Official Title:	**A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor**
NCT Number:	NCT02426086
Document Date:	Protocol Amendment 5: 28 March 2019

Geron Corporation*

Clinical Protocol

A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

Protocol 63935937MYF2001; Phase 2
AMENDMENT 5

GRN163L (imetelstat)

* As of protocol amendment 5, the term "sponsor", as used throughout this protocol, refers to Geron Corporation. Prior to protocol amendment 5, this study was sponsored by Janssen Research & Development or its related legal entities.

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

EudraCT NUMBER: 2015-000946-41

Status: Approved
Date: 28 March 2019
Prepared by: Geron Corporation

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	8 Apr 2015
Amendment 1	23 November 2015
Amendment 2	29 September 2016
Amendment 3	13 March 2018
Amendment 4	20 December 2018
Amendment 5	28 March 2019

Amendments are listed beginning with the most recent amendment.

Amendment 5 (28 March 2019)

The overall reason for the amendment: To update sponsorship change to Geron Corporation.

Applicable Section(s)	Description of Change(s)
Rationale: To reflect change of sponsorship as of protocol amendment 5.	
Cover page, 3.2.1. Rationale for Protocol Changes Following the First Interim Review, 6. Dosage and Administration, Investigator Agreement	Change of sponsor name from Janssen Research & Development to Geron Corporation, including change of product designation.
Rationale: To align with new sponsor policies and manuals and to provide the most up-to-date version of the investigator brochure.	
7.Treatment Compliance, 14.4 Preparation. Handling, and Storage, 15. Study-specific Materials	To replace the 2 Janssen Pharmacy Manuals (Site Investigational Product Procedures Manual [SIPPM] and the Investigator Product Procedure Manual [IPPM]) by 1 manual, named ‘Site Investigational Product Manual (SIPM)”.
12. Adverse Event Reporting	Added “or its affiliates” to the statement mentioning that the sponsor has established Standard Operating Procedures in conformity with regulatory requirements.
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.
References	To provide the most up-to-date version of the investigator brochure (ie, Edition 14, dated 30 October 2018).

Amendment 4 (20 December 2018)

The overall reason for the amendment: This amendment allows the Extension Phase established in Amendment 3 to continue for a second year.

Applicable Section(s)	Description of Change(s)
Rationale: Continuation of the Extension Phase is required to allow subjects still benefiting from study drug to continue treatment. It is anticipated that increasing the duration of the Extension Phase from 1 year to 2 years will allow all subjects to receive adequate treatment and will allow for additional maturity of the survival data and a more precise estimate of overall survival.	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 3.2.2 Rationale for the Extension Phase; 9.1.5 Extension Phase; 17.9.1 Study Completion	The duration of the Extension Phase was increased from 1 year to 2 years. The Extension Phase will end approximately 2 years after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first.
3.2.2 Rationale for the Extension Phase	Text added: [redacted]
Rationale: Clarification of text was required.	
Title page	The underlined text was added: "US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)."
Time and Events (Extension Phase)	Footnote b was clarified for consistency with reporting requirements: "Submit a Serious Adverse Event Form to the sponsor within 24 hours of ~~onset~~ awareness of the event for all serious adverse events."
Amendment 3 (13 March 2018)	
The overall reason for the amendment: Sufficient data for the final study analysis have been collected. An Extension Phase was added to the protocol to allow continued treatment for subjects benefiting from treatment with study drug. The Extension Phase includes safety follow-up of subjects via serious adverse event collection and continued follow-up for survival status.	

Applicable Section(s)	Description of Change(s)
Rationale: The study is closed to further subject enrollment. Subjects who have not withdrawn from the main study may continue study participation in an Extension Phase. It is anticipated that 1 year will allow sufficient time for all subjects to receive adequate treatment and allow additional maturity of the survival data.	
Synopsis (Overview of Study Design); 3.1. Overview of Study Design	Subjects who are benefiting from imetelstat treatment when the end of the main study is reached may continue treatment in the newly added Extension Phase. Treatment may continue until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. Subjects in the Posttreatment Follow-up Phase will enter the Extension Phase to continue follow-up of survival status. The Extension Phase will end approximately 1 year after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first.
Synopsis (Dosage and Administration); 6. Dosage and Administration	Text was added stating that guidelines for imetelstat dosage and administration for subjects who continue treatment during the Extension Phase will follow those described for the Treatment Phase.

Applicable Section(s)	Description of Change(s)
Synopsis (Safety Evaluations); 3.1. Overview of Study Design; 11.11. Data Analysis Committee	Confirmation was added that the Hepatic Expert Committee and Sponsor Committee will continue to review data collected during the Extension Phase, as required.
3.1. Overview of Study Design	A schematic overview of the Extension Phase was added as Figure 2.
3.2.2. Rationale for Extension Phase; 9.1.5. Extension Phase	New sections were added.
7. Treatment Compliance	A statement was added to clarify that guidelines for study drug administration and data collection in place during earlier phases of the study are in effect for the Extension Phase.
8. Prestudy and Concomitant Therapy	A statement was added to clarify that all recommendations regarding the use of concomitant therapy are applicable to the Extension Phