. However, as outlined in the protocol, the ultimate decision on the appropriate course of action and risk/benefit for each subject will be made by the local investigator. As further developments in the COVID-19 pandemic emerge, the sponsor will continually assess the need for any additional changes to the study conduct and implement, as appropriate.

With the emergence of approved vaccines for COVID-19, investigators should discuss the benefit versus risk of COVID-19 vaccination prior to enrollment or while on study.

# 2. OBJECTIVES AND HYPOTHESES

## 2.1. Objectives

**Primary Objectives**

**Part 1**: To evaluate the efficacy and safety of imetelstat in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

**Part 2**: To compare the efficacy, in terms of RBC TI, of imetelstat to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

**Extension Phase:** To evaluate the long-term safety, OS, and disease progression, including progression to AML in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment receiving imetelstat.

**Secondary Objectives (Part 1 and Part 2)**

The secondary objectives of this study are:

- To assess the safety of imetelstat in subjects with MDS
- To assess the time to RBC TI and duration of RBC TI
- To assess the rate of hematologic improvement
- To assess the rates of CR, PR, and mCR
- To assess OS
- To assess progression free survival (PFS)
- To assess time to progression to AML
- To assess the rate and amount of supportive care, including transfusions and myeloid growth factors (Part 2 only)
- To evaluate the pharmacokinetics and immunogenicity of imetelstat in subjects with MDS
- To assess the effect of imetelstat treatment on patient-reported outcomes (PROs)
- To assess the effect of treatment on medical resource utilization (Part 2 only)
- To assess the effect of imetelstat on corrected QT (QTc) interval in subjects in the Ventricular Repolarization substudy (to be reported separately from Part 2)

**Exploratory Objectives (Part 1 and Part 2)**

The exploratory objectives of this study are:

- To evaluate pharmacodynamic biomarkers such as TA, TL and hTERT and to explore the association between baseline results and clinical response
- To evaluate change of cytogenetic abnormalities and explore the association between baseline cytogenetic status and clinical response

- To evaluate baseline mutational status and mutation changes during treatment for exploring the association with clinical response
- To explore the effects of imetelstat on immune profiles through immunophenotyping (Part 1 only)
- To evaluate the exposure-response relationship between pharmacokinetics and pharmacodynamic biomarkers, efficacy, and safety

## 2.2. Hypothesis

The primary hypothesis is that imetelstat will improve the rate of RBC TI as compared to placebo in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

# 3. STUDY DESIGN AND RATIONALE

## 3.1. Overview of Study Design

This is a Phase 2/3, multicenter study of imetelstat in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment (see Inclusion Criterion 5, Section 4.1). The study will consist of 2 parts, and approximately 270 subjects may be enrolled (Figure 2). Part 1 was an open-label, single-arm design to assess the efficacy and safety of imetelstat, which enrolled 57 subjects. Part 2 is a double-blind, randomized, placebo-controlled design to compare the efficacy of imetelstat with placebo. In addition to the approximately 170 subjects to be enrolled in the main study in Part 2, approximately 45 subjects will be enrolled in a separate Ventricular Repolarization substudy. Subjects should be enrolled in the main study of Part 2 until enrollment is complete unless a subject is known to meet criteria that would make the subject ineligible for the main study (eg, del 5 q, prior HMA therapy). See Figure 2 for schematic overview of the study.

Part 1 was an open-label, single-arm design to assess the efficacy and safety of imetelstat. Fifty-seven subjects were enrolled in Part 1, including the expansion cohort, and were followed-up for safety, hematologic improvement, and reduction in transfusion requirement. The sponsor has reviewed and assessed all available data in Part 1, including blood counts, transfusion requirement, tolerability, pharmacokinetics, and pharmacodynamic biomarker data.

The futility criteria before Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (eg, transfusion reduction, erythroid improvement). Upon review of the efficacy and safety data observed with the 7.5 mg/kg dose among 32 subjects in Part 1, a subset of 13 subjects was identified with higher hematologic response rates. These were subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. As of Amendment 2, Part 1 was expanded to include only subjects who meet these criteria, with the goal to confirm the safety and efficacy data seen in this subset and to re-confirm the dose. Twenty-five additional subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide,

so called target population, were enrolled for a total of 38 (from 57 enrolled in Part 1) that met these criteria.

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat (see Section 3.2 for a summary of data from the 38 subjects in the target population), Part 2 of the study has been initiated in subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. Enrollment into the study was temporarily held between Part 1 and Part 2 while safety and efficacy data were analyzed.

Part 2 is a double-blind, randomized design to compare the efficacy of imetelstat with placebo. Approximately 170 eligible subjects (non-del(5q); no prior lenalidomide or hypomethylating agents) will be randomized in a 2:1 ratio to receive either imetelstat or placebo, respectively in the main study. Randomization will be stratified by prior RBC transfusion burden (≤6 or >6 units RBC) and by IPSS risk group (low risk versus intermediate-1 risk). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to Randomization. In addition to the main study of Part 2, a Ventricular Repolarization substudy will enroll approximately 45 subjects to be randomized 2:1 to receive either imetelstat or placebo.

Each part of the study will consist of 3 phases: a Screening Phase of up to 28 days during which subject eligibility will be reviewed and approved by the sponsor prior to C1D1 (Part 1) or Randomization (Part 2); a Treatment Phase that will extend from C1D1 (Part 1) or C1D1 (Part 2) until disease progression (PD), or unacceptable toxicity, or withdrawal of consent; and a Posttreatment Follow-up Phase which will continue until death, lost to follow-up, withdrawal of consent, or the end of the study (whichever occurs first). The end of the main study is defined as 24 months after the randomization of the last subject in the main study of Part 2. The end of the study is defined as after all subjects have completed participation in the Extension Phase (at least 5 years from the first dose of imetelstat in Part 2 of the main study, or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up).

Subjects enrolled in Part 1 will continue through the Part 1 treatment and posttreatment follow-up phases after initiation of Part 2. Subjects enrolled in Part 1 of the study are not eligible to enroll in Part 2.

For Part 2, an additional 45 evaluable subjects will be enrolled in a separate substudy investigating the effects of imetelstat exposure on ventricular repolarization. Details regarding the Ventricular Repolarization substudy, including eligibility criteria and study procedures (including Time and Events Table) for participating subjects are provided in Attachment 11.

The term 'Study Drug', as used in this protocol, refers to either imetelstat or placebo in Part 2. Each treatment cycle will consist of 4 weeks (28 days). All subjects receiving study drug must be premedicated to prevent infusion reactions (see Section 6.2). The starting dose of the study drug is 7.5 mg/kg every 4 weeks. In Part 1 of the study, subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose. Study drug dose delay or reduction

for Grade 3 or Grade 4 toxicities will be instituted as per the instructions provided in Table 7, Table 8, Table 9, and Table 10.

Supportive care, including transfusions or myeloid growth factors, is to be administered to all subjects as needed per investigator discretion and according to local standard practices.

All study procedures will be conducted according to the Time and Event Schedules for Part 1 and Part 2 as per Table 1 and Table 3, respectively. Subjects who have enrolled into the Ventricular Repolarization substudy of Part 2 prior to Protocol Amendment 7 will continue the study assessments as required for the main study. Assessment of disease response and disease progression will be conducted based on the modified IWG Response Criteria 2006 for MDS (Modified IWG 2006),[7] and robust transfusion data will be collected for all subjects (see Section 9.3.1.1 for details). For Part 2, in addition to local disease response evaluations, which may be used for treatment decisions, an Independent Central Pathology Reviewer will review bone marrow assessments performed at screening to confirm diagnosis and eligibility at the time of each bone marrow assessment throughout the duration of the main study. Following investigator-assessed CR, PR, or mCR, in subjects with >5% baseline bone marrow aspirate blasts, aspirate should be repeated 4 to 8 weeks later for confirmatory purposes, if clinically feasible. An Independent Review Committee (IRC) will be established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response). Central laboratory results will also be used for assessment of the HI-E response. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (including hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

The sponsor will review the safety data on an ongoing basis to ensure the safety of the subjects enrolled in this study. In addition, all hepatic adverse events and LFT abnormalities will be reviewed at least on a quarterly basis, and more frequently if needed, by an Independent Hepatic Expert Committee (HEC) (see Section 11.12). An Independent Data Monitoring Committee (DMC) will be established for the study to monitor safety data. The DMC will meet periodically to review safety data and after the review, the DMC will make recommendations regarding the conduct of the study. The details will be provided in a separate independent DMC charter. Refer to Section 11.11, Independent Data Monitoring Committee, for additional details.

Subjects benefiting from imetelstat treatment at the end of the main study (ie, 24 months after last subject randomized in the main study of Part 2) per investigator assessment may continue to receive imetelstat during the Extension Phase. All subjects in the Posttreatment Follow-up Phase of the main study will also continue in the Extension Phase for assessment of survival status, subsequent anticancer therapy, and monitoring of disease progression, including progression to AML (Table 5 and Figure 3). Subjects will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat received in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to

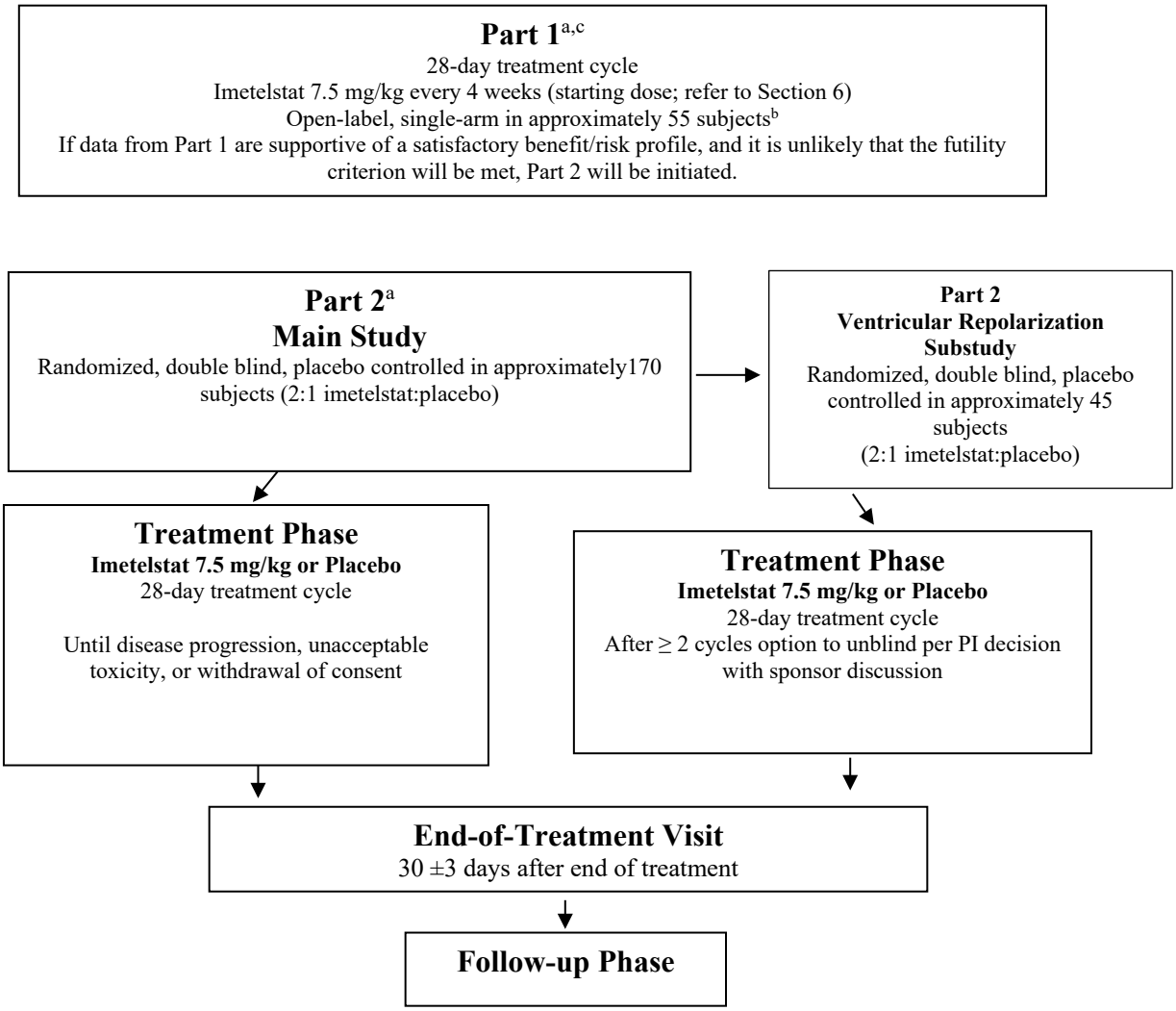
follow-up. Subjects in the QTc substudy may also enter the Extension Phase after the clinical cut off for the primary analysis is reached for the substudy.

During the Extension Phase, the Independent HEC will be available to review all hepatic adverse events and liver function test abnormalities at least on a quarterly basis, or more frequently if needed.

With Protocol Amendment 8, Part 1 of the study will close as all subjects in Part 1 have already discontinued treatment and study will have already met the duration of follow-up defined for the Extension Phase (ie, at least 5 years from the first dose of imetelstat, or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later). Any subjects remaining in follow-up will be discontinued from the study. Therefore, the Extension Phase does not apply to Part 1 subjects.

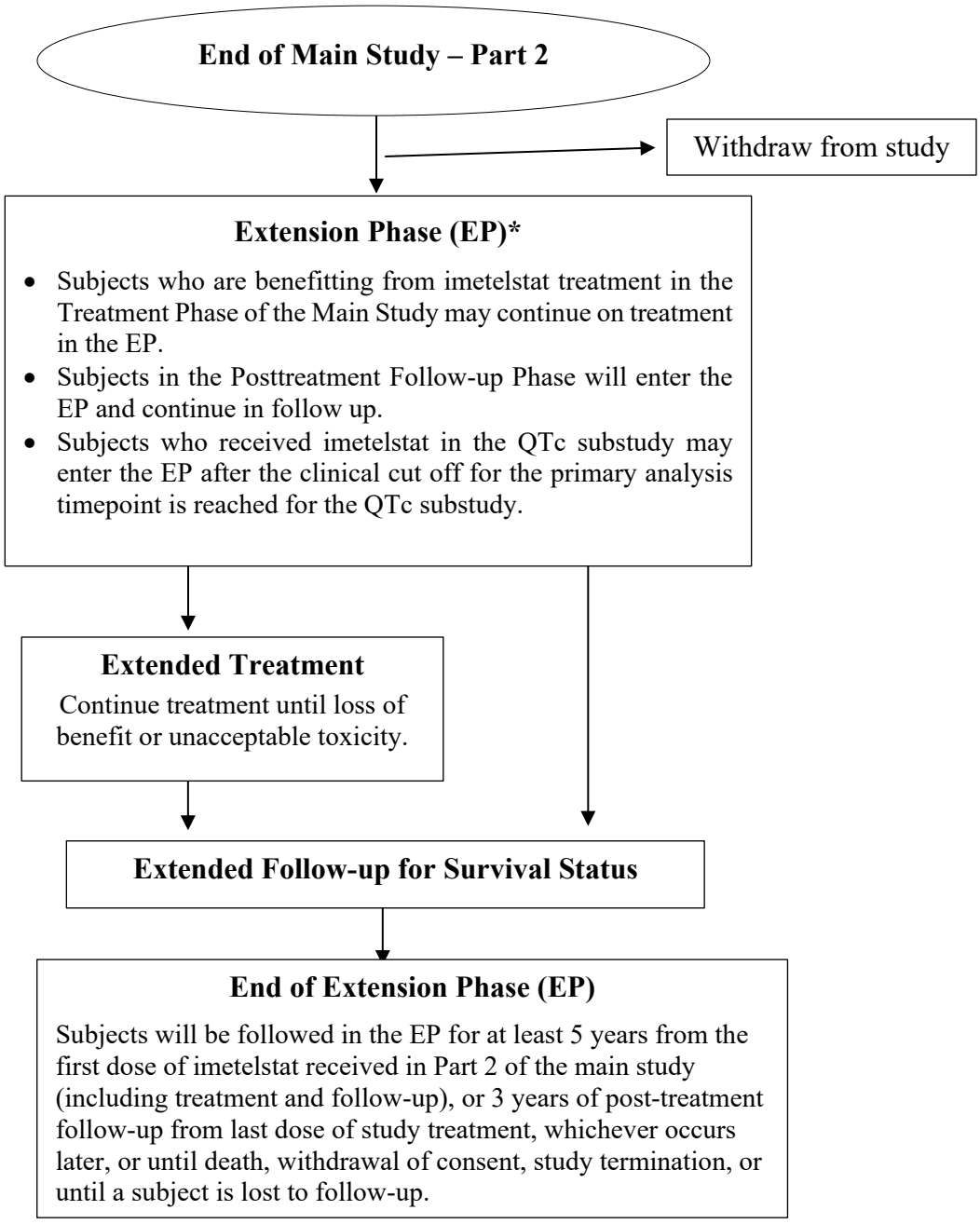
The study endpoints are listed in Section 9.2.

**Figure 2: Schematic Overview of the Study: Part 1 and Main Study of Part 2**




a. Supportive care, including transfusions or myeloid growth factors, is to be administered as needed per investigator discretion and according to local standard practices.
b. Enrollment in Part 1 was expanded from up to 30 subjects to approximately 55 subjects in Amendment 2.
c. Beginning with Amendment 2, dose escalation to 9.4 mg/kg is no longer permitted for subjects enrolled in Part 1. Part 1 subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose.

**Figure 3 Overview of the Extension Phase Following Amendment 8**




*Subjects randomized to the placebo arm in the main study will enter the Extended Follow-up Phase part of the Extension Phase.

## 3.2. Study Design Rationale

Myelodysplastic syndromes are characterized by clonal myeloproliferation that arises from malignant progenitor cell clones that have shorter telomeres and multiple clonal genetic abnormalities. Telomerase is highly activated and continually upregulated in malignant progenitor

clones enabling continued and uncontrolled proliferation. While TA is generally undetectable in normal somatic cells, it is expressed in approximately 85% of human cancers as well as in cancer progenitor cells, which are believed to play a critical role in dysregulated cell growth and tumor metastasis.[20] In MDS, TA and expression of hTERT are significantly increased as compared to healthy controls.[4,5] Myelodysplastic syndrome patients with high TA have been shown to have a significantly shorter OS as compared to those with lower TA.[17] In addition, the average TL has been shown to be significantly shorter in MDS patients as compared to healthy controls[30,40] and progression of the disease and conversion of MDS to AML are connected with progressive decrease in TL.[43] Several studies showed that higher TA and hTERT, and shorter TL correlate with IPSS risk score in MDS.[5,38,52] In low risk MDS patients, short telomeres and high TA in addition to other factors were reported as poor prognostic features.[37,51] Given the role of TA in preventing cell senescence and apoptotic cell death in immortalized cells such as tumor cells,[24] inhibition of TA constitutes an attractive therapeutic approach in MDS.

**Randomization and Treatment Groups**

This is a multicenter, 2-part, study to compare the efficacy of imetelstat to placebo in transfusion-dependent subjects who have MDS that is relapsed/refractory to ESA treatment.

Part 1 of the study was an open-label single-arm design. Randomization will be used in Part 2 of the study to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. The 2:1 randomization scheme has been chosen to limit the number of subjects in the placebo group, to increase the likelihood of subjects receiving active treatment of imetelstat for low or intermediate-1 risk MDS, and to study safety of imetelstat in a larger cohort.

Subjects will be stratified in the randomization process according to prior RBC transfusion burden (≤6 or >6 units RBC) and by IPSS risk group (low versus intermediate-1) to ensure equal distribution across treatment groups. Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to C1D1 (Part 1) or Randomization (Part 2).

Blinded treatment will be used to minimize the potential influence of treatment assignment knowledge on clinical decision making, such as transfusion administration, and to reduce potential bias during data collection and evaluation of clinical endpoints; thus, ensuring the robustness and integrity of the study. The primary objective and secondary efficacy objectives of Part 2 of the main study are to compare RBC TI, time to RBC TI, and duration of RBC TI between the 2 treatment groups (imetelstat and placebo). The use of the modified IWG 2006 criteria to assess disease progression is intended to promote uniformity across study centers. It is the intent that all subjects, investigators, and study team members, except some required project roles (eg, members associated with DMC and HEC), will remain blinded to treatment group assignment at least until the primary efficacy analysis (12 months after the last subject is randomized in the main study of Part 2). As of Protocol Amendment 8, subjects, investigators, and study team members will be

unblinded after primary efficacy analysis. Upon unblinding the subjects after the primary analysis, subjects on imetelstat may continue treatment per investigator discretion. Subjects on placebo may discontinue treatment and enter the posttreatment follow-up phase of the study. The investigator will discuss treatment options with subject's discontinuing study treatment and record treatment selection as part of subsequent therapy.

**Study Population**

Limited treatment options are available for patients who are RBC transfusion dependent, who have IPSS low risk or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment whether because they have already received at least one prior treatment with an ESA without achieving or maintaining a response or have high levels of endogenous erythropoietin and are considered unlikely to respond. The median survival for low-risk MDS patients for whom ESA treatment has failed is about 3.5 years, which is considerably shorter than predicted at the time of diagnosis. Therefore, there remains a highly unmet need for effective treatments for these patients.

Review of the data of Part 1 (Section 1.1.5) support further evaluation of imetelstat in subjects that are non-del(5q) and have not been previously treated with either a hypomethylating agent or lenalidomide, hence this represents the target population of Part 2 of the main study.

**Endpoints**

The primary endpoint of this main study is the proportion of subjects who achieve 8-week RBC TI, defined as absence of RBC transfusion during any consecutive 8-week period. Transfusion independence for 8 weeks is a clinically meaningful and robust endpoint which is included in the modified IWG 2006 response criteria and has been the basis for regulatory approvals.

The rate of hematologic improvement-erythroid (HI-E) will provide further explanation of the hematologic response (as per modified IWG 2006 response criteria). The time to progression to AML and OS are important endpoints considering that the natural history of MDS includes transformation to AML in a proportion of patients.

The depth of the response will be captured by assessment of CR, PR, and mCR per modified IWG 2006 response criteria. The data from Study CP14B019 suggest the potential for disease modification and long-term benefit to patients. Duration of responses will be assessed. Subjects will be followed for OS.

***Pharmacokinetic and Immunogenicity Evaluations***

Pharmacokinetics of imetelstat have not been characterized in MDS patients. Intensive pharmacokinetic sampling analysis was performed in up to approximately 15 subjects in Part 1 and will be performed in up to approximately 30 subjects (active treatment) in the Ventricular Repolarization substudy (Part 2). Along with sparse pharmacokinetic sampling in the remainder of subjects, this will allow for estimation of individual pharmacokinetic parameters and build a population pharmacokinetic model. The specific time points for measurement of imetelstat plasma concentrations are chosen to gather information about the pharmacokinetic properties of imetelstat. Anti-drug antibodies will be assessed during the study.

***Biomarkers***

Based on the mechanism of action of imetelstat and results from preclinical and previous clinical studies, imetelstat is expected to cause TA inhibition, TL shortening and hTERT level reduction. Blood samples will be collected from all subjects to evaluate TA, TL, or hTERT RNA level changes as pharmacodynamic biomarkers. Karyotyping on bone marrow samples from all subjects in the main study (imetelstat and placebo) will be performed to evaluate cytogenetic response by assessing the reduction or depletion of clones with cytogenetic abnormalities. Blood and bone marrow samples from all subjects in the main study will be analyzed to characterize mutation status and mutation change, immunophenotyping, and perform RNA seq for evaluation of potential inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to imetelstat.

***Patient-Reported Outcomes***

The Functional Assessment of Cancer Therapy – Anemia (FACT-An), is included in order to provide an assessment of the subject's functional status, well-being, and symptoms over time. The Quality of Life in Myelodysplasia Scale (QUALMS)[1] is a new MDS-specific health-related quality-of-life measure, and the Patient Global Impression of Change (PGIC) captures the patient's perspective of improvement or decline in MDS over time. The EuroQol-EQ-5D-5L (EQ-5D-5L) assessment is included to provide estimates of utility to include in future cost effectiveness models.

**Imetelstat Dose and Regimen Selection**

In Study CP14B019, subjects with MDS received a starting imetelstat dose of 7.5 mg/kg every 4 weeks. Subsequent doses were adjusted based on investigator assessment of toxicity and clinical response, resulting in individualized regimens that included 6.0 mg/kg, 7.5 mg/kg and 9.4 mg/kg every 4 weeks. In addition, neither prolonged thrombocytopenia nor neutropenia were observed in the MDS cohort. Based on the available data, a starting dose regimen of 7.5 mg/kg every 4 weeks demonstrated an acceptable safety profile and favorable efficacy that warrants further clinical investigation. Efficacy and safety data from Part 1 of the current study support the use of this dosing regimen in Part 2 of the study.

## 3.3. Rationale for the Extension Phase

Once the end of the main study has been reached (Section 17.9.1), accommodation must be made to allow subjects benefiting from imetelstat to continue treatment, until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. Subjects will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat received in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up. Subjects receiving imetelstat in the QTc substudy may also enter the Extension Phase after the clinical cut off for the primary analysis is reached for the substudy. It is anticipated that the Extension Phase will allow sufficient time for all subjects to receive adequate treatment and for collection of long-term survival data, and additional maturity of the survival data for a more precise estimate of OS. It is also anticipated that during this time the rate of observed deaths will reach approximately

65%, indicating a mature data set. Because sufficient efficacy data will have been collected during the main study to allow the planned final analysis for the main study, data collection during the Extension Phase will be limited to imetelstat treatment information (exposure), transfusion collection, survival status, routine safety reporting, laboratory assessments for safety monitoring, and disease progression including progression to AML.

# 4. SUBJECT POPULATION

Subject eligibility will be reviewed and approved by the sponsor prior to C1D1 (Part 1) or Randomization (Part 2) (as defined in Section 3.1). Screening will be performed within 28 days prior to C1D1 (Part 1) or Randomization (Part 2).

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections for Part 1 and main study of Part 2.

For subjects participating in the Ventricular Repolarization substudy after Protocol Amendment 7 (Part 2 only), the eligibility criteria are provided in Attachment 11.

If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before C1D1 (Part 1) or Randomization (Part 2). Waivers are not allowed.

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening. The last laboratory result obtained prior to enrollment/randomization will be used to determine eligibility. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before C1D1 (Part 1) or Randomization (Part 2) (as defined in Section 3.1) such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation until all eligibility criteria have been met (retesting information in Section 9.1.3). Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

## 4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be entered in the study.

1. Man or woman ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place);
2. Criterion modified per Amendment 1.
   - 2.1. Criterion modified per Amendment 2.
   - 2.2. Criterion modified per Amendment 3
   - 2.3 In Part 1, diagnosis of MDS according to WHO criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to C1D1. A local laboratory report from this diagnostic bone marrow aspirate and biopsy must be reviewed and approved by the sponsor (Attachment 1).

     In Part 2, diagnosis of MDS according to WHO criteria confirmed by bone marrow

aspirate and biopsy within 12 weeks prior to Randomization (Attachment 1). A sample of the baseline bone marrow aspirate and biopsy must be submitted to the Independent Central Pathology Reviewer for diagnostic confirmation. Central laboratory review is required to confirm diagnosis prior to Randomization.

3. IPSS low or intermediate-1 risk MDS (Attachment 3);
4. Criterion modified per Amendment 1.
   4.1. RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to C1D1 (Part 1) or Randomization (Part 2) (defined in Section 3.1); pre-transfusion Hb should be ≤9.0 g/dL to count towards the 4 units total;
5. Has MDS that is relapsed/refractory to ESA treatment; as defined by meeting any one of the criteria below:
   5.1. Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U or darbepoetin alfa 150 mcg (or equivalent agent/dose), without having achieved a Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks
   5.2. Criterion 5.2 replaced by criterion 5.2.1 per Amendment 5.
   5.2.1 Transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from at least 8 weeks of treatment with therapies outlined in inclusion criteria 5.1, in the absence of another explanation.
   5.3. Criterion 5.3 replaced by criterion 5.4 per Amendment 1.
   5.4. Endogenous serum EPO level >500 mU/mL;
6. Criterion modified per Amendment 1.
   6.1. Adequate iron stores, defined as transferrin saturation greater than 20% and serum ferritin greater than 400 ng/mL, measured within the screening period, or adequate iron stores as demonstrated by recent (within 12 weeks prior to C1D1 [Part 1] or Randomization [Part 2]) bone marrow examination with iron stain
7. ECOG performance status 0, 1 or 2 (Attachment 4);
8. Hematology lab test values within the following limits:
   8.1. ANC ≥1.5 x $10^9$/L independent of growth factor support (defined in Section 9.1.3)
   8.2. Platelets ≥75 x $10^9$/L independent of platelet transfusion support (defined in Section 9.1.3);
9. Biochemical laboratory test values must be within the following limits:
   9.1. AST, ALT and ALP ≤2.5 times the upper limit of normal (x ULN)
   9.2. Serum creatinine ≤2.0 x ULN
   9.3. Criterion 9.3 replaced by criterion 9.4 per Amendment 1.
   9.4. Criterion 9.4 replaced by criterion 9.4.1 per Amendment 5.
   9.4.1 Total bilirubin ≤3 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion) **AND**

Direct bilirubin ≤2 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion, where a direct bilirubin value of ≤3 x ULN or less than 1/3 of the total bilirubin value is acceptable);

10.1. Women of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject). For females, these restrictions apply for 1 month after the end of dosing. Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above;

10.2. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening and agree to be tested on Day 1 of every cycle and at end of study (30 days post last dose);

11. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study. For males, these restrictions apply for 3 months after the end of dosing.

12. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

13. Criterion deleted per Amendment 2.

## 4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Subject has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients (refer to the IB[25]);

2. Criterion 2 modified per Amendment 5.

   2.1 Subject has received an experimental or investigational drug or used an invasive investigational medical device within 30 days prior to C1D1 (Part 1) or Randomization (Part 2) (defined in Section 3.1) or is currently enrolled in an investigational study;

3. Prior treatment with imetelstat;

4. Criterion modified per Amendment 2.
   4.1 Have received corticosteroids >30 mg/day prednisone or equivalent; or growth factor treatment within 4 weeks prior to C1D1 (Part 1) or Randomization (Part 2);

5. Criterion modified per Amendment 2.
   5.1 Prior treatment with a hypomethylating agent (eg, azacitidine, decitabine);

   5.2 Criterion 5.2 replaced by criterion 5.2.1 per Amendment 5.

   5.2.1 Prior treatment with lenalidomide, thalidomide, or other thalidomide analogues;

   5.3 Criterion 5.3 replaced by criterion 5.3.1 per Amendment 5.

   5.3.1 Has received an ESA or any anti-MDS therapy, chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to C1D1 (Part 1) or Randomization (Part 2) (8 weeks for long-acting ESAs);
6. Prior history of hematopoietic stem cell transplant;
7. Anemia attributed to factors other than MDS (including hemolysis, chronic renal failure, hepatitis, gastrointestinal bleeding);
8. Major surgery within 4 weeks prior to C1D1 (Part 1) or Randomization (Part 2) (excluding the placement of vascular access and other minor surgical procedures);
9. Diagnosed or treated for malignancy other than MDS, except:
   9.1. Malignancy treated with curative intent and with no known active disease present for ≥3 years before C1D1 (Part 1) or Randomization (Part 2)

   9.2. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

   9.3. Adequately treated cervical carcinoma in situ without evidence of disease;
10. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of C1D1 (Part 1) or Randomization (Part 2), or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification;
11. Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics;
12. Criterion modified per Amendment 1.
    12.1. Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or known acute or chronic liver disease including cirrhosis;
13. Females who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 1 month after the end of dosing;
14. Subject is a man who plans to father a child while enrolled in this study or within 3 months after the end of dosing;
15. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments;

16. Subject was previously assessed as having IPSS intermediate-2 or high risk MDS;
17. Subject with del(5q) karyotype;
18. Subject with MDS/myeloproliferative neoplasm Overlap Syndrome.

### 4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. A woman of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria) during the study. For females, these restrictions apply for 1 month after the end of dosing.
2. A man who is sexually active with a woman of childbearing potential must use an adequate method of birth control and all men must also not donate sperm during the study. For males, these restrictions apply for 3 months after the end of dosing.
3. Section 8 details prestudy and concomitant therapies used in this study.

## 5. TREATMENT ALLOCATION AND BLINDING

### 5.1. Treatment Allocation

Part 1: Randomization will not be used in Part 1; all subjects will receive imetelstat. As Part 1 is an open-label design, blinding procedures are not applicable.

Part 2: Subjects will be randomly assigned 2:1 in Part 2 to receive either imetelstat or placebo. Randomization will be based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Randomization will be stratified by prior RBC transfusion burden (≤6 or >6 units RBC) and by IPSS risk group (low versus intermediate-1). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to Randomization. Pre-transfusion Hb should be ≤9.0 g/dL to count towards the 4 units total unless there is clinical rationale for transfusing at a higher Hb level. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

### 5.2. Blinding and Unblinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This may include making special provisions, such as segregating

the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations and with sponsor approval may continue study drug. It is the intent that all subjects, investigators, and study team members, except some required project roles (eg, members associated with DMC and HEC), will remain blinded to treatment group assignment at least until the primary efficacy analysis (12 months after the last subject is randomized in the main study of Part 2). As of Protocol Amendment 8, subjects, investigators, and study team members will be unblinded after primary efficacy analysis.

For subjects participating in the Ventricular Repolarization substudy (Part 2) after Protocol Amendment 7, additional information for unblinding is provided in Attachment 11.

## 6. DOSAGE AND ADMINISTRATION

The term 'Study Drug' refers to treatment with either imetelstat or placebo.

Subjects may receive study drug until disease progression, unacceptable toxicity, or withdrawal of consent.

### Supportive Care

All subjects will receive supportive care (including transfusions or myeloid growth factors) as needed per investigator discretion and according to local standard practices. Should an exceptional situation arise where it is deemed clinically necessary to give a transfusion for a Hb >11 g/dL, the reasons should be documented in the CRF.

### Study Drug (Imetelstat or Placebo)

Imetelstat Sodium (GRN163L) for injection (imetelstat) is the investigational product in this study and will be provided by the sponsor.

Placebo will be supplied by the sponsor.

Study drug will be administered as a 2-hour IV infusion (± 10 minutes) at a constant rate using an infusion pump.

The baseline weight (ie, body weight determined at Screening) will be used to calculate the dose of study drug to the nearest 0.1 mg. The dose should be recalculated if there is a ≥ 10% weight change from baseline. Note that the total dose may be recalculated more frequently (eg, at each study visit) depending on local practice. Study drug will be administered IV on a 28-day cycle.

The first dose of study drug should be administered within 72 hours of enrollment (Part 1) or randomization (Part 2) in IWRS.

All subjects in Parts 1 and 2 will receive a starting dose of 7.5 mg/kg of study drug given IV every 4 weeks. Subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose. Study drug dose delay or reduction for Grade 3 or Grade 4 toxicity will be instituted as needed, per the instructions provided in Table 7, Table 8, Table 9, Table 10, and Table 11. Note that these instructions are intended for Grade 3 or Grade 4 toxicities observed at the time of the planned dose on Day 1 of the next cycle. These instructions are not applicable when toxicities occur mid-cycle and subsequently resolve to Grade <3 by the time of the next planned dose.

The study drug may be held for up to 28 days from the expected start date of the scheduled cycle; a hold >28 days must be reviewed and approved by the sponsor. The study drug should be discontinued permanently if it cannot be restarted within 28 days due to toxicity. If the subject is exhibiting an otherwise positive clinical response to treatment and the toxicity appears to be manageable, contact the sponsor to discuss the specific case before study drug is discontinued.

**Treatment During the Extension Phase**

Dose modification guidelines provided in the following sections will continue in the Extension Phase. Subjects may receive treatment in the Extension Phase until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care.

## 6.1. Dose Modifications

Study Drug dose modifications will be performed as described in Table 6. All dose modifications must be recorded in the Dosage Administration electronic case report form (eCRF).

**Table 6: Dose Titration**

| **Titration*** | | **Dose Regimen** (imetelstat or equivalent volume of placebo) |
|---|---|---|
| **0** | **Starting dose** | **7.5 mg/kg IV every 4 weeks** |
| -1 | Dose reduction #1 | 6.0 mg/kg IV every 4 weeks |
| -2 | Dose reduction #2 (Minimum dose) | 4.7 mg/kg IV every 4 weeks |

Part 1 subjects whose dose was previously escalated (before Amendment 2) may continue at the 9.4 mg/kg dose.

### 6.1.1. Dose Modifications for Hematologic Toxicities

For any occurrence of Grade ≥3 thrombocytopenia or neutropenia, additional weekly blood counts should be performed until there is a return to baseline values. For treatment of hematologic toxicities, granulocyte-colony stimulating factors (G-CSF) are permitted for neutropenia as well as blood transfusions for anemia or thrombocytopenia.

The actions in Table 7 should be taken for Grade 3 hematologic toxicities present at the planned start of a dosing cycle. The actions in Table 8 should be taken for imetelstat-related Grade 4 hematologic toxicities at the planned start of a dosing cycle. It is recommended to contact the sponsor before discontinuing treatment due to Grade 3 or Grade 4 hematologic toxicity, particularly when the hematologic toxicity is without clinical consequences. Note that for Grade 3 or Grade 4 hematologic toxicities that are not considered related to imetelstat, the dose should still be held until recovery to ANC 1 x $10^9$/L and platelets 50 x $10^9$L.

**Table 7: Dose Modifications for Grade 3 Hematologic Toxicities**

| **Occurrence** | **Action** |
|---|---|
| First | Hold study drug until recovery to ANC 1.0 x $10^9$/L and platelets 50 x $10^9$/L*; may restart at most recent dose level |
| Second | Hold study drug until recovery to ANC 1.0 x $10^9$/L and platelets 50 x $10^9$/L*; restart at 1 dose level lower |
| Third | Hold study drug until recovery to ANC 1.0 x $10^9$/L and platelets 50 x $10^9$/L*; restart at 1 dose level lower |
| Fourth | Discontinue study drug** |

*For any other hematologic toxicities, the minimum counts for restarting should be at the Investigator's discretion
** Contact the sponsor to discuss the specific case before study drug is discontinued for hematologic toxicity

**Table 8: Dose Modifications for Grade 4 Hematologic Toxicities**

| Occurrence | Action |
|---|---|
| First | Hold study drug until recovery to ANC 1.0 x $10^9$/L and platelets 50 x $10^9$/L*; restart at 1 dose level lower |
| Second | Hold study drug until recovery to ANC 1.0 x $10^9$/L and platelets 50 x $10^9$/L*; restart at 1 dose level lower |
| Third | Discontinue study drug** |

*For any other hematologic toxicities, the minimum counts for restarting should be at the Investigator's discretion
** Contact the sponsor to discuss the specific case before study drug is discontinued for hematologic toxicity

### 6.1.2. Dose Modifications for Non-hematologic Toxicities, Excluding Hepatic Toxicities

The actions in Table 9 should be taken for Grade 3 or 4 non-hematologic/non-hepatic toxicities present at the planned start of a dosing cycle. For nausea and vomiting, only Grade 3 or 4 events which persist despite optimal antiemetic therapy should be considered for dose modification.

**Table 9: Dose Modifications for Grade 3 and 4 Non-hematologic/Non-hepatic Toxicities**

| Occurrence | Action |
|---|---|
| First | Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower |
| Second | Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower |
| Third | Discontinue study drug |

### 6.1.3. Dose Modifications for Liver Function Test Elevations and Hepatic Adverse Events

The actions in Table 10 should be taken for Grade 3 or 4 LFT elevations (AST, ALT and bilirubin), Grade 3 or 4 hepatic adverse events, and Grade ≥2 AST or ALT with Grade ≥2 bilirubin present at the planned start of a dosing cycle.

**Table 10: Dose Modifications for Liver Function Test Elevations and Hepatic Adverse Events**

| Adverse Event | Action to be taken |
|---|---|
| Grade 3 or 4<br>AST, ALT, or bilirubin<br><br>For ALT or AST >8xULN or baseline, contact sponsor and consider discontinuing drug altogether | • HOLD study drug and report as adverse event of interest (AEI)<br>• Determine relatedness to study drug (i.e. extensive investigation[a] to determine an alternative likely cause(s) for the event)<br>o If considered at least possibly related, after recovery to baseline, restart study drug at one dose level lower.<br>o If not related, after recovery to baseline, restart study drug without dose reduction.<br>• If the event recurs and is related, study drug should be discontinued |

| Adverse Event | Action to be taken |
|---|---|
| Grade 3 or 4<br><br>hepatic adverse event | • HOLD study drug and report as AEI<br>• Determine relatedness to study drug (i.e. extensive investigation[a] to determine an alternative likely cause(s) for the event)<br>o If considered at least possibly related, after recovery to baseline, restart study drug at one dose level lower.<br>o If not related, after recovery to baseline, restart study drug without dose reduction.<br>• If the event recurs and is related, study drug should be discontinued |
| Grade ≥ 2 AST or ALT with concomitant Grade ≥2 bilirubin*<br><br>*Subjects with Grade 2 bilirubin at study entry should have worsening bilirubin with concomitant Grade 2 AST or ALT elevation | • HOLD study drug and report as AEI<br>• Determine relatedness to study drug (i.e. extensive investigation[a] to determine an alternative likely cause(s) for the event)<br>o If considered at least possibly related, discontinue study drug<br>o If not related, after recovery to baseline, study drug can be restarted at same dose<br>▪ If upon rechallenge the event recurs, study drug should be discontinued |

[a] Extensive investigation includes repeating liver enzyme and serum bilirubin tests with fractionation once or twice weekly until levels return to baseline. Obtain additional tests to evaluate liver function, as appropriate (i.e., INR, albumin). In addition, obtain a detailed history of symptoms, prior or concomitant disease, concomitant medications (including nonprescription herbal and dietary supplements), alcohol use, recreational drug use, special diets and environmental chemical agents. The following should be ruled out: acute viral hepatitis types A, B, C, D and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease and may require gastroenterology and hepatology consultations. Consider hepatology (or gastroenterology) consultation. Document findings in the Imetelstat Questionnaire for Adverse Event of Interest eCRF.

### 6.1.4. Dose Modifications for COVID-19 Symptoms or Positivity (any Grade)

As of Amendment 4, due to the COVID-19 pandemic the following guidance must be followed for subjects on treatment:

- Closely monitor for clinical signs and symptoms of COVID-19 (eg, fever, cough, shortness of breath, breathing difficulties). For more comprehensive overview on signs and symptoms please refer to guidance from the WHO and regional health authority guidance.
- For subjects on treatment who have clinical signs and symptoms, if possible, perform COVID-19 testing according to local recommendations per local standard of care to assess COVID-19 status. Study treatment must be held for subjects who meet any of the following:
  - have confirmed COVID-19 infection based on testing
  - have clinical signs and symptoms consistent with COVID-19 infection in the absence of testing
  - do not have clinical signs and symptoms consistent with COVID-19 infection but have been exposed to a person with confirmed COVID-19 infection based on local recommendations for quarantine

- Study treatment can resume only after the subject has tested negative for COVID-19 according to local guidelines or, if testing was not performed, is asymptomatic (eg, no fever, no cough, no shortness of breath, no breathing difficulties) and it has been at least 14 days since start of symptoms. If a subject tests positive for COVID-19 while on study, treatment may begin/resume after 14 days from positive test and only after symptom free for at least 24 hours (smell and taste changes may linger and should not prevent from restarting treatment).
- Cases of confirmed, suspected, or exposed COVID-19 infection leading to changes in study conduct or COVID-19 vaccination and/or potential dosing delays should be documented in the eCRF, as applicable.

## 6.2. Infusion-Related Reactions

All subjects receiving an infusion of study drug must be premedicated with an antihistamine (diphenhydramine 25 to 50 mg or equivalent) and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent), either intravenously or orally. Premedications may be administered per local standard of care approximately 1 hour prior to study drug infusion. If per Investigator's discretion premedication(s) is/are contraindicated for a subject, modifications should be reviewed and approved by the sponsor's Medical Monitor. It is recommended that subjects are monitored for at least 1 hour after the infusion has been completed.

Subjects should be carefully observed during study drug infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions. If an infusion-related reaction develops, then the infusion should be temporarily interrupted and the actions in Table 11 should be taken. If possible, an unscheduled blood sample to determine antibodies to imetelstat (immunogenicity) should be drawn as soon as possible after the infusion-related reaction for potential immune response analysis.

**Table 11: Management of Infusion-Related Reactions**

| **Severity** [per CTCAE 4.03] | **Recommended action** |
|---|---|
| **Grade 1**<br>[Mild transient reaction; infusion interruption not indicated; intervention not indicated] | • Evaluate and manage symptomatically as needed<br>• May complete infusion if reaction remains mild, with stable vital signs and does not worsen to Grade 2 |
| **Grade 2**<br>[Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs] | • Stop infusion<br>• Manage symptomatically as needed<br>• After recovery to Grade ≤1, resume infusion at half the previous rate for 30 minutes<br>– If no further symptoms occur, complete the infusion at the full dose rate<br>– If the intensity of the adverse event returns to Grade 2 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 2 for a third time, discontinue imetelstat for that cycle. |
| **Grade 3**<br>[Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae] | • Stop infusion<br>• Administer supportive care as indicated<br>• Observe subject carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.<br>– If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, discontinue imetelstat |
| **Grade 4**<br>[Life-threatening consequences; urgent intervention indicated] | • Stop infusion<br>• Administer supportive care as indicated<br>• Discontinue imetelstat |

# 7. TREATMENT COMPLIANCE

Study drug will be administered by qualified site staff, and the details of each administration will be recorded in the eCRF. Additional details are provided in the Site Investigational Product Manual (SIPM) or equivalent document.

These guidelines for study drug administration and data collection will continue in the Extension Phase.

# 8. PRESTUDY AND CONCOMITANT THERAPY

## 8.1. Prestudy Therapy

Prestudy therapies administered up to 30 days before C1D1 (Part 1) or Randomization (Part 2) must be recorded at screening. Transfusions up to 16 weeks prior to screening also must be recorded at screening.

## 8.2. Premedication

All subjects receiving an infusion of study drug must be premedicated with an antihistamine (diphenhydramine 25 to 50 mg or equivalent) and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent), either intravenously or orally. Premedications may be administered per local standard of care approximately 1 hour prior to study drug infusion. If per Investigator's discretion premedication(s) is/are contraindicated for a subject, modifications should be reviewed and approved by the sponsor's Medical Monitor. It is recommended that subjects are monitored for at least 1 hour after the infusion has been completed.

## 8.3. Concomitant Medications

All recommendations regarding the use of concomitant therapy are applicable to the Extension Phase.

Subjects should receive supportive care as clinically indicated. This includes blood product support (blood transfusions and use of myeloid growth factors [eg, granulocyte-colony stimulating factor], to be administered as needed per investigator discretion and according to local standard practices), iron chelation therapy, anti-diarrheals, anti-emetics, analgesics, antibiotic treatment, and treatment of other medical conditions.

The following medications are prohibited during the study: ESA therapy, chemotherapy (anticancer/hypomethylating agents) including any anti-MDS therapy, immunomodulatory drugs (eg, lenalidomide), immunotherapy, experimental therapy, and radiotherapy. Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for more than 10 days is prohibited unless reviewed and approved by the sponsor's medical monitor. Long-term, chronic use of corticosteroids at any dose should also be reviewed and approved by the sponsor's medical monitor. Corticosteroids used as premedication are permitted. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements), including myeloid growth factors, transfusions, iron-chelation therapy, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-histamines, anti-emetics, anti-diarrheals, and anti-coagulants must be recorded throughout the study beginning with signing of the ICF to 30 days after the end of dosing or until the start of subsequent anticancer treatment, if earlier. Collection of concomitant medications includes any vaccinations received, including COVID-19 vaccination. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a

subject into the study. Over the course of the study, concomitant therapy may need to be adjusted based on the subject's clinical status. Subjects receiving iron chelating agents should be assessed regularly for the need for dose reductions and/or continued use of iron chelating agents according to local prescribing information (eg, hold dose for ferritin levels <500 mcg/L) in order to reduce the potential risk of hepatic toxicity. Concomitant therapies should be recorded beyond 30 days only in conjunction with new or worsening adverse events or serious adverse events that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

# 9. STUDY EVALUATIONS

## 9.1. Study Procedures (Part 1 and Part 2)

The study procedures will be conducted in Part 1 and the main study of Part 2 as per the Time and Events Schedules included in the Synopsis. For the Ventricular Repolarization substudy of Part 2, refer to the Time and Events Table in Attachment 11. A subject can only participate in 1 part of the study.

The term 'study drug' refers to treatment with imetelstat in Part 1 and treatment with imetelstat or placebo in Part 2.

### 9.1.1. Overview

The Time and Events Schedules for Part 1, the main study of Part 2, and the Ventricular Repolarization substudy of Part 2 (Table 1, Table 3, and Table 14, respectively) summarizes the frequency and timing of safety, efficacy, pharmacokinetic, immunogenicity and biomarker measurements as applicable for both Part 1 and Part 2. As of Amendment 8, an additional Time and Events Schedule was added for subjects who enter the Extension Phase (Table 5). Additional details for the Extension Phase is provided in Section 9.1.6.

It is recommended that PRO assessments be completed before any tests, procedures, dosing, or other consultations for that visit to prevent influencing subject perceptions. Actual dates and times of assessments will be recorded in the source documentation and CRF.

### 9.1.2. Blood Volume

The total blood volume collected is approximately 594 mL for Part 1 and 569 mL for Part 2 over the course of the study (see Table 12).

**Table 12: Volume of Blood to be Collected from Each Subject - Part 1 and Part 2 Main Study**

| Type of Sample | Volume per Sample (mL) | No. of Samples per Subject [a] | Total Volume of Blood (mL) [b] |
|---|---|---|---|
| Safety (including screening and posttreatment assessments) | | | |
| - Hematology | 5 | 28 [e] | 140 |
| - Prothrombin time (PT)/ international normalized ratio (INR) and activated partial thromboplastin time (aPTT) | 5 | 2 | 10 |
| - Serum EPO level | 2 | 1 | 2 |
| - Serum chemistry [c] | 10 | 17 | 170 |
| - B12/folic acid/reticulocytes, serum ferritin (screening), transferrin saturation [f] | 5 | 1 | 5 |
| - Serum Ferritin (post-screening) | 5 | 12 | 60 |
| - Hepatitis serologies | 13 | 1 | 13 |
| - Serum β-hCG pregnancy tests | 2 | 1 | 2 |
| Pharmacokinetic/immunogenicity samples [d] | 2 | 19 | 38 |
| Part 1 Pharmacodynamics (TA, TL, hTERT) | 14.5 | 5 | 72.5 |
| Part 2 Pharmacodynamics (TL) | 6 | 1 | 6 |
| Part 2 Pharmacodynamics (TA, hTERT) | 8.5 | 5 | 42.5 |
| Part 1 Biomarkers (mutation analysis) | 5 | 1 | 5 |
| Part 2 Biomarkers (mutation analysis) | 5 | 4 | 20 |
| Biomarkers(immunophenotyping) – Part 1 only | 4 | 4 | 16 |
| Central laboratory hematology – Part 2 only | 5 | 12 | 60 |
| Approximate Total [d] | | | 594 mL (Part 1)<br>569 mL(Part 2) |

a. Volumes below derived for median 12 cycle duration and includes end of treatment visit.
b. Calculated as number of samples multiplied by amount of blood per sample.
c. Serum chemistry includes basic liver function tests. An expanded panel of liver function tests may also be required for safety reasons.
d. The blood volume associated with participation in the Ventricular Repolarization substudy is described in Attachment 11.
e. Including 8 unscheduled blood samples for central testing, if required.
f. Total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site.

Note: An indwelling intravenous cannula may be used for blood sample collection.

In the Extension Phase, the total blood volume collected is approximately 325 mL (see Table 13).

**Table 13: Volume of Blood to be Collected from Each Subject – Extension Phase**

| Type of Sample | Volume per Sample (mL) | No. of Samples per Subject [a] | Total Volume of Blood (mL) [b] |
|---|---|---|---|
| Safety (including screening and posttreatment assessments) | | | |
| - Hematology | 5 | 21 [d] | 105 |
| - Prothrombin time (PT)/ international normalized ratio (INR) and activated partial thromboplastin time (aPTT) | 5 | 2 | 10 |
| - Serum chemistry [c] | 10 | 21 [d] | 210 |
| Approximate Total | | | 325 mL |

a. Volumes below derived for median 12 cycle duration and includes end of treatment visit.
b. Calculated as number of samples multiplied by amount of blood per sample.
c. Serum chemistry includes basic liver function tests. An expanded panel of liver function tests may also be required for safety reasons.
d. Including 8 unscheduled blood samples for additional testing, if required.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Repeat or unscheduled samples (including an expanded panel of liver function tests) may be taken for safety reasons or for technical issues with the samples.

Additional serum or urine pregnancy tests may be performed, at the local laboratory as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

### 9.1.3. Screening Phase and Predose

All subjects must sign an ICF prior to the conduct of any study-related procedures. Screening procedures other than bone marrow aspirate and biopsy will be performed up to 28 days before C1D1 (Part 1) or Randomization (Part 2) (see definition in Section 3.1).

The bone marrow aspirate and biopsy must be performed within the screening period or up to 12 weeks prior to C1D1 (Part 1) or Randomization (Part 2); however, the sample must be of adequate quality for central review. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed ICF has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to C1D1 (Part 1) or Randomization (Part 2). Central Pathology Review (Part 2): A sample of the baseline bone marrow aspirate and biopsy must be submitted to the Independent Central Pathology Reviewer for diagnostic confirmation prior to randomization. Central laboratory review is required to confirm diagnosis of MDS prior to randomization in Part 2. Supporting laboratory samples or results (eg, historic bone marrow slides, hematology results) may be requested by the central pathologist and/or sponsor to support the screening MDS diagnosis confirmation. Central pathology laboratory diagnosis confirmation is not required for subjects participating in the Ventricular Repolarization substudy after Protocol Amendment 7.

Laboratory tests noted in the inclusion criteria must be performed and the results within the limits specified in the inclusion criteria. Limited retesting of abnormal screening values that lead to exclusion are allowed using an unscheduled visit during the screening period (to reassess eligibility). If the subject is receiving a transfusion on the same day as the screening labs, screening labs should be collected prior to transfusions. The last result obtained prior to C1D1 (Part 1) or Randomization (Part 2) will be used to determine eligibility.

- For the screening ANC to be considered growth factor independent, a 7-day period after stopping the growth factor should be observed, or 7 half-lives of growth factor used, whichever is longer. ANC should then be retested, and results must be within specified limits per inclusion criteria.

- For the screening platelets $\geq 75 \times 10^9$/L to be considered independent of platelet transfusion support; platelet count must be stable for 3-4 days after the transfusion. Platelets should then be retested, and results must be within specified limits.

The screening period may extend beyond 28 days upon approval from the sponsor. In these cases, all screening procedures with the exception of the ICF, will still be assessed within the protocol-specified windows prior to Randomization as described per protocol.

Prestudy transfusion history data will be collected for 16-week period prior to C1D1 (Part 1) or Randomization (Part 2). RBC transfusion requirements in the 16-week period prior to C1D1 (Part 1) or Randomization (Part 2) will be considered for the eligibility assessment.

The first QUALMS, FACT-An and EQ-5D-5L assessments will be administered prior to administration of study drug on Day 1 of Cycle 1, and before any tests, procedures, dosing or other consultations are performed, when possible (see Section 9.6).

As of Amendment 4, due to the COVID-19 pandemic all subjects in screening who have or develop clinical signs and symptoms of COVID-19 infection, if possible, should have COVID-19 testing performed according to local recommendations to assess COVID-19 status. Subjects should not be randomized under any of the following conditions:

- Subject has confirmed COVID-19 infection based on testing
- Subject has clinical signs and symptoms consistent with COVID-19 infection in the absence of testing
- Subject does not have clinical signs and symptoms consistent with COVID-19 infection but have been exposed to a person with confirmed COVID-19 infection based on testing

Enrollment can be considered after the subject has tested negative for COVID-19 infection according to local guidelines or, if testing was not performed, is asymptomatic (eg, no fever, no cough, no shortness of breath, no breathing difficulties) and it has been at least 14 days since the start of symptoms. If a subject tests positive for COVID-19 while on study, treatment may

begin/resume after 14 days from positive test and only after symptom free for at least 24 hours (smell and taste changes may linger and should not prevent from restarting treatment).

The guidance included above regarding the screening period also apply to the Ventricular Repolarization substudy.

### 9.1.4. Treatment Phase

The Treatment Phase will begin on Day 1 of Cycle 1 and will continue until discontinuation of study drug.

**Treatment Phase**

A treatment cycle is defined as 28 days. A window of ±3 days is allowed for visits to the clinic. Details of the procedures performed during the Treatment Phase for Part 1 and Part 2 are outlined in the Time and Events Schedules (Table 1 and Table 3). Subjects will be monitored for adverse events, laboratory abnormalities, and clinical response. All Treatment Phase visit procedures are to be done predose, unless otherwise specified, and laboratory test results must be reviewed prior to administering study drug. Adverse events and changes to concomitant medications will be recorded (see Section 11.11). Dose modifications will be made according to criteria described in Sections 6.1.1, 6.1.2, and 6.1.3. The investigator will assess subject response to therapy using the efficacy measurements and disease response criteria according to the modified IWG 2006 criteria (Attachment 5) (see Section 11.13 for adjudication of assessments by independent review).

All clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. Note that additional weekly blood counts should be performed to follow-up any occurrence of Grade ≥3 thrombocytopenia or neutropenia until there is a return to baseline values. Additional coagulation testing should be performed if the subject experiences a hemorrhagic event.

Disease Evaluations must be performed every 12 weeks from Cycle 1 Day 1 (±7 days) up to Week 72, then every 24 weeks (±7 days) until suspected PD, and at the time of suspected PD or suspected CR, PR, mCR (only for subjects with baseline bone marrow aspirate blasts >5%). The required assessments at these disease evaluations are detailed in the Time and Events Schedule (Table 1, Table 3, and Table 14). In the main study of Part 2, follow up samples of bone marrow aspirate/biopsy must be submitted for central review at the time of suspected response (CR, PR, or mCR) and at the time of suspected PD; however, local assessment will be used for investigator-assessed response evaluations and treatment decisions. In case of an investigator-assessed CR, PR, or mCR per modified IWG 2006 criteria (Attachment 5), all disease assessments including bone marrow aspirate should be repeated 4-8 weeks from time of initial assessment of CR, PR, or mCR for confirmatory purposes, if clinically feasible. If the confirmatory bone marrow assessment is not feasible, stability of improved blood counts for 8 weeks is sufficient to define CR and PR per modified IWG 2006 criteria.

Subjects enrolled in the Ventricular Repolarization substudy after Protocol Amendment 7 will haver bone marrow aspirate and biopsy per local standard of care or investigator discretion.

If PD is diagnosed, or the subject discontinues study drug for other reasons, then the subject will complete the End of Treatment Visit within 30 ±3 days after the last dose of study drug and enter the Posttreatment Follow-up Phase.

**End of Treatment/Early Withdrawal**

An End of Treatment Visit will be scheduled within 30 ±3 days after the last dose of study drug for all subjects, including those discontinuing study drug for any reason, except for lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinued from study drug due to disease progression, adverse event, lack of response, or other reasons and enter the Posttreatment Follow-up Phase should have the End of Treatment Visit completed before starting any subsequent MDS treatment. If a subject is unable to return to the site for the End of Treatment Visit, then the subject should be contacted to collect adverse events that occur within 30 days after the last dose of the last study drug. Additional information on reporting adverse events may be found in Section 11.11.

The PGIC, FACT-An, QUALMS, and EQ-5D-5L questionnaires should also be completed at the End of Treatment Visit (before any tests, procedures, or other consultations are performed, when possible, see Section 9.6). If the questionnaires are conducted over a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the questionnaires. If the subject is unable to complete the assessment during the End-of-Treatment Visit, then the reason for not completing the questionnaire will be documented (eg, too ill, subject refused). Subjects enrolled in the Ventricular Repolarization substudy after Protocol Amendment 7 are not required to perform PRO assessments.

### 9.1.5. Posttreatment Phase (Follow-Up)

The Posttreatment Follow-up Phase is the time between the End-of-Treatment Visit and the end of study participation or end of study. During this phase, contact will be made as detailed in the Time and Events Schedules (Table 1 and Table 3) until the subject has died, is lost to follow-up, or has withdrawn consent.

If study drug is discontinued for any reason other than disease progression, a response assessment should be performed at the time of suspected disease progression.

Collection of transfusion data should continue every 4 to 6 weeks until the first transfusion in the posttreatment follow-up phase.

If the information on survival status and subsequent therapy is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the eCRF. Where allowed by local law, public records may be used to document death for the purpose of obtaining survival status.

As per the Time and Events Schedule for the main study of Part 2 (Table 3), sites should attempt to administer the PRO questionnaires before any tests, procedures, or other consultations are

performed, when possible, (see Section 9.6). Subjects who visit the site for the follow-up assessments should complete the questionnaires at that time. If the assessments are conducted via a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the questionnaires. If the subject is unable to complete the assessments during the Posttreatment Follow-up Phase, then the reason for not completing the questionnaires will be documented (eg, too ill, subject refused). Subjects will be required to complete PRO questionnaires in posttreatment follow-up until the start of subsequent therapy.

The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue treatment after the End of the Study. Subjects who were assigned to the placebo arm in the main study will be instructed that they should return to their primary physician to determine standard of care.

### 9.1.6. Extension Phase

Subjects benefiting from imetelstat treatment at the end of the main study (ie, 24 months after last subject randomized in the main study of Part 2) per investigator assessment may continue to receive imetelstat during the Extension Phase. Subjects in the Posttreatment Follow-up Phase of the main study will also continue in the Extension Phase for extended follow-up for assessment of survival status, subsequent anticancer therapy, and monitoring of disease progression, including progression to AML (Table 5). Subjects will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat received in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up. During the Extension Phase, the Independent HEC will be available to review all hepatic adverse events and liver function test abnormalities at least on a quarterly basis, or more frequently if needed.

Imetelstat-treated subjects in the QTc substudy may also enter the Extension Phase after the clinical cut off for the primary analysis is reached for the substudy. The end of study for the QTc substudy subjects will be when the subjects from the main study complete the Extension Phase.

Prior to entering the Extension Phase, subjects must sign and date an updated ICF. After sponsor communication of the completion of the main study, the Extension Phase will begin and subjects will follow the Time and Events Schedule for the Extension Phase (Table 5). All requirements for administration of imetelstat, including guidelines for dose modification, will continue during the Extension Phase (see Section 6). Treatment may continue until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care, or end of the Extension Phase.

Subjects who discontinue imetelstat during the Extension Phase, or who have already discontinued study treatment before entering the Extension Phase, will be contacted to determine survival status and disease progression, including progression to AML every 16 weeks ±7 days (from the EOT

visit date) until the Extension Phase ends. Procedures for documentation of survival follow-up are described in Section 9.1.5.

## 9.2. Endpoints

Additional details and definitions are provided in Section 11, Statistical Methods.

### 9.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the rate of RBC TI lasting at least 8 weeks. The 8-week RBC TI rate is defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks (56 days) starting from Study Day 1. Study Day 1 is defined as the day of the first dose for subjects enrolled in Part 1 and the day of randomization for subjects enrolled in Part 2.

### 9.2.2. Secondary Endpoints

- Safety of imetelstat in subjects with MDS (eg, incidence, intensity, and type of adverse events, vital signs measurements, clinical laboratory values, ECGs changes, and deaths);
- 24-week RBC TI rate, defined as the proportion of subjects without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1;
- Time to the 8-week (24-week) RBC TI, defined as the interval from Study Day 1 to the first day of the first 8-week (24-week) RBC TI period;
- Duration of RBC TI, defined as the first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period starts;
- Rate of hematologic improvement, including HI-E, per modified IWG 2006;
- Rates of CR, PR, or mCR per modified IWG 2006;
- OS, defined as the interval from Study Day 1 to death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up;
- Progression free survival, defined as the time interval from Study Day 1 to the first date of disease progression or death from any cause, whichever occurs first. For subjects who do not have documented disease progression and who are still alive at the end of the study or clinical cutoff will be censored at the last disease evaluation date.
- Time to progression to AML, defined as the interval from Study Day 1 to the date of AML diagnosis. For subjects who have not progressed to AML and are still alive at the cutoff date for the analysis or who withdraw from the study (withdrawal of consent or lost to follow-up), data will be censored at the date of the last disease evaluation;
- Amount and relative change in RBC transfusions;
- Rate of myeloid growth factors usage, defined as the proportion of subjects receive any myeloid growth factors starting from Study Day 1; duration of myeloid growth factor administered starting from Study Day 1;
- Assessment of QUALMS, FACT-An, and EQ-5D-5L;

- Pharmacokinetic parameters (eg, $C_{max}$, $AUC_{0-t}$), and immunogenicity of imetelstat (eg, antibodies to imetelstat);
- Medical resource utilization data including hospitalization, emergency room visits, and hematology specialist visits ;
- ECG parameters including change in QT interval by Fridericia's correction method (ΔQTcF) in the Ventricular Repolarization substudy (Part 2 only).

#### 9.2.3. Exploratory

Exploratory endpoints are not applicable for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7);

- TA and hTERT at baseline and the change from baseline, TL at baseline only;
- Cytogenetic status at baseline and change over time for cytogenetic response;
- Mutation status at baseline and change over time including at the time of suspected response (CR, PR, mCR, HI-E [Hb]) or PD;
- Immune profiles at baseline and change from baseline (Part 1 only).

### 9.3. Efficacy

Evaluations of efficacy are based on the modified IWG Response Criteria for MDS, as revised in 2006 (see Attachment 5).[7]

#### 9.3.1. Evaluations

Refer to Table 1 for Part 1 and Table 3 for the main study of Part 2 for a schedule of assessments. Subjects participating in the Ventricular Repolarization substudy after Amendment 7 will have study evaluations performed as per the Time and Events Schedule in Table 14 of Attachment 11. Study evaluations performed in the Extension Phase can be found in Table 5.

#### 9.3.1.1. Transfusions

Transfusion data will be collected during the treatment and posttreatment periods throughout the study as specified in the Time and Event Schedules. Transfusion is monitored at each visit for imetelstat infusion (every 4-week cycle), at each disease evaluation visit, and at all unscheduled visits during treatment. During the posttreatment phase, transfusion data will be collected every 4 to 6 weeks until the first transfusion in follow-up. Enhanced operational monitoring will be implemented to seek tranfusion information from other documented sources. Enhanced and continuous medical review will be implemented to identify any sudden but unsustained increase of Hb values and to query whether tranfusion has occurred.

Data to be collected include the date of transfusion, number of units and type of blood products transfused and the pre-transfusion Hb and platelet count. Red blood cell transfusions may be administered based on Hb level, investigator's assessment of the subject's clinical signs and symptoms, and local clinical practice. As the volume of 1 unit of RBC transfusion may vary regionally, one unit is defined as the amount that is intended to raise Hb by approximately 1 g/dL

in an adult patient (ie, one standard pRBC unit or equivalent). The total number of RBC units required over rolling 8-week time periods will be calculated to identify subjects who achieve RBC TI or transfusion reduction.

#### 9.3.1.2. Hemoglobin Assessment

Hemoglobin levels will be measured as detailed in the Time and Event Schedules for Part 1 and Part 2 as per Table 1 and Table 3, respectively. For a given subject, the same local laboratory should be used for each hematology assessment throughout the study, to the extent possible. In Part 2, in addition to the local laboratory, a central laboratory will be used for all planned Hb assessments. Subjects enrolled in the Ventricular Repolarization substudy (after Protocol Amendment 7) are not required to send samples for central Hb laboratory assessments. Treatment decision and investigator-assessed disease response evaluations will be based on the local laboratory results (see Section 11.13 for adjudication of assessments by independent review). Sponsor assessed HI-E will primarily be based on the central laboratory results. Investigator- and sponsor assessments based on local laboratory data will also be presented.

Hematologic improvement-erythroid (HI-E) response is defined as i) a Hb rise of at least 1.5 g/dL above the pretreatment level and lasts at least 8 weeks or ii), reduction of at least 4 units of RBC transfusion units/8 weeks compared with the prior RBC transfusion burden (criterion adapted from the modified IWG 2006 [Attachment 5]). Pretreatment Hb level is defined as the average of all the Hb values in the 8 weeks prior to C1D1, including the value on C1D1 (Part 1 or Part 2) and excluding values that were within 14 days after transfusion (thus considered to be influenced by transfusion). If there were no Hb values that met this definition of not being influenced by transfusions, then the baseline value is used.

#### 9.3.1.3. Bone Marrow Assessment

Bone marrow aspirate and biopsy must be performed as detailed in the Time and Event Schedules for Part 1 and the main study of Part 2 as per Table 1 and Table 3, respectively. Bone marrow aspirate and biopsy must be available for submission for central pathology review prior to the Randomization in the main study of Part 2 to confirm diagnosis and eligibility for study. Central pathology review is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

**Central Pathology Review (Main Study of Part 2)**

A sample of the baseline bone marrow aspirate and biopsy must be submitted to the Independent Central Pathology Reviewer for diagnostic confirmation. These samples will consist of bone marrow aspirate smears, peripheral blood smears, and bone marrow biopsy (either in formalin or unstained recut sections). (Refer to the manual for further instructions on sample preparation, handling and shipping.)

All subsequent bone marrow samples performed for Disease Evaluations, including those at the time of suspected response (CR, PR, or mCR in subjects with >5% baseline bone marrow aspirate blasts) and PD must be submitted for central review. These samples will consist of bone marrow aspirate smears, peripheral blood smears, and in the case of PD, bone marrow biopsy (either in

formalin or unstained recut sections). (Refer to the manual for further instructions on sample preparation, handling and shipping.)

Samples of bone marrow aspirate will be used for central cytogenetic assessment (refer to Section 9.5).

## 9.4. Pharmacokinetics and Immunogenicity

### 9.4.1. Sample Collection and Handling

Plasma samples (sparse sampling) will be collected from all subjects as described in the Time and Events Schedule for Pharmacokinetic Sampling for Part 1 (Table 2) and for the main study of Part 2 (Table 4). A serial sampling schedule was carried out in up to approximately 15 subjects before implementation of Amendment 2. In the Ventricular Repolarization substudy after Protocol Amendment 7, blood for PK samples will be collected on C1D1 prior to study drug administration through 8 hours after start of infusion (see schedule of events in Attachment 11).

Samples will be used to evaluate the pharmacokinetics as well as the immunogenicity of imetelstat (antibodies to imetelstat). Venous blood samples will be collected, and the plasma will be divided into 2 to 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back-up). Samples collected for analyses of imetelstat plasma concentration and antibodies to imetelstat may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers or metabolites of imetelstat. Genetic analyses will not be performed on these samples. Subject confidentiality will be maintained.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual.

### 9.4.2. Analytical Procedures

**Pharmacokinetics**

Plasma samples will be analyzed to determine concentrations of imetelstat using a validated, specific, and sensitive hybridization enzyme-linked immunosorbent assay method by or under the supervision of the sponsor. Only samples from imetelstat treated subjects will be analyzed for imetelstat concentration.

**Immunogenicity**

The detection and characterization of antibodies to imetelstat will be performed using a validated assay method by or under the supervision of the sponsor. All plasma samples collected for detection of antibodies to imetelstat will also be evaluated for imetelstat plasma concentration to enable interpretation of the antibody data. Only samples from imetelstat treated subjects will be analyzed for immunogenicity and corresponding imetelstat concentration.

### 9.4.3. Pharmacokinetic Parameters

**Intensive Pharmacokinetic Sample Analysis**

Pharmacokinetic parameters ($C_{max}$, $AUC_{0-t}$) will be derived, for subjects in Part 1 (up to approximately 15 subjects), from plasma concentration versus time data for imetelstat, but more parameters may be estimated if needed. The pharmacokinetic parameters for imetelstat are defined as follows:

| | |
|---|---|
| $C_{max}$ | Maximum observed plasma concentration |
| $AUC_{0-t}$ | Area under the plasma concentration-time curve from time 0 to t |

More parameters may be estimated if warranted by the data.

**Sparse Pharmacokinetic Sample Analysis**

Descriptive statistics (geometric and arithmetic means, standard deviation, coefficient of variation [%]) will be provided to summarize imetelstat plasma concentrations at each sampling time point for both Part 1 and the main study of Part 2. Population pharmacokinetic analysis will be performed to estimate pharmacokinetic parameters such as clearance and volume of distribution. In addition, exposure parameters (eg, $C_{max}$ or AUC) may be selected to further explore pharmacokinetic-pharmacodynamic relationships between exposure and relevant pharmacodynamic, or biomarker information.

### 9.4.4. Immunogenicity Assessments

Antibodies to imetelstat (anti-drug antibodies) will be evaluated in all subjects in Part 1 and the main study of Part 2 according to the Time and Events Schedules (Table 1 and Table 3).

Samples will be used to evaluate the pharmacokinetics as well as the immunogenicity of imetelstat (antibodies to imetelstat) (see Section 9.4.1). If possible, any time an infusion-related reaction is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential immune response analysis. These samples will be tested by the sponsor or sponsor's designee. Plasma samples will be screened for antibodies binding to imetelstat and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to imetelstat and/or further characterize the immunogenicity of imetelstat.

## 9.5. Biomarkers

Subjects enrolled in the Ventricular Repolarization substudy (after Amendment 7) are not required to have biomarker assessments performed.

**Telomerase Activity and Telomere Length Analyses:**

Baseline (predose on Day 1 of Cycle 1) peripheral blood samples will be collected from all subjects in both Part 1 and Part 2, and on-treatment peripheral blood samples will be collected from all subjects, as outlined in the Time and Events Schedules (Table 1 and Table 3), to isolate leukocytes

and analyze TA. Baseline (C1D1 predose) samples will be collected to analyze TL in Part 1 and Part 2 as outlined in Table 1 and Table 3.

**hTERT RNA Expression Analysis:**

Baseline (C1D1 predose) peripheral blood samples will be collected from all subjects in both Part 1 and Part 2. Additional on-treatment peripheral blood samples will be collected from all subjects as outlined in the Time and Events Schedules (Table 1 and Table 3) to assess hTERT level.

**Mutation Analysis:**

Peripheral blood samples will be collected from all subjects as outlined in the Time and Events Schedules (Table 1 and Table 3) for mutation analysis. For Part 1, blood samples at baseline and at the time of suspected response (CR, PR, mCR, HI-E [Hb]) or PD will be collected to evaluate the change of mutation. For Part 2, blood samples will be collected at baseline, every 12 weeks after C1D1, at time of suspected response (CR, PR, mCR, HI-E [Hb]) or PD. Genomic DNA will be prepared from blood to characterize mutation status on a panel of MDS related genes by next-generation sequencing or other methodology to evaluate the association of baseline mutation status and the change of mutation with clinical response.

**Immunophenotype Analysis (Part 1 only):**

Blood samples will be collected from all subjects as outlined in the Time and Events Schedules (Table 1 and Table 3) and may be used to explore imetelstat effects on myeloid progenitor cells differentiated into terminal functional myeloid cells by immunophenotyping and functional profiling using flow cytometer or cytometry by time of flight (CyTOF) or similar assays. A portion of the previously collected blood samples may be used to evaluate imetelstat effects on key cytokine and chemokines that are involved in inflammation, immune response, and repair by immuno-multiplexing analysis or other methodology where necessary.

**Cytogenetic Analysis:**

Bone marrow aspirate samples will be collected from all subjects as outlined in the Time and Events Schedules (Table 1 and Table 3) for karyotype analysis to characterize cytogenetics at screening to correlate with clinical response.

For subjects with a cytogenetic abnormality at baseline, follow up samples should be collected every 24 weeks after C1D1, at the time of suspected CR or PR and every 24 weeks thereafter up to and including PD to evaluate eradication or reduction of a pre-existing abnormality for assessing cytogenetic response. For subjects with a normal baseline cytogenetic result, a sample should be collected at disease progression to evaluate appearance of a new abnormality for assessing possible mechanisms of progression. Peripheral blood may be submitted in place of an aspirate only if a bone marrow aspirate cannot be obtained (eg, dry tap). The same sample type collected at screening must be collected throughout the subject's participation in the study when possible. Sites will be provided with the baseline result report to determine what follow up samples should be collected.

Bone marrow sampling for cytogenetics on treatment is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

**Bone marrow aspirate for RNA Seq or CyTOF:**

If sufficient sample is obtained, bone marrow aspirates may be characterized by technologies such as quantitative real-time polymerase chain reaction (qRT-PCR), gene expression profiling, microRNA, methylation, mutation, RNA sequencing and CyTOF analyses or other similar technologies utilized for analysis of RNA expression or proteins. Bone marrow sampling for RNA Seq or CyTOF is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

**Stopping Analysis**

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Samples will be collected only at sites where local regulations and shipping logistics permit. Biomarker analysis may be deferred or not performed, if during or at the End of the Study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Additionally, if sufficient pharmacodynamic information is obtained from TA, TL and hTERT testing of at least 30 subjects, further on-treatment sample collections may cease, without requiring a protocol deviation or waiver.

## 9.6. Patient Reported Outcomes (Part 2 Only)

Patient-reported outcomes will be assessed in subjects with MDS at the visits indicated in the Time and Events Schedule (Table 3) using the PRO measures described below. The questionnaires and instructions will be provided as separate paper documents, and subject responses will be transcribed to the eCRF by site staff. The protocol assessment questionnaires need to be done in the same order at each visit and for each subject to ensure that the subject is answering these as consistently as possible. At all visits, the questionnaires should be completed before any tests, procedures, dosing, or other consultations are performed and before the subject is informed of any assessment results (eg, Hb values), when possible. Subjects should be provided a private, quiet area to complete the questionnaires. During the posttreatment period, if the questionnaires are conducted over a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the questionnaires. If the subject is unable to complete the assessment during the EOT visit, then the reason for not completing the questionnaire will be documented (eg, too ill, subject refused). The study site staff should instruct the subject to carefully read the instructions and questions of the PRO instrument(s) prior to marking responses, that there are no right or wrong answers, and that their responses to the questionnaire will not be used to determine their study eligibility.

PRO evaluation is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

The **EQ-5D-5L** is a generic measure of health status (Attachment 7). For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[8,29] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

The **FACT-An** (version 4) is one of the scales from the Functional Assessment of Chronic Illness Therapy Measurement System (Attachment 6). It consists of the FACT-G (General version) and 20 questions labeled "Additional concerns" which measure anemia/fatigue.

The FACT-G (version 4) is a 27-item compilation of general questions divided into 4 primary quality-of-life domains:

- Physical well-being
- Social/family well-being
- Emotional well-being
- Functional well-being

The FACT-G (version 4) is considered appropriate for use with subjects with any form of cancer and has also been used and validated in other chronic illness conditions. The additional items of the FACT-An allow for constructing a Fatigue subscale. The subject is asked to rate the scale items as it applies to the past 7 days, on a 5-point scale (0=Not at all, 1=A little bit, 2=Somewhat, 3=Quite a bit, 4=Very much). Negatively stated items will be reversed by subtracting the response from 4. After reversing the proper items, items are summed to a total to generate a score on a (sub)scale.[6,53]

The **QUALMS**[1] is a 38-item measure that assesses health-related quality of life for subjects with MDS (Attachment 8). Thirty-three items are used to calculate the total score, as well as the 14-item physical burden (QUALMS-P), 3-item benefit-finding (QUALMS-BF), and 11-item emotional burden (QUALMS-E) subscales. There are also 5 single-item questions presented at the end of the measure that do not form part of the overall scale, as they are not applicable to all subjects with MDS.

The **PGIC** is used to capture the patient's perspective of improvement or decline in MDS over time (Attachment 9). The PGIC has a 7–point response scale ranging from 1 (very much improved) to 7 (very much worse), with 4 representing no change. It will be used as one of the anchors for certain psychometric performance tests and estimating meaningful important difference.

## 9.7. Medical Resource Utilization (Part 2 Only)

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF in Part 2 by the investigator and study-site personnel for all subjects throughout the study from the time of first dose until EOT visit or 30 days after the last dose of study drug, whichever occurs later. Medical resource utilization data collection is not required for subjects participating in the Ventricular Repolarization substudy (after Protocol Amendment 7).

Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Frequency and duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Outpatient medical encounters and treatments (including physician or emergency room visits, selected tests and procedures, and medications)

## 9.8. Safety Evaluations

All subjects who receive at least 1 dose of study drug will be considered evaluable for toxicity. Any clinically relevant changes occurring during the study must be recorded in the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule for Part 1 and Part 2 (Table 1 and Table 3, respectively).

**Adverse Events**

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12 Adverse Event Reporting. Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

**Adverse Events of Interest (AEI)**

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the sponsor. These events will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious adverse events) following the procedure described in the protocol for serious adverse events and will require enhanced data collection. The Imetelstat Questionnaire for Adverse Events Of Interest eCRFs must be completed for each AEI. For this study the adverse events of special interest are:

- ALT Grade ≥3 (>5.0 x ULN)
- AST Grade ≥3 (>5.0 x ULN)

- Bilirubin Grade ≥3 (>3.0 x ULN)
- ALP Grade ≥ 3 (>5.0 x ULN)
- All hepatic adverse events
- ALT or AST Grade ≥ 2 (>3.0 x ULN) **WITH** Bilirubin Grade ≥ 2 (>2.0 x ULN)

For these events, laboratory assessments should be repeated once or twice weekly until bilirubin with fractionation return to baseline levels. Additionally, subjects with Grade 1 and Grade 2 treatment-emergent elevations in AST, ALT, ALP and bilirubin at the time of treatment discontinuation should continue to have laboratory assessments monthly until resolution to at least baseline or until the start of subsequent therapy, whichever comes first. All hepatic adverse events and LFT abnormalities will be reviewed by an Independent Hepatic Expert Committee, at least quarterly, and as needed.

### 9.8.1. Clinical Laboratory Tests

All laboratory tests should be performed at the laboratory facilities associated with the investigational site. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject has the laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well. The laboratory reports must be filed with the source documents. In addition, central laboratory will be utilized for hematology panel (hemoglobin, platelet count, white blood cell count, ANC and manual absolute peripheral blast count) and will be used for HI-E efficacy assessment. Local hematology panel results may be used for investigator-assessed response evaluations and treatment decision.

Blood samples for serum chemistry and hematology to assess the safety of study drug will be collected. Required laboratory tests must be performed within 48 hours of the scheduled visit. For C1D1 only, clinical laboratory tests do not need to be repeated if the screening tests were performed within 5 days of the start of study drug. For all cycles, if tests are repeated on the day of the visit, the most recent results should be reviewed before dosing.

For a given subject, the same local laboratory should be used for each hematology assessment throughout the study, to the extent possible. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. For example, laboratory abnormalities leading to an action regarding any study drug (dose reduction, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤ 1 or to baseline values.

The following tests will be performed by the local laboratory at the time points shown in the Time and Events Schedule. All clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. In some cases, if a site's local laboratory does not assess the laboratory tests noted below, other laboratory tests may be performed to calculate the values to be assessed (eg, total iron binding capacity and serum iron may be collected to calculate transferrin saturation).

- **Hematology Panel:** hemoglobin, platelet count, white blood cell count, absolute peripheral blast count, ANC

  Additional weekly blood counts should be performed to follow-up any occurrence of Grade ≥3 thrombocytopenia or neutropenia until there is a return to baseline values.

- **Coagulation:** international normalized ratio (INR), (or prothrombin time [PT]), and activated partial thromboplastin time (aPTT)

  Additional coagulation testing should be performed if the subject experiences a hemorrhagic event.

- **Serum Chemistry Panel (Routine):** sodium, potassium, blood urea nitrogen (or urea), creatinine, total bilirubin, ALT, AST, ALP, lactate dehydrogenase, and albumin. Assessment of total bilirubin with fractionation is required at screening; fractionation post-screening is also required if total bilirubin is abnormal.

  Additional labs may be assessed locally to demonstrate eligibility if the subject will be enrolled with elevated bilirubin levels due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion.

- **Expanded Chemistry Panel for LFT Investigations:** gamma-glutamyl transpeptidase (GGT), chloride, bicarbonate, magnesium, and fractionated bilirubin required at screening for subject eligibility or as applicable for adverse event of interest.

- **Viral Hepatitis**: Screening for hepatitis will include comprehensive hepatitis serology A through E. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg). Assessment may be performed by local or central laboratory.

- **Serum Erythropoietin**

- **Serum Ferritin, Transferrin Saturation**

  Total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site.

- **Anemia Supplemental Panel**: B12, folic acid, reticulocytes

- **Pregnancy Testing:** Serum or urine pregnancy test for β-hCG

In addition, the following hematology tests will be performed at the central laboratory: hemoglobin, platelet count, white blood cell count and ANC; and manual absolute peripheral blast count.

### 9.8.2. Electrocardiogram

A 12-lead electrocardiogram will be performed in all subjects in Part 1 and in the main study of Part 2 during screening as specified in the Time and Events Schedules (Table 1 and Table 3). During the collection of ECG, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. ECG abnormalities that are considered to be clinically relevant by the investigator (not present prior to or worsening from C1D1) are to be documented as adverse events.

In Part 2, a separate Ventricular Repolarization substudy will be performed with serial ECG and PK sampling. See Attachment 11 for additional information.

### 9.8.3. Vital Signs

Temperature, pulse/heart rate, and blood pressure will be recorded, preferably while the subject is in a seated position, at the time points specified in the Time and Events Schedules (Table 1, Table 3, Table 5, and Table 14). Vital signs abnormalities that are considered to be clinically relevant by the investigator are to be documented as adverse events.

### 9.8.4. Physical Examination

Screening physical examination should include body weight, height, and the evaluation of head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Only a limited symptom-directed physical examination and weight assessment is required on Day 1 of all cycles after baseline. New or worsened abnormalities should be recorded as adverse events if appropriate.

As of Amendment 4, due to the COVID-19 pandemic all subjects should be closely monitored for signs and symptoms of COVID-19 infection. Subjects that develop clinical signs and symptoms should have COVID-19 tests performed according to local recommendations per local standard of care to assess COVID-19 status. Refer to Section 6.1.4 for treatment modification guidelines. Cases of suspected or confirmed COVID-19 infection should be reported as an AE or SAE, as appropriate.

### 9.8.5. ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's activities of daily living.

## 9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the Time and Events Schedules (Table 1, Table 3, Table 5, and Table 14) for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided.

# 10. SUBJECT COMPLETION/WITHDRAWAL

## 10.1. Completion

A subject will be considered to have completed the study if he or she has died, has not been lost to follow-up, or has not withdrawn consent for study participation before the end of the study.

## 10.2. Discontinuation of Study Treatment

If a subject is experiencing clinical benefit in the study without significant toxicity that puts the subject at risk, or routine noncompliance that puts the study outcomes at risk, investigators should consider continuing the subject on treatment. If a subject shows evidence of progressive disease, but the investigator feels they are still experiencing clinical benefit from imetelstat, the sponsor should be contacted to discuss potential continuation of treatment. If a subject's study treatment must be discontinued, the event will not result in automatic withdrawal of the subject from the study and investigators should reinforce the need for subjects to stay in the study for survival follow-up.

A subject's study drug should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event or subject experiences unacceptable toxicity) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject experiences overt disease progression or relapse
- The subject refuses further treatment
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

End-of-Treatment and posttreatment follow-up assessments should be obtained. The reason(s) a subject discontinues treatment will be recorded on the eCRF.

## 10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- The sponsor discontinues the study

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject

withdraws from the study before the end of the Treatment Phase, the End-of-Treatment visit procedures and the posttreatment follow-up phase assessments should be obtained.

### 10.3.1. Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

## 11. STATISTICAL METHODS

A general description of the statistical methods to be used to analyze the efficacy and safety data in Part 1 and the main study in Part 2 is outlined below. Specific details will be provided in the Statistical Analysis Plan. The cardiac safety analysis in regard to ECG and concentration-QTc analysis in the Ventricular Repolarization substudy based on the additional 45 subjects will be performed separately from the primary analysis of 170 subjects in the main study of Part 2. These data may be available after the primary analysis of the main study has already been completed. Statistical methods for the substudy are in Attachment 11 and detailed in the Ventricular Repolarization Statistical Analysis Plan.

With Protocol Amendment 8, the Extension Phase analysis focused on disease progression, including progression to AML, OS, PFS, and long-term safety data will be conducted at the end of the Extension Phase.

## 11.1. Analysis Populations

**For Part 1**: Efficacy and safety analyses will be performed using the treated population, which will include all subjects who receive at least 1 dose of study drug.

**For Part 2**: The primary analysis population will be the intent to treat (ITT) population from the main study, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. Subgroup analyses will be performed as appropriate, and details will be specified in the Statistical Analysis Plan.

The biomarker analysis will consist of all subjects in the main study who received at least 1 dose of study drug and had at least 1 sample collected during treatment. The same subjects will be included in population pharmacokinetic/pharmacodynamic modeling if it is to be performed.

## 11.2. Subject Information

Study Day 1 (ie, Study Entry) is defined as the day of the first dose for subjects enrolled in Part 1 and the day of randomization for subjects enrolled in Part 2. Continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation, 25th/75th percentiles, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

## 11.3. Sample Size Determination

Approximately 270 subjects (57 subjects enrolled in Part 1, approximately 170 subjects in the main study of Part 2, and approximately 45 subjects in Ventricular Repolarization substudy of Part 2) will be enrolled in the study. The initial cohort of 32 subjects enrolled into Part 1 was expanded with Amendment 2 to include an additional 25 subjects who meet the revised entrance criteria, for a total of 57 subjects in Part 1.

On the basis of historical data, the RBC TI rate is expected to be approximately 7.5%[39,41] in subjects with low or intermediate-1 risk MDS without any active treatment. The RBC TI rate with imetelstat treatment is expected to be approximately 30% based on preliminary data from Study CP14B019. The futility criteria before Amendment 2 were defined as follows: If 4 or fewer subjects among 30 subjects in Part 1 achieve RBC TI lasting at least 8 weeks, the study will be stopped unless there is compelling clinical evidence of efficacy in one or more other endpoints (eg, transfusion reduction, erythroid improvement). The assumption was that if the RBC TI rate of 30% with imetelstat treatment is true, the probability of passing the futility criterion would be 97%.

Upon review of the efficacy and safety data observed with the 7.5 mg/kg dose among 32 subjects in the initial cohort of Part 1, a subset of 13 subjects was identified with higher hematologic response rates. These were subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide. As of Amendment 2, Part 1 was expanded to include only subjects who meet these criteria, with the goal to confirm the safety and efficacy data seen in this subset and to re-confirm the dose. Twenty-five additional subjects with non-del(5q) MDS and without prior exposure to either hypomethylating agents or lenalidomide were enrolled for a total of 38 (from 57 enrolled in Part 1) that met these criteria.

Since data from Part 1 for this target population show clinical benefit of treatment with imetelstat (see Section 1.1.5 for summary of data from the 38 subjects in the target population), Part 2 of the study will be initiated.

In the main study of Part 2, approximately 170 subjects will be randomized in a 2:1 ratio to receive either imetelstat or placebo. Using a 2:1 ratio randomization and a 2-group continuity corrected Chi-square test with 0.05 (2-sided) significance level, 150 subjects are needed to achieve a power of approximately 88% to detect the difference between a RBC TI rate of 30% in the imetelstat group and a RBC TI rate of 7.5% in the placebo group. After correction for a 10% drop-out rate, a total of approximately 170 subjects (115 in imetelstat group and 55 in placebo group) will be needed. The overall study power from Part 1 and the main study of Part 2 is approximately 85%.

## 11.4. Efficacy Analyses

The primary efficacy analysis is planned at 12 months after the last subject is randomized in the main study of Part 2, and the final analysis for the main study is planned at 24 months after randomization of the last subject in the main study of Part 2. Efficacy data in Part 1 will be descriptively summarized based on the treated population. Efficacy data in Part 2 will be compared between the imetelstat and placebo groups based on the ITT population. Any available efficacy data from Ventricular Repolarization substudy will be descriptively summarized in addition to the

efficacy data from the main study in Part 2.

**Part 1**

The proportion of subjects with 8-week RBC TI, 24-week RBC TI, CR, PR, and hematologic improvement, and other binary endpoints, will be summarized with percentage along with its 95% 2-sided exact confidence interval. The time to 8-week RBC TI and time to 24-week RBC TI will be summarized descriptively based on 8-week and 24-week RBC TI responders, respectively. The Kaplan-Meier method will be used to estimate the distribution of duration of RBC TI based on 8-week and 24-week RBC TI responders, respectively. The distributions of OS, PFS, and time to progression to AML will be summarized using similar Kaplan-Meier methods.

**Part 2 Main Study**

The analysis for the primary endpoint, 8-week RBC TI, will be based on the ITT population from the main study in Part 2 (approximately 170 subjects). The RBC TI rates will be summarized with frequency and percentage along with a 2-sided 95% confidence interval for each treatment group. The comparison will be based on the stratified Cochran-Mantel-Haenszel test adjusting for the stratification factors at a two-sided significance level of 0.05. Note that in order to be considered transfusion independent, a subject must have completed continuous transfusion assessment throughout the observation period during which his or her transfusion independence is determined.

The proportion of subjects with 24-week RBC TI, CR, PR, mCR, and other binary endpoints, will be evaluated using the same statistical methods as for the primary endpoint.

The distributions of OS, PFS, and time to progression to AML will be compared using a stratified log rank test for the ITT population. The Kaplan-Meier method will be used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The reasons of censoring in time to progression to AML will be tabulated.

The time to 8-week and 24-week RBC TI will be summarized descriptively based on ITT 8-week and 24-week RBC TI responders, respectively. The Kaplan-Meier method will be used to estimate the distribution of duration of RBC TI based on ITT 8-week and 24-week RBC TI responders, respectively.

The amount and relative change in RBC transfusions will be summarized descriptively by treatment by time point.

Change from baseline in scores from QUALMS, FACT-An, and EQ-5D-5L will be summarized descriptively by treatment group. The PRO measure of interest and analysis methods (eg, responder analysis, longitudinal analysis with repeated measures) will be specified in the Statistical Analysis Plan.

A sequential gate-keeping procedure will be implemented to ensure that the overall type I error rate for the secondary endpoints is controlled. Details of selected secondary endpoints to be tested

and the testing procedure will be specified in the Statistical Analysis Plan.

## 11.5. Pharmacokinetic Analyses

The pharmacokinetic-evaluable population is defined as subjects who have received 1 dose of study drug and at least 1 post infusion sample. All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be excluded in the calculation of summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report. Descriptive statistics will be used to summarize imetelstat plasma concentrations at each nominal sampling time point for pharmacokinetic-evaluable population. Details of planned pharmacokinetic analysis will be provided in a specific PK-statistical analysis plan (SAP).

Descriptive statistics will be provided to summarize imetelstat plasma concentrations at each sampling time point for subjects undergoing serial pharmacokinetic sampling in Part 1. Non-compartmental pharmacokinetic analysis will be performed on these subsets of subjects. Pharmacokinetic parameters as listed in Section 9.4.3 will be derived and descriptive statistics provided.

## 11.6. Immunogenicity Analyses

The incidence of antibodies to imetelstat will be summarized for all subjects who receive at least 1 dose of imetelstat and have appropriate samples for detection of antibodies to imetelstat (ie, subjects with at least 1 sample obtained after administration of at least 1 dose of imetelstat). The results will be summarized for subjects with appropriate samples for the detection of antibodies to imetelstat.

## 11.7. Pharmacokinetic/Pharmacodynamic Analyses

If required, a population pharmacokinetic/pharmacodynamic analysis may be performed using nonlinear mixed-effects modeling. Data may be combined with relevant Phase 1 and/or Phase 2 studies for the analyses. If the analysis is conducted, then details will be provided in a separate report with the population pharmacokinetics analysis results.

## 11.8. Biomarker Analyses

Biomarker measures and the change from baseline will be listed, tabulated, and plotted where appropriate. Subjects may be grouped by treatment, biomarker subgroups, or clinical response. Correlation of baseline or changes of biomarkers with clinical parameters will be analyzed by appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate).

Results of biomarker analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

## 11.9. Medical Resource Utilization Analyses (Part 2 only)

Frequency and duration of hospitalization, frequency of emergency room visit, and specialty physician visit will be listed and summarized where appropriate. Results may be grouped by treatment, subgroups, or clinical response.

## 11.10. Safety Analyses

Safety analyses will be performed using the treated population. Safety will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.03). The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings, vital signs measurements, clinical laboratory results (hematology and chemistry), and deaths. Exposure to study drug and reasons for discontinuation will be tabulated. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent).

### Adverse Events

Treatment-emergent adverse events are adverse events that occur after the start of study drug administration, through the Treatment Phase, and for 30 days following the last dose of study drug; any adverse event considered treatment-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI-CTCAE, Version 4.03) and drug relationship as well as categorized by System Organ Class and preferred term by treatment arm.

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Subjects with adverse events of special interest may be counted or listed.

### Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be included in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

**Electrocardiogram**

Electrocardiogram data from Part 1 and the main study of Part 2 will be listed. Attachment 11 includes an analysis plan for ECG data from the additional 45 subjects participating in the Ventricular Repolarization substudy.

**Vital Signs**

Descriptive statistics of temperature, heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

## 11.11. Independent Data Monitoring Committee

An independent DMC will be established to monitor safety data. The DMC will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. For Part 1 of the study, the DMC performed ad hoc expedited reviews of any ≥Grade 4 hemorrhagic event occurring on the study or any other safety concerns identified by the sponsor. During Part 2, the DMC will meet periodically to review overall safety data and will also perform ad hoc expedited review of all ≥Grade 4 hemorrhagic events as they are reported. After each review during Part 1 or Part 2 of the study, the DMC will make recommendations regarding the conduct of the study. The roles, responsibilities, and memberships of the DMC, Statistical-Support Group, and study team are described a separate DMC charter.

## 11.12. Independent Hepatic Expert Committee

An Independent HEC consisting of 3 hepatologists will be established to monitor all hepatic adverse events and LFT abnormalities will be reviewed at least on a quarterly basis, and more frequently if needed. This same committee may also review hepatic safety events from other ongoing studies with imetelstat. The Independent HEC responsibilities, authorities, and procedures will be documented in a charter. Review of hepatic AEs and LFT abnormalities will continue in the Extension Phase.

## 11.13. Independent Review Committee

An IRC will be established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) and response (CR, PR, mCR, or cytogenetic response) for subjects with >5% baseline bone marrow aspirate blasts based on the central pathology reviewer's assessment in the main study of Part 2. The IRC will assess response based on the modified IWG Response Criteria 2006 for MDS as outlined in Attachment 5. The IRC responsibilities, authorities, and procedures will be documented in a charter.

# 12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

## 12.1. Definitions

### 12.1.1. Adverse Event Definitions and Classifications

**Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Note: The sponsor collects adverse events starting from the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

**Serious Adverse Event**

A serious adverse event based on ICH and European Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Female subjects who become pregnant during the course of the study up to 30 days after the last dose or a female partner of a male subject who becomes pregnant up to 90 days of the last dose for the male subject. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

**Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For imetelstat, the expectedness/listedness of an adverse event will be determined by the sponsor as to whether or not it is listed in the Investigator's Brochure.

**Adverse Event Associated with the Use of the Drug**

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

### 12.1.2. Attribution Definitions

**Not Related**

An adverse event that is not related to the use of the drug.

**Doubtful**

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

**Possible**

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable**

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

**Very Likely**

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

### 12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (Version 4.03) as follows:

**Grade 1 (Mild)**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Grade 2 (Moderate)**: Sufficient discomfort is present to cause interference with normal activity.

**Grade 3 (Severe)**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

**Grade 4 (Life-threatening)**: Urgent intervention indicated.

**Grade 5 (Death)**: Death.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

## 12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

- Female subject becomes pregnant during the course of the study and up to 30 days after the last dose or the female partner of a male subject becomes pregnant during the course of the study up to 90 days after the last dose for the male subject

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF, as well as on the SAE Form.

## 12.3. Procedures

### 12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event/Adverse Event of Interest Form. Any adverse event thought to be potentially related to study drug must be reported to the sponsor irrespective of timing from the last dose of study drug. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AE and pregnancy reporting will continue to be collected in the Extension Phase.

Progressive disease of MDS should NOT be reported as an adverse event, but instead symptoms/clinical signs of disease progression may be reported. Otherwise, all events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 10.

Adverse events of interest are listed in Section 12.3.3.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events, the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence

and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute, where required).

The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

### 12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the sponsor's delegated Safety CRO by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event/Adverse Event of Interest Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) or email.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- A standard procedure for study medication administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of study medication administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

### 12.3.3. Adverse Events of Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the sponsor. These events must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious adverse events of interest),

following the procedure described above for serious adverse events and will require enhanced data collection. For this study, the adverse events of special interest are:

#### 12.3.3.1. Elevated Liver Function Tests (LFTs)

Elevations in the following LFTs will be captured as adverse events of interest:

- ALT Grade ≥3 (>5.0 x ULN)
- AST Grade ≥3 (>5.0 x ULN)
- Bilirubin Grade ≥3 (>3.0 x ULN)
- ALP Grade ≥ 3 (>5.0 x ULN)
- ALT or AST Grade ≥ 2 (>3.0 x ULN) **WITH** Bilirubin Grade ≥ 2 (>2.0 x ULN)

#### 12.3.3.2. Hepatic Adverse Events

All hepatic adverse events will be captured as adverse events of interest.

### 12.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event/Adverse Event of Interest Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

## 12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

# 13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and

analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

### 13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor or its designee according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

### 13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the sponsor or its designee who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

## 14. STUDY DRUG INFORMATION

### 14.1. Physical Description of Study Drug(s)

The imetelstat supplied for this study is supplied as a sterile lyophilized powder in a sealed, stoppered, clear glass vial. Each single-dose 10 mL or 8 mL vial contains 210 mg of imetelstat sodium per vial and is designed to deliver 200 mg of reconstituted Imetelstat Sodium for Injection at a concentration of 33.33 mg/mL. It will be manufactured and provided under the responsibility of the sponsor. Refer to the imetelstat IB[25] for a list of excipients.

The placebo supplied for this study is supplied as a non-active lyophilized product with similar appearance as imetelstat and provided in the same primary packaging components (vial, stopper and cap) as the active drug product that will be supplied.

### 14.2. Packaging

Imetelstat is supplied in glass vials that when reconstituted, contains imetelstat at a concentration of 33.33 mg/mL.

During Part 1, imetelstat will be supplied to the site/pharmacy in bulk supply with unblinded labels. During Part 2, imetelstat and placebo will be provided to the site in matching vials with blinded labels. Once the study is unblinded, imetelstat will be provided to the site/pharmacy as open label bulk supply, except QTc subjects who will continue to receive blinded IP until they are crossed-over to open label IP.

### 14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

## 14.4. Preparation, Handling, and Storage

All study drug must be stored in the original carton in a refrigerator ranging from 2°C to 8°C (36°F to 46°F, refrigerated) and must not be utilized after the expiry date printed on the label. The product must not be frozen. Imetelstat and placebo do not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Imetelstat and placebo will be reconstituted with 0.9% Sodium Chloride. Refer to the SIPM for details regarding dose preparation, storage, and handling.

## 14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented in the IWRS. All study drug will be stored and disposed of according to the sponsor's instructions.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented in the IWRS. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented in the IWRS.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

# 15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Subject study tools (appointment card, emergency ID card etc., as applicable per country)
- Investigator study tools and quick reference cards
- Imetelstat IB
- Trial Center File, and corresponding specific documentation
- Site Investigational Product Manual, including the investigational product preparation instructions

- Central Laboratory Manual and supplies
- NCI-CTCAE Version 4.03
- PRO questionnaires and user manuals
- IWRS Manual and supplies
- Electronic Data Capture Manual and eCRF Completion Guidelines
- Sample ICFs for Part 1, Part 2 (includes the Extension Phase) of the main study, and the Ventricular Repolarization (QTc) substudy

# 16. ETHICAL ASPECTS

## 16.1. Study-Specific Design Considerations

Part 1 is designed as an open-label, single-arm treatment study to evaluate the efficacy and safety of imetelstat; all subjects will receive treatment with imetelstat in Part 1. Part 2 is a double-blind, randomized design to compare the efficacy of imetelstat to placebo. Discussion on the study design rationale is provided in Section 3.1.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected from each subject will be approximately 594 mL in Part 1 and 569 mL for the main study of Part 2 (see Table 12) and 361 mL in Ventricular Repolarization substudy of Part 2 over the course of the study (see Table 16). In the Extension Phase, the total blood volume to be collected from subjects who are on imetelstat treatment will be approximately 325 mL (see Table 13). The total volume of blood includes laboratory assessments associated with screening and treatment including pharmacokinetic and biomarker samples. Subjects enrolled in Part 1 of the study are not eligible to enroll in Part 2. The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will be performed by the investigator according to modified IWG response criteria 2006 for MDS. Safety assessments will occur through regular clinic visits including laboratory analyses. The sponsor will review the safety data on an ongoing basis to ensure the safety of the subjects enrolled in this study. An Independent Hepatic Expert Committee will review all hepatic adverse events and LFT abnormalities on an ongoing basis. An IRC will be established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) in the main study of Part 2 based on the modified IWG 2006 (see Section 11.13). An independent DMC will be used in Parts 1 and 2 of the study.

## 16.2. Regulatory Ethics Compliance

### 16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

### 16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor

- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

### 16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her

disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain or have access to a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or their legally acceptable representative) is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject (or their legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject (or their legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or their legally acceptable representative) is obtained.

### 16.2.4. Privacy of Personal Data

Personal data collected from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study and processed in compliance with the Patient Information and Informed Consent Form (ICF) and agreement(s) with the sponsor governing the conduct of the study at the clinical sites.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be utilized. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records for purposes such as study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also permits the transfer of the data to other entities and to other countries in compliance with applicable data privacy protection laws and regulations.

The subject has the data privacy rights set out in the ICF and the applicable data privacy laws and regulations in the country in which the study is being conducted. The ICF directs subjects to submit

data privacy requests to the study site. The site will report the request to the CRO and/or the sponsor. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable data privacy laws and regulations.

Exploratory pharmacodynamics, biomarker, pharmacokinetic and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

#### 16.2.5. Long-Term Retention of Samples and Use of Data for Additional Future Research

In addition to the procedures and analyses expressly specified in this protocol, samples or data collected from subjects may be further analyzed under this protocol to 1) further understand the mechanism of action of imetelstat; 2) to understand MDS and why subjects may respond differently to imetelstat; 3) to develop and validate imetelstat-related tests/assays (protocol-related research). Any research other than described above (including protocol-related research), is considered future research. Subjects are given the option to provide express consent to future research in the ICF.

Provided that express consent is obtained from the subject in the ICF, samples collected in this study may be stored for up to 15 years (or according to local regulations) for future research. The future research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored or used for future research (refer to Section 10.3, Withdrawal from the Study (Withdrawal from the Use of Samples in Future Research).

#### 16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

## 17. ADMINISTRATIVE REQUIREMENTS

### 17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be

promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

## 17.2. Regulatory Documentation

### 17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

### 17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required

- Signed and dated clinical trial agreement, which includes the financial agreement or study budget
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

## 17.3. Subject Identification

The investigator agrees to complete a subject identification log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification number. In cases where the subject is not randomized into the study, the subject number will be used.

## 17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; subject worksheets for PROs and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

## 17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF and transmitted in a secure manner to the

sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eCRF. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eCRF at their own initiative or as a response to an auto query (generated in the eCRF).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

## 17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

## 17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable laws and regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

## 17.8. Monitoring

The sponsor or its designee will use a combination of monitoring techniques: On-Site Monitoring Visits, Remote Telephone Contacts and Central Data Surveillance to monitor this study.

The sponsor or its designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records, subject PRO worksheets) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. During these remote contacts, there may be a requirement to provide source

documents outside of the site. Home healthcare visits may also occur if the subject is unable to be seen at the study site. The process for these will be described in the monitoring guidelines (or another equivalent document).

Central monitoring will take place for data identified by the sponsor as requiring central review.

## 17.9. Study Completion/Termination

### 17.9.1. Study Completion

The end of the main study is defined as 24 months after randomization of the last subject in the main study of Part 2. The end of Extension Phase will occur once all subjects in the main study have received at least 5 years of imetelstat from the first dose in Part 2 of the main study (including treatment and follow-up), or 3 years post-treatment from last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up. The end of study for the QTc substudy subjects will be when the subjects from the main study complete the Extension Phase. The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue treatment after the end of the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the clinical trial agreement.

### 17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time permitted under the signed clinical trial agreement, provided there is reasonable cause and sufficient notice is given to the sponsor in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

## 17.10. On-Site Audits

Representatives of the sponsor's or its designee's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. The investigator and study-site personnel are responsible for being present and available for

consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

## 17.11. Use of Information and Publication

All information, including but not limited to information regarding imetelstat or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory or biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of imetelstat, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report generated by the sponsor ("Clinical Study Report") and will contain eCRF data from all study sites that participated in the study, data directly transmitted into the sponsor's database (eg, bone marrow cytogenetics). Results of exploratory or biomarker or pharmacokinetic analyses performed after the Clinical Study Report has been issued may be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews may be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 90 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will

not mandate modifications to scientific content and does not have the right to suppress information, but the confidentiality of sponsor's information will be respected. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

**Registration of Clinical Studies and Disclosure of Results**

The sponsor will register and/or disclose the existence and the results of clinical studies as required by law.

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**Attachment 1: World Health Organization (WHO) 2008 Classification (Used in Part 2)**

| MDS Subtype | Findings: Peripheral Blood | Findings: Bone Marrow |
|---|---|---|
| Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT]) | Unicytopenia or bicytopenia<br>No or rare blasts (< 1%) | Unilineage dysplasia: ≥10% of the cells in one myeloid lineage<br><5% blasts<br><15% of erythroid precursors are ring sideroblast |
| Refractory anemia with ring sideroblasts (RARS) | Anemia<br>No blasts | ≥15% of erythroid precursors are ring sideroblasts<br>Erythroid dysplasia *only*<br><5% blasts |
| Refractory cytopenia with multi-lineage dysplasia (RCMD) | Cytopenia(s)<br>No or rare blasts (<1%)<br>No Auer rods<br><1 x $10^9$/L monocytes | Dysplasia in ≥10% of 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) | Cytopenias<br><5% blasts<br>No Auer rods<br><1 x $10^9$/L monocytes | Uni-lineage or multi-lineage dysplasia<br>5% to 9% blasts<br>No Auer rods |
| Refractory anemia with excess blasts-2 (RAEB-2) | Cytopenia(s)<br>5% to 19% blasts<br>Auer rods<br>± <1 x $10^9$/L monocytes | Uni-lineage or multi-lineage dysplasia<br>10% to 19% blasts<br>Auer rods ± |
| Myelodysplastic syndromes, unclassified (MDS-U) | Cytopenias<br><1% blasts | Unequivocal dysplasia in <10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS <5% blasts |
| Myelodysplastic syndromes associated with isolated del(5q) | Anemia<br>Usually normal or increased platelet count<br>No or rare blasts (<1%)<br>Platelets normal or increased | Normal to increased megakaryocytes with hypolobated nuclei<br><5% blasts<br>Isolated del(5q) cytogenetic abnormality<br>No Auer rods |

SOURCE: Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-951.

### Attachment 2: French-American-British (FAB) Cooperative Group Classification

Once a diagnosis of myelodysplastic syndrome (MDS) is established, 5 subtypes of MDS are recognized in the FAB classification that are distinguished by the percentage of myeloblasts, presence or absence ringed sideroblasts (ie, erythroid precursors with iron deposits surrounding the nucleus), or a monocytosis as summarized in the following table:

| FAB Category | Myeloblasts, % Bone Marrow | Blood | % Ringed Sideroblasts | Monocytes >1 x $10^9$/L |
|---|---|---|---|---|
| Refractory anemia (RA) | <5 | <1 | <15 | - |
| RA with ringed sideroblasts (RARS) | <5 | <1 | >15 | - |
| RA with excess blasts (RAEB) | 5–20 | <5 | Variable | - |
| Chronic myelomonocytic leukemia (CMML) | ≤20 | <5 | Variable | + |
| RAEB in transformation (RAEB-t) | 21–30 | ≥Auer rods | Variable | + / - |

SOURCE: Bennett JM, Catovsky D, Daniel MT et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-199.

**Attachment 3: International Prognostic Scoring System (IPSS) for Myelodysplastic Syndrome**

| Prognostic Variable | Survival and AML Evolution Score Value | | | | |
|---|---|---|---|---|---|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Marrow Blasts (%) | <5 | 5 to 10 | n/a | 11 to 20 | 21 to 30 |
| Karyotype[a] | Good | Intermediate | Poor | N/A | N/A |
| Cytopenias:<br>Neutrophil count <1800/µL<br>Platelets <100,000/µL<br>Hemoglobin <10 g/dL | 0 or 1 | 2 or 3 | N/A | N/A | N/A |

a Good: normal or any one of the following: -Y, del 5q, del 20q; Intermediate: any other abnormality; Poor: chromosome 7 abnormalities, complex, ≥3 abnormalities
N/A = not applicable.

| Risk Category: | Combined Score (Sum of Marrow Blast + Karyotype + Cytopenia Score) |
|---|---|
| Low | 0 |
| Intermediate-1 | 0.5 to 1.0 |
| Intermediate-2 | 1.5 to 2.0 |
| High | ≥2.5 |

SOURCE: Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.

**Attachment 4: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale**

| Grade | Score |
|---|---|
| 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 housework, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |

SOURCE: Eastern Cooperative Oncology Group (ECOG).
http://www.npcrc.org/files/news/ECOG_performance_status.pdf

## Attachment 5: International Working Group (IWG) Response Criteria 2006

**Proposed modified International Working Group response criteria for altering natural history of MDS**

| Category | Response Criteria (responses must last ≥4 weeks) |
|---|---|
| Complete remission (CR) | **Bone marrow**: ≤5% myeloblasts with normal maturation of all cell lines*<br>Persistent dysplasia will be noted*†<br>**Peripheral blood**‡: Hb ≥11 g/dL; platelets ≥100 x $10^9$/L; neutrophils ≥1.0 x $10^9$/L†; blasts, 0% |
| Partial remission (PR) | All CR criteria if abnormal before treatment except:<br>Bone marrow blasts decreased by ≥50% over pretreatment but still >5%<br>Cellularity and morphology not relevant |
| Marrow CR† | **Bone marrow**: ≤5% myeloblasts and decrease by ≥50% over pretreatment†<br>**Peripheral blood**: if HI responses, they will be noted in addition to marrow CR† |
| Stable disease | Failure to achieve at least PR but no evidence of progression for >8 weeks |
| Failure | Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment |
| Relapse after CR or PR | At least 1 of the following:<br>Return to pretreatment bone marrow blast percentage<br>Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets<br>Reduction in Hb concentration by ≥1.5 g/dL or transfusion dependence |
| Cytogenetic response | **Complete**: Disappearance of the chromosomal abnormality without appearance of new ones<br>**Partial**: At least 50% reduction of the chromosomal abnormality |
| Disease progression | For patients with:<br><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: ≥50% increase to >30% blasts<br>Any of the following:<br>≥50% decrement from maximum remission/response in granulocytes or platelets<br>Reduction in Hb by ≥2 g/dL<br>Transfusion dependence |

∗ Dysplastic changes should consider the normal range of dysplastic changes (modification).
† Modification to IWG response criteria.
‡ In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

**Attachment 5: (Continued): International Working Group (IWG) Response Criteria 2006**

**Proposed modified International Working Group response criteria for hematologic improvement**

| Hematologic Improvement* | Response criteria (responses must last ≥8 weeks)† |
|---|---|
| Erythroid response (pretreatment, <11 g/dL) | Hb increase by ≥1.5 g/dL<br>Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusion units/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of ≤9 g/dL pretreatment will count in the RBC transfusion response evaluation† |
| Platelet response (pretreatment, <100 x $10^9$/L) | Absolute increase of ≥30 x $10^9$/L for patients 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%† |
| Neutrophil response (pretreatment, <1 x $10^9$/L) | At least 100% increase and an absolute increase >0.5 x $10^9$/L† |
| Progression or relapse after HI‡ | At least 1 of the following:<br>At least 50% decrement from maximum response levels in granulocytes or platelets<br>Reduction in Hb by ≥1.5 g/dL<br>Transfusion dependence |

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

† Modification to IWG response criteria.

‡ 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 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

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

Abbreviations: CR: complete remission; DFS: disease-free survival; FAB: French-American-British; Hb: hemoglobin; HI: hematologic improvement; IWG: International Working Group; MDS: myelodysplastic syndromes; PFS: progression-free survival; PR: partial remission; RBC: red blood cell

SOURCE: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

## Attachment 6: Functional Assessment of Cancer Therapy – Anemia-Related Effects (FACT-An©)

### FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**Attachment 6 (Continued): Functional Assessment of Cancer Therapy – Anemia-Related Effects (FACT-An)**

## FACT-An (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**Attachment 6 (Continued): Functional Assessment of Cancer Therapy – Anemia-Related Effects (FACT-An)**

## FACT-An (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| HI7 | I feel fatigued | 0 | 1 | 2 | 3 | 4 |
| HI12 | I feel weak all over | 0 | 1 | 2 | 3 | 4 |
| An1 | I feel listless ("washed out") | 0 | 1 | 2 | 3 | 4 |
| An2 | I feel tired | 0 | 1 | 2 | 3 | 4 |
| An3 | I have trouble starting things because I am tired | 0 | 1 | 2 | 3 | 4 |
| An4 | I have trouble finishing things because I am tired | 0 | 1 | 2 | 3 | 4 |
| An5 | I have energy | 0 | 1 | 2 | 3 | 4 |
| An6 | I have trouble walking | 0 | 1 | 2 | 3 | 4 |
| An7 | I am able to do my usual activities | 0 | 1 | 2 | 3 | 4 |
| An8 | I need to sleep during the day | 0 | 1 | 2 | 3 | 4 |
| An9 | I feel lightheaded (dizzy) | 0 | 1 | 2 | 3 | 4 |
| An10 | I get headaches | 0 | 1 | 2 | 3 | 4 |
| B1 | I have been short of breath | 0 | 1 | 2 | 3 | 4 |
| An11 | I have pain in my chest | 0 | 1 | 2 | 3 | 4 |
| An12 | I am too tired to eat | 0 | 1 | 2 | 3 | 4 |
| BL4 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| An13 | I am motivated to do my usual activities | 0 | 1 | 2 | 3 | 4 |
| An14 | I need help doing my usual activities | 0 | 1 | 2 | 3 | 4 |
| An15 | I am frustrated by being too tired to do the things I want to do | 0 | 1 | 2 | 3 | 4 |
| An16 | I have to limit my social activity because I am tired | 0 | 1 | 2 | 3 | 4 |







Source: Cella D. Functional Assessment of Cancer Therapy – Anemia (FACT-An). Available at: https://eprovide.mapi-trust.org/instruments/functional-assessment-of-cancer-therapy-anemia#member_access_content. Copyright: FACT-An© David Cella, 1997. All rights reserved.

**Attachment 7: EuroQol 5-Dimension Questionnaire (EQ-5D-5L)**




**Health Questionnaire**

**English version for the USA**

## Attachment 7: EuroQol 5-Dimension Questionnaire (EQ-5D-5L) (Continued)

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

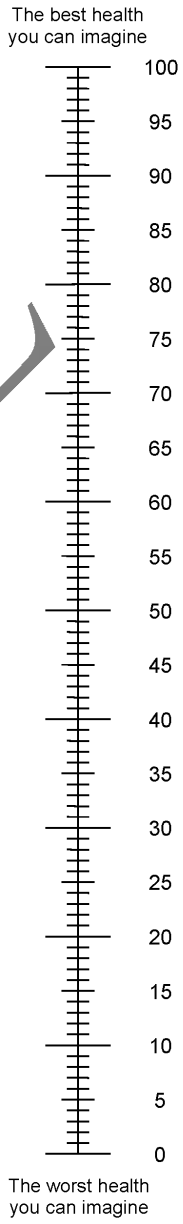
**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

## Attachment 7: EuroQol 5-Dimension Questionnaire (EQ-5D-5L) (Continued)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



**Attachment 8: QUALMS Questionnaire**

# The QUALMS

*The Quality of Life in Myelodysplasia Scale*



Patients often have different experiences over the course of their illness; however, please limit your responses to your experience **over the past week only**. The information you provide will remain strictly confidential.

| | During the past week, how often… | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| 1 | …did you feel as though there was a lack of clear information about your disease? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2 | …have you felt there was limited emotional support available for patients with MDS beyond their families? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3 | …did you feel as though you couldn't do anything about your disease? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4 | …did you feel the course of your disease was unpredictable? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5 | …did you have difficulty explaining MDS to your friends or family? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6 | …did you have trouble concentrating? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7 | …have you considered changing long-term plans due to health concerns? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8 | …have you experienced shortness of breath? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9 | …did low energy levels cause you to change your schedule? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10 | …did you feel as though your life was organized around medical appointments? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11 | …have you felt a sense of hopelessness? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12 | …have you been worried about getting an infection? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13 | …have you had sufficient energy for routine tasks? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14 | …were you afraid of dying? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15 | …did you feel angry about your diagnosis? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16 | …were you worried about bleeding? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 17 | …did you feel a sense of gratitude for a part of life that you took for granted before? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18 | …did you feel nauseated? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 19 | …did you worry about your MDS progressing or developing into leukemia? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 20 | …did you take into account that you might be fatigued when planning your activities? | ☐ | ☐ | ☐ | ☐ | ☐ |

Version 3

***Please continue on to the next page →***

## Attachment 8: QUALMS Questionnaire (Continued)

For the following questions, please again mark the answer choice that best represents your experiences and feelings **over the past week**. The information you provide will remain strictly confidential.

| | During the past week, how often… | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| 21 | …were you concerned that your MDS caused a financial burden for you or your family? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 22 | …did you feel your family relationships were strained by your disease? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 23 | …have you felt weak? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 24 | …have you been too tired to take on the responsibilities you used to have? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 25 | …did you worry about becoming a burden to your friends or family? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 26 | …were you unable to participate in activities you are used to doing? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 27 | …have you felt anxious about test or lab results? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 28 | …did you avoid crowds because of fear of getting an infection? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 29 | …did you find yourself grateful for tomorrow? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 30 | …did you feel you were able to find quality information about MDS treatments? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 31 | …were you concerned about bruising? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 32 | …did you feel as though there were a lack of concrete answers about what will happen with your MDS? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 33 | …did you experience a change in bowel habits? | ☐ | ☐ | ☐ | ☐ | ☐ |

For the following questions, **you may select "not applicable"** if the question does not apply to you.

| | During the past week, how often… | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| 34 | …were you afraid of losing your job? (**check here** ☐ if not applicable because you are unemployed/retired) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 35 | …did you feel too tired to drive? (**check here** ☐ if not applicable because you do not drive) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 36 | …were you afraid to have sex due to your blood counts? (**check here** ☐ if not applicable because you are not currently sexually active) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 37 | …were you afraid that your MDS treatment would stop working? (**check here** ☐ if not applicable because you are not currently being treated) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 38 | …have you been too tired to take care of a family member or loved one? (**check here** ☐ if not applicable because you are not providing such care) | ☐ | ☐ | ☐ | ☐ | ☐ |

Version 3

***Thank you for completing the QUALMS.***

**Attachment 9: PGIC Questionnaire**

**Patient's Global Impression of Change**

Since the start of the treatment you've received in this study, symptoms of your Myelodysplastic Syndrome are:

- ☐ 1. Very much improved
- ☐ 2. Somewhat improved
- ☐ 3. A little improved
- ☐ 4. No change
- ☐ 5. A little worse
- ☐ 6. Somewhat worse
- ☐ 7. Very much worse

## Attachment 10: Anticipated Events

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

***Disease-related***

- Dyspnea
- Fatigue
- Malaise
- Asthenia
- Pyrexia (fever)
- Infection
- Cytopenia
  - Anemia
  - Thrombocytopenia
  - Neutropenia
  - Febrile neutropenia
  - Leukopenia
  - Lymphopenia
  - Pancytopenia

***Population-related (Subjects ≥65 years)***

- Arrhythmia
  - Atrial fibrillation
- Cardiac failure congestive
- Myocardial infarction
- Cerebrovascular accident

**Reporting of Anticipated Events**

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events.

For anticipated events reported as individual SAEs, the sponsor will make the determination of relatedness in addition to and independent of the investigator's assessment. If an anticipated event is possibly related to study drug and meets criteria for expedited reporting, the sponsor will submit a safety report in an expedited manner.

**Statistical Analysis**

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

## Attachment 11: Ventricular Repolarization (QTc) Substudy

Subjects should not be enrolled in the Ventricular Repolarization Substudy until enrollment in the main study of Part 2 is complete unless a subject is known to meet criteria that would make the subject ineligible for the main study (eg, del 5 q, prior HMA therapy).

### Study Objectives

To evaluate the effect of imetelstat on ventricular repolarization in approximately 45 subjects:

The primary objective of this substudy is to determine the relationship between the plasma concentrations of imetelstat and QTc interval changes.

The secondary objectives of this substudy are as follows:

To investigate the effect of imetelstat on the following ECG parameters: heart rate, PR, QRS, and T-Wave morphology by using baseline adjusted ECGs on study drug versus placebo

To evaluate the pharmacokinetics of imetelstat

Safety and limited efficacy will be assessed as per the Time and Events Schedule below (Table 14). At the time of the primary analysis of this substudy, all safety data from the main study will be provided along with data specific to this set of subjects. In particular, any cardiac-related adverse events will be summarized in both main study and substudy populations. The DMC will review all substudy events on an ongoing basis.

### Study Design

The effect of imetelstat on ventricular repolarization will be centrally analyzed by a third-party cardiac safety laboratory in approximately 45 evaluable subjects (approximately 30 and 15 subjects in the imetelstat and placebo groups, respectively) enrolled at sites that are participating in the main study protocol. Subjects in both the imetelstat and placebo groups will be enrolled in a blinded manner as per the main protocol randomization criteria.

The subjects will undergo the same screening procedures as the main protocol in order to be randomized into the study with **the exception of** central submission and review of bone marrow exam for confirmation of diagnosis and central hematology sampling, which are not required. On study follow up bone marrow examinations are also not required for subjects enrolled on the substudy and are to be performed per investigator discretion and local standard of care.

If after a minimum of two cycles of treatment a subject enrolled on the substudy has no significant change to pRBC transfusion burden or evidence of clinical benefit per Investigator, after discussion with the sponsor, the subject may be unblinded. If the subject was on placebo treatment, he/she may be permitted to start treatment with imetelstat provided the subject meets criteria for dosing per Section 6.1 of the main study. If after unblinding the subject is on imetelstat, the subject may continue to receive treatment if the investigator determines there is a favorable risk-benefit profile. Subjects who are unblinded will follow the Time and Events Schedule (Table 14) depending on the study treatment to which they were initially randomized:

- Placebo: initiate imetelstat and restart assessments at Cycle 1 Day 1, except for the ECG and PK evaluations.
- Imetelstat: continue with the next planned cycle as per the Time and Events Schedule (Table 14).

## Substudy Eligibility Criteria

Subject eligibility will be reviewed and approved by the sponsor prior to randomization (as defined in Section 3.1).

***Inclusion Criteria:***

1. Man or woman ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place);
2. Diagnosis of MDS or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) according to WHO criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to C1D1.
3. IPSS low or intermediate-1 risk MDS (Attachment 3);
4. RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to Randomization (defined in Section 3.1); pre-transfusion Hb should be ≤9.0 g/dL to count towards the 4 units total;
5. Has MDS that is relapsed/refractory to ESA treatment as defined by meeting any one of the criteria below:
    5.1. Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U or darbepoetin alfa 150 mcg (or equivalent agent/dose), without having achieved a Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks
    5.2. Transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from at least 8 weeks of treatment with therapies outlined in inclusion criteria 5.1, in the absence of another explanation.
    5.3. Endogenous serum EPO level >500 mU/mL
6. Adequate iron stores, defined as transferrin saturation greater than 20% and serum ferritin greater than 400 ng/mL, measured within the screening period, or adequate iron stores as demonstrated by recent (within 12 weeks prior Randomization) bone marrow examination with iron stain
7. ECOG performance status 0, 1 or 2 (Attachment 4)
8. Hematology lab test values within the following limits:
    8.1. ANC ≥1.5 x $10^9$/L independent of growth factor support (defined in Section 9.1.3)
    8.2. Platelets ≥75 x $10^9$/L independent of platelet transfusion support (defined in Section 9.1.3);
9. Biochemical laboratory test values must be within the following limits:
    9.1. AST, ALT and ALP ≤2.5 times the upper limit of normal (x ULN)
    9.2. Serum creatinine ≤2.0 x ULN
    9.3. Total bilirubin ≤3 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion) **AND**

    Direct bilirubin ≤2 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion, where a direct bilirubin value of ≤3 x ULN or less than 1/3 of the total bilirubin value is acceptable);
10. Women of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception;

placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject). For females, these restrictions apply for 1 month after the end of dosing. Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening and agree to be tested on Day 1 of every cycle and at end of treatment (30 days post last dose);

11. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study. For males, these restrictions apply for 3 months after the end of dosing.
12. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of the procedures required for the study and are willing to participate in the study.
13. Provide informed consent for participation in this Ventricular Repolarization substudy.

***Exclusion Criteria:***

1. Subject has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients (refer to the IB[25]);
2. Subject has received an experimental or investigational drug or used an invasive investigational medical device within 30 days prior to randomization (defined in Section 3.1) or is currently enrolled in an interventional investigational study;
3. Prior treatment with imetelstat;
4. Have received corticosteroids >30 mg/day prednisone or equivalent within 4 weeks prior to randomization;
5. Has received an ESA or any anti-MDS therapy, chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to Randomization (8 weeks for long-acting ESAs);
6. Prior history of hematopoietic stem cell transplant;
7. Anemia attributed to factors other than MDS (including hemolysis, chronic renal failure, hepatitis, and gastrointestinal bleeding);
8. Major surgery within 4 weeks prior to randomization (excluding the placement of vascular access and other minor surgical procedures);
9. Diagnosed or treated for malignancy other than MDS, except:
    9.1. Malignancy treated with curative intent and with no known active disease present for ≥3 years before randomization
    9.2. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    9.3. Adequately treated cervical carcinoma in situ without evidence of disease;
10. Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics;

11. Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or known acute or chronic liver disease including cirrhosis;
12. Females who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 1 month after the end of dosing;
13. Males who plan to father a child while enrolled in this study or within 3 months after the end of dosing;
14. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments;
15. Subject was previously assessed as having IPSS intermediate-2 or high risk MDS;
16. Concurrent therapy with medications known to prolong the QT interval and have been associated with Torsade de pointes arrhythmia (TdP) (refer to www.crediblemeds.org for the list of drugs to avoid)
17. Cardiac function abnormalities on screening ECG as follows:
    - Resting heart rate outside of 50 to 100 beats per minute
    - QTcF >470 msec (or QTcF >490 msec in the presence of a right bundle branch block or ventricular conduction delay [QRS >119 msec]), as determined by central assessment based on the average value of a triplicate set of ECGs
    - Diagnosed or suspected congenital long QT syndrome
    - Family history of sudden unexpected death from cardiac-related causes if indicative of a pathogenic mutation of cardiac ion channels
    - Family history of congenital long QT syndrome
    - History of Mobitz II second degree or third degree heart block
    - Implantable pacemaker or automatic implantable cardioverter defibrillator
    - Complete left bundle branch block
    - Chronic or persistent atrial arrhythmia including atrial fibrillation and atrial flutter
    - History or presence of clinically relevant heart rhythm disturbances including atrial, junctional, re-entry, and ventricular tachycardia
    - Unusual T-wave morphology (ie, bifid T-wave) likely to interfere with QT measurements.
18. History or evidence for any of the following: severe or unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks) within 12 months prior to Cycle 1 Day 1, New York Heart Association (NYHA) Class II to IV heart disease
19. Presence of uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension are permitted, provided that BP is controlled to within these limits by anti-hypertensive treatment
20. Any skin condition likely to interfere with electrocardiographic electrode placement or adhesion.
21. History of thoracic surgery likely to cause abnormality of the electrical conduction through thoracic tissues.

**Schedule of Events**

Subjects on the Ventricular Repolarization substudy will follow the Ventricular Repolarization Time and Events Schedule (Table 14) below.

**Table 14 Time and Events Schedule for Part 2 Ventricular Repolarization Substudy[a]**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| Study Procedures | Comments | Up to 28 days before Randomization | Cycle 1 Day 1 (predose) | Cycle 1 Day 8, 15, 22 | Cycle 2 Day 1, 8, 15, 22 | Cycle 3 Day 1 until EOT | EOT Visit 30 ±3 days after last dose | Survival Follow-up Every 12-16 weeks |
| ***Screening*** | | | | | | | | |
| Informed consent | Refer to Section 9.1.3for guidance regarding COVID-19 and further clarification of screening procedures. | X | | | | | | |
| Inclusion/exclusion criteria | | X | X | | | | | |
| Medical history and demographics | | X | | | | | | |
| ***Study Medication Administration*** | | | | | | | | |
| Randomization | Randomization will occur on C1D1 or up to 72h prior to study drug administration | | X | | | | | |
| Dispense/administer study drug | Refers to Imetelstat or placebo (see Section 6). The screening weight is considered baseline for dose calculation. Recalculate dose if ≥10% weight change from baseline. Dosing should begin within 72 hours of randomization in IWRS. | | X | | X (D1 only) | X | | |
| ***Safety Assessments*** | | | | | | | | |
| Physical exam (including weight) | Full PE at Screening; limited symptom-directed PE thereafter. Refer to Section 9.8.4 for guidance regarding COVID-19. | X | X | | X (D1 only) | X | X | |
| Vital signs | Includes temperature, HR, SBP and DBP (preferably in a seated position). Measured and recorded prior to infusion. | X | X | | X (D1 only) | X | X | |
| 12-lead ECG | | Refer to Table 15 | | | | | | |
| ***Efficacy Assessments*** | | | | | | | | |
| Transfusion history and status; myeloid growth factor treatment | Assessment of RBC transfusion requirement 16 weeks prior to Randomization and at each clinic visit until the end of treatment. Sites should make every attempt to obtain complete information, including both in-patient and out-patient transfusions (see Section 9.3.1.1 for additional information). Pre-transfusion Hb must be documented. Note: if DE Visit does not align with a Cycle Day 1 visit, then hematology (local) is required at the DE Visit. | X | X | | X (D1 only) | X | X | X (every 4-6 weeks) until first transfusion in Posttreatment follow-up |
| Hematology (local laboratory) | Screening tests should be within 14 days prior to Randomization. For C1D1, no need to repeat if Screening tests performed within 5 days. Refer to Inclusion Criteria above for further details. After C1D1, tests must be performed within 48h before the scheduled visit. For all cycles, if tests are repeated on the day of the visit, the most recent results should be reviewed before dosing. Perform unscheduled weekly follow-up after any Grade ≥3 thrombocytopenia or neutropenia until values return to baseline. | X | X | X | X | X | X | X (first visit if feasible) |

**Table 14 Time and Events Schedule for Part 2 Ventricular Repolarization Substudy[a]**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| Study Procedures | Comments | Up to 28 days before Randomization | Cycle 1 Day 1 (predose) | Cycle 1 Day 8, 15, 22 | Cycle 2 Day 1, 8, 15, 22 | Cycle 3 Day 1 until EOT | EOT Visit 30 ±3 days after last dose | Survival Follow-up Every 12-16 weeks |
| | Testing should be conducted pre-transfusion, if feasible. Hematology panel includes hemoglobin, platelet count, white blood cell count, ANC. Absolute peripheral blast count should be done prior to randomization and on D1 of each cycle only. Note: if DE Visit does not align with a Cycle Day 1 visit, then hematology (local) is required at the DE Visit. | | | | | | | |
| BM aspirate, biopsy | A BM aspirate and biopsy with iron stain performed locally within12 weeks prior to Randomization will be used for determination of eligibility. Local cytogenetics results within 12 months prior to randomization are also required to determine eligibility per IPSS. If cytogenetic testing cannot be performed locally, a sample may be sent for central review. | X | BM aspirate and biopsy per local standard of care or investigator discretion. | | | | | |
| Response assessment | Per modified IWG 2006; see Attachment 5. Response assessments to be performed per local standard or investigator discretion. Note: CR, PR or mCR only to be assessed in subjects with >5% baseline bone marrow aspirate blasts | | Every 12 weeks from C1D1 (±1 week) up to week 72, then every 24 weeks until suspected PD | | | | | At suspected PD, if feasible |
| ECOG performance status | See Attachment 4 | X | X | | X (D1 only) | X | X | |
| Survival status and subsequent therapy | Survival status and subsequent therapy are planned to be collected at the EOT visit and throughout survival follow-up period at least every 12 to 16 weeks (data may be collected more frequently, if needed). | | | | | | X | X |
| ***Clinical Laboratory Assessments*** | | | | | | | | |
| Chemistry (local laboratory) | Screening tests should be performed within 14 days prior to Randomization. For C1D1, no need to repeat if Screening tests performed within 5 days. After C1D1, tests must be performed within 48h before the scheduled visit. Refer to Inclusion Criteria above for further details. Refer to Sections 9.8 and 9.8.1 for additional detail on required clinical laboratory testing. | X | X | X | X (D1 only) | X | X | |
| Chemistry panel for LFT investigations (local laboratory) | Includes GGT, chloride, bicarbonate, magnesium, and fractionated bilirubin. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, repeat chemistry panel and LFT investigations panel weekly until bilirubin with fractionation is <3x ULN, and AST, ALT and ALP is <5x ULN. Subjects with Grade 1 or Grade 2 elevations in AST, ALT, ALP or bilirubin at time of treatment discontinuation should continue to have tests monthly until resolution to at least baseline grade or until the start of subsequent therapy, whichever comes first. | | If an adverse event of interest occurs | | | | | |
| INR (or PT) and aPTT (local laboratory) | With additional assessments performed during treatment phase if subject has a hemorrhagic event. | X | Repeat during study if subject has a Grade ≥3 bleeding event | | | | | |
| Serum EPO level (local laboratory) | | X | Repeat during study per local standard of care or investigator discretion. | | | | | |

**Table 14 Time and Events Schedule for Part 2 Ventricular Repolarization Substudy[a]**

| | PHASE | Screening Phase | Treatment Phase (4-week cycles ±3 days) | | | | | Posttreatment Follow-up Phase |
|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | **Comments** | **Up to 28 days before Randomization** | **Cycle 1 Day 1 (predose )** | **Cycle 1 Day 8, 15, 22** | **Cycle 2 Day 1, 8, 15, 22** | **Cycle 3 Day 1 until EOT** | **EOT Visit 30 ±3 days after last dose** | **Survival Follow-up Every 12-16 weeks** |
| Serum ferritin, transferrin saturation (local laboratory) | Total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site. | X | X | | X (D1 only) | X | X | |
| B12 / folic acid / reticulocytes (local laboratory) | | X | | | | | | |
| Hepatitis serologies | Comprehensive hepatitis serology panel A through E. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg). If the subject screening window is >28 days (Section 9.1.3), hepatitis screening results may still be used to determine eligibility outside of the initial 28-day screening period provided the subject is asymptomatic and does not meet Exclusion Criteria no. 11 above. | X | | | | | | |
| Serum or urine pregnancy test | | X | | | X (D1 only) | X | X | |
| ***Pharmacokinetics*** | | | | | | | | |
| Pharmacokinetic samples | Refer to Table 15 | | | | | | | |
| ***Ongoing Subject Review*** | | | | | | | | |
| Concomitant therapy | | X | Continuous | | | | X | |
| Adverse events | | X | Continuous | | | | X | |

Abbreviations: BM=Bone Marrow; C=Cycle; CR=complete remission; CyTOF=cytometry by time of flight ; D=Day; DBP=diastolic blood pressure; EOT=end of treatment; EPO=erythropoietin; EQ-5D-5L=EuroQol-EQ-5D-5L; FACT-An= Functional Assessment of Cancer Therapy - Anemia-Related Effects; HI-E (Hb)=hematologic improvement-erythroid (hemoglobin); HR=heart rate; GGT= gamma-glutamyl transpeptidase; hTERT= human telomerase reverse transcriptase; INR=international normalized ratio; IRR=infusion-related reaction; IWRS= interactive web response system; PD=disease progression; PE=physical exam; PGIC= Patient Global Impression of Change; PK=pharmacokinetic; PR=partial remission; PT=prothrombin time; QUALMS= Quality of Life in Myelodysplasia Scale; SBP=systolic blood pressure; TA=telomerase activity; TL=telomerase length; ULN=upper limit of normal

[a] Subjects who are unblinded will follow the schedule depending on the study treatment to which they were initially randomized. If placebo, initiate imetelstat and restart assessments at Cycle 1 Day 1 (except for the ECG and PK evaluations). If imetelstat, continue with the next planned cycle.

**Table 15 ECG and PK Assessments for Part 2 Ventricular Repolarization Substudy**

| Study Procedure | Screening | Cycle 1 Day 1[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | - | -1 hr (1hr prior to dose) | -0.5 hr (half hour prior to dose) | 0 hr (immediately pre-dose) | 0.5 hr | 1 hr | 2 hr (immediately before end of infusion) | 4 hr | 6 hr | 8 hr |
| Triplicate 12-lead ECG | X | X | X | X | X | X | X | X | X | X |
| PK samples[b] | | | | | X | X | X | X | X | X |

hr=hours

[a] All times on Cycle 1 Day 1 are relative to the start of infusion

[b] PK samples are to be collected immediately after the triplicate ECG assessment is completed. Exact time of PK sample collection should be recorded. Subjects participating in the Ventricular Repolarization substudy will have a total of 6 mL additional blood collected (3 additional samples) for PK assessment than in the Part 2 main study.

**Methods specific to the Ventricular Repolarization Assessments:**

Digital 12-lead ECG equipment will be provided to each clinical site participating in this substudy by the central laboratory for the duration of the substudy.

ECGs will be collected via Holter Monitoring using a 12-lead ambulatory device. ECGs should be collected after the subject has rested quietly and is awake in a fully supine (or semi-recumbent, if supine is not tolerated) position for 10 minutes and prior to any blood collection. For each subject, the same position (eg, supine or semi-recumbent) should be used for all ECGs collected. Starting on Cycle 1, Day 1, 0.5 hr time point matched blood samples for pharmacokinetic analyses will be collected immediately following the collection of ECGs and before the collection of blood for all other clinical evaluations. ECGs will be read by independent cardiologists from the central laboratory in a blinded manner and via a single reader paradigm.

**Schedule of Events Specific to the Ventricular Repolarization Assessments:**

A detailed list and schedule of the required assessments for Ventricular Repolarization assessment is provided below and in Table 14.

The subject should be maintained in the same supine position for each of the 12-lead ECGs. The total volume of blood anticipated for the Ventricular Repolarization substudy due to the intensive PK sampling is expected to be 6 mL (3 additional samples) more than the main study population.

☐ **Screening**

Collect a set of triplicate 12-lead ECGs, 2 minutes apart.

☐ **Cycle 1, Day 1**

At 1 hour and a half hour prior to administering the first dose of study drug, collect a set of triplicate 12-lead ECGs, 2 minutes apart for each time point, respectively.

At time 0, just prior to administering the first dose of study drug, collect a set of triplicate 12-lead ECGs, 2 minutes apart.

Administer blinded study drug.

At 0.5 hours after start of infusion (SOI), 1 hour after SOI, immediately before the end of 2-hour infusion, 4, 6, and 8 hours after SOI, collect a set of triplicate ECGs, 2 minutes apart, and 1 blood sample for PK analysis for each time point, respectively.

**Blood Volume for the Ventricular Repolarization Substudy**

**Table 16: Volume of Blood to be Collected from Each Subject in the Ventricular Repolarization Substudy**

| Type of Sample | Volume per Sample (mL) | No. of Samples per Subject [a] | Total Volume of Blood (mL) [b] |
|---|---|---|---|
| Safety (including screening and posttreatment assessments) | | | |
| - Hematology | 5 | 18 | 90 |
| - Prothrombin time (PT)/ international normalized ratio (INR) and activated partial thromboplastin time (aPTT) | 5 | 1 | 5 |
| - Serum EPO level | 2 | 1 | 4 |
| - Serum chemistry [c] | 10 | 17 | 170 |
| - B12/folic acid/reticulocytes, serum ferritin (screening), transferrin saturation [d] | 5 | 1 | 5 |
| - Serum Ferritin (post-screening) | 5 | 12 | 60 |
| - Hepatitis serologies | 13 | 1 | 13 |
| - Serum β-hCG pregnancy tests | 2 | 1 | 2 |
| Pharmacokinetic samples | 2 | 6 | 12 |
| Approximate Total | | | 361 mL |

Note: An indwelling intravenous cannula may be used for blood sample collection.
[a] Volumes below derived for median 12 cycle duration and includes end of treatment visit.
[b] Calculated as number of samples multiplied by amount of blood per sample.
[c] Serum chemistry includes basic liver function tests. An expanded panel of liver function tests may also be required for safety reasons. See Time and Events Schedule above.
[d] Total iron binding capacity and serum iron (Fe) may be performed to calculate transferrin saturation if transferrin saturation is not available at the site

**Rationale for the Study Design**

In accordance with ICH E14 guideline, QT evaluation is now expected to be routine in oncology drug development, and a thorough QT (TQT) study should be conducted, if possible, in healthy subjects.

Due to the mechanism of action and safety profile of imetelstat (predominantly cytopenia), administration of imetelstat to healthy subjects at clinically relevant doses is not advised. The maximum tolerated dose is different in various patient populations: 7.5 mg/kg every 4 weeks (q4w) in MDS patients; 9.4 mg/kg every 3 weeks (q3w) in MF patients, and 11.7 mg/kg q4w in solid tumor subjects. Various Phase 1 and 2 solid-tumor studies did not show meaningful clinical activity and do not warrant further clinical investigation. The current focus of clinical development is on hematologic malignancies, namely MDS and MF. Although the clinical dose in MDS subjects (7.5 mg/kg) is lower than that in MF subjects (9.4 mg/kg), the exposure in MDS subjects at 7.5 mg/kg is higher than that achieved in MF subjects with 9.4 mg/kg. Therefore, the exposure in MDS subjects dosed at 7.5 mg/kg represents the highest clinical exposure among hematologic malignancies under active clinical development. A supratherapeutic dose is not feasible since 7.5 mg/kg appears to be the maximum tolerated dose for MDS subjects.

Part 1 of MDS3001 enrolled both males and females, with females on average exhibiting 27% and 20% higher $C_{max}$ and AUC than males respectively. Enrollment of both males and females is expected in the Ventricular Repolarization substudy in Part 2, which should lead to adequate representation of each sex in the QT evaluation.

Pharmacokinetics data from Study MDS3001 (Part 1) and Study MYF2001 consistently demonstrated a plasma half-life of approximately 4 to 5 hours and no plasma accumulation at later cycles (starting from Cycle 2 Day 1) when imetelstat is given q3w or q4w. The catabolism of the oligonucleotide is expected to produce shorter-length oligonucleotides and thus expected to have similar or shorter half-lives in plasma. Time points for ECG and pharmacokinetic measurements have been selected to match the expected pharmacokinetic profile of imetelstat so that correlations between ECG changes and drug exposure may be appropriately evaluated. In addition, to assess potential delayed QT effects, time-matched PK and ECG samples are collected at later time points when the plasma concentration of imetelstat is expected to be very low. Given these considerations, triplicate ECGs followed by blood samples for pharmacokinetic assessment will be collected at 0.5 and 1 hour post start of infusion, 2 hour (immediately before end of infusion; EOI), 4, 6, and 8 hours after SOI on Cycle 1 Day 1.

To assess the QT interval prior to imetelstat exposure, baseline triplicate ECG assessments will be performed prior to the first study drug administration at three separate time points on Cycle 1 Day 1 (1 hour pre-dose, half hour pre-dose and immediately pre-dose). Because this is a randomized placebo-controlled blinded study design, the inclusion of the placebo data allows for the detection of diurnal variation (Garnett et al 2018[c]), baseline triplicate ECG assessment will be collected on Cycle 1 Day 1 at the time points noted previously. Following the hour 0 assessments, time-matched triplicate ECG assessment will be collected at hour 0.5, 1, 2 (immediately before EOI), 4, 6, and 8 on Cycle 1 Day 1. PK samples are to be collected immediately after ECGs.

Based on the known and expected pharmacokinetic properties of imetelstat, the proposed pharmacokinetic and ECG time points on Cycle 1 Day 1 are deemed adequate to characterize the relationship between exposure and effect on QT/QTc.

**Sample Size Determination**

The Innovation and Quality in Pharmaceutical Development — Cardiac Safety Research Consortium (IQ-CSRC) prospective study[a] showed that QT assessments performed in a small single ascending dose like clinical pharmacology study, using an intense ECG schedule and exposure-response (ER) analysis, can detect, and therefore also exclude, small QT effects with the same level of confidence as would a TQT study.

In the current substudy, approximately 45 evaluable subjects will be required to enroll with the aim to obtain ECG and pharmacokinetic data from 30 subjects on active treatment and 15 subjects on placebo. Subjects who are not evaluable for QTc substudy primary ECG endpoint may be replaced with new subjects. Garnett et al[b] evaluated the operating characteristics of the ER models via simulation, focusing on the performance of concentration-QTc models applied to data obtained in crossover and parallel studies. False negatives were 2% to 6% for crossover and 2% to 9% for parallel studies, with 12 to 60 subjects per treatment for a

[a] Darpo B, Benson C, Dota C, et al. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. 2015 Apr;97(4):326-335.

[b] Garnett C, Needleman K, Liu J, Brundage R, Wang Y. Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther. 2016 Aug;100(2):170-178.

[c] Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. [Published correction appears in J Pharmacokinet Pharmacodyn. 2018;45(3):399]. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

dose with 10-ms mean effect. Therefore, 30 subjects on active treatment and 15 subjects on placebo used in the current study should have sufficient power to conduct a proper ER analysis. Subjects in the QTc substudy may enter the Extension Phase after the clinical cut off for the primary analysis (the exposure-response analysis) for the QTc substudy is reached. After the primary analysis, the investigator will unblind remaining subjects and, per investigator decision, have the subject crossover to imetelstat prior to entering Extension Phase. The subjects will undergo the same screening procedures as the main protocol (see Section 9.1.6).

**Statistical Methods**

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. The exposure-response (ER) analysis (primary analysis for the QTc substudy) in the substudy based on approximately 45 evaluable subjects and will be performed when all evaluable subjects have completed Cycle 2. The analysis will be completed separately from the primary analysis of 170 subjects in the main study of Part 2. These data may be available after the primary analysis of the main study has already been completed. A general description of the statistical methods to be used to analyze the QTc data is outlined below. Additional details for ECG and ER analysis will be provided in the Ventricular Repolarization Substudy Cardiac Statistical Analysis Plan (SAP). Other Safety data and available efficacy data from the substudy will be summarized as described in the main study SAP.

Standard ECG parameters will be determined for each ECG recording. Corrected QTc intervals will be determined using QTcF and QTcB. Changes in ECG intervals from time-matched baseline will be calculated. Baseline will be defined as the mean of the values for the triplicate ECG measurements taken at 3 time points (-1 hour, -0.5 hour, and 0 hour) prior to treatment administration on Cycle 1 Day 1. In addition, QTcFs will be categorized based on ICH E14 guidelines. Tables will present the number and percentage of subjects meeting or exceeding the following categories:

QTc interval prolongation:

Absolute values >450 to ≤480 msec

Absolute values >480 to ≤500 msec

Absolute values >500 msec

QTc interval change from baseline:

Increase from baseline >30 to ≤60 msec

Increase from baseline >60 msec

The primary analysis for this substudy will be based on an ER analysis of the relationship between time-matched, baseline-adjusted QTcF (ΔQTcF) and imetelstat plasma concentrations by linear mixed-effects modeling approach. The ΔΔQTcF value will be calculated as the placebo-corrected ΔQTcF estimated from the model. Subjects who received study drug and had at least 1 pair of predose and postdose QTc data for at least 1 time point will be included in the ER analysis.

The exposure-response relationship will be evaluated using linear model of ΔQTcF as the dependent variable. The data from the study drug and placebo treatment will be included in the model. The drug concentration level will be set to zero for placebo treatment. The independent variables included in the model will be imetelstat plasma concentrations as the explanatory variate (0 for placebo), centered baseline QTcF (i.e., baseline QTcF for individual subject minus the population mean baseline QTcF for all subjects)

as an additional covariate, treatment (active = 1 or placebo = 0), time (i.e., nominal post-dose time point) as fixed effects, and random effects on the intercept and slope per subject (Garnett et al 2018[c]).

The key assumptions of the linear mixed-effects model will be absence of hysteresis and linearity of the concentration-response relationship. The linearity of the concentration-response relationship will be evaluated by visual inspection of relevant goodness-of-fit (GOF) plots. If the linear concentration-response relationship model appears to be inappropriate, a non-linear model, such as $E_{max}$, log-linear or other sigmoid relationships, will be explored. To detect hysteresis, mean ΔΔQTcF at each nominal time point will be calculated as the difference between the mean ΔQTcF for study drug minus mean ΔQTcF for placebo. Mean ΔΔQTcF will be plotted against nominal time to evaluate the nominal time point of maximum response. Absence of hysteresis will be concluded if the time point of maximal effect does not differ from the time of peak plasma concentration ($t_{max}$) by more than an hour. If the assumption of absence of hysteresis does not appear to hold, pharmacokinetic-pharmacodynamic models, such as an effect compartment model or an indirect response model, will be explored. If deemed necessary, the concentration-ΔQTc models will be fit for QTc calculated using other appropriate methods.

**Criteria for a "QT negative" result**

The criterion for a "QT negative" drug is that the upper bound of the 2-sided 90% confidence interval (CI) of the predicted mean ΔΔQTc is <20 ms at the observed geometric mean $C_{max}$ at 7.5 mg/kg dose of imetelstat.[a,b]

[a] Rock EP, Finkle J, Fingert HJ, et al. Assessing proarrhythmic potential of drugs when optimal studies are infeasible. Am Heart J. 2009;5:827-836.

[b] Sarapa N, Britto MR Challenges of characterizing proarrhythmic risk due to QTc prolongation induced by nonadjuvant anticancer agents. Expert Opin. Drug Safety. 2008;7: 305–318.

INVESTIGATOR AGREEMENT

**PROTOCOL AMENDMENT ACCEPTANCE FORM**

| | |
|---|---|
| **TITLE:** | A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment |
| **PROTOCOL:** | 63935937MDS3001, Amendment 8/USA-1 |
| **IND:** | N/A |
| **EUDRACT NUMBER:** | 2015-002874-19 |
| **STUDY DRUG:** | Imetelstat Sodium for Injection (GRN163L for Injection) |
| **SPONSOR:** | Geron Corporation<br>919 E. Hillsdale Blvd., Suite 250<br>Foster City, CA 94404 USA |

I agree to conduct the study in accordance with the current protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

Please return a copy to Geron at the address provided below. Please retain the original for your study files.
Geron Corporation, Clinical Operations
919 E. Hillsdale Blvd., Suite 250
Foster City, CA 94404 USA

## PROTOCOL FINALIZATION SIGNATURE PAGE

| | |
|---|---|
| **TITLE:** | A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment |
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| **IND:** | N/A |
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| **STUDY DRUG:** | Imetelstat Sodium for Injection (GRN163L for Injection) |
| **SPONSOR:** | Geron Corporation<br>919 E. Hillsdale Blvd., Suite 250<br>Foster City, CA 94404 USA |

[redacted], MD [redacted]

Date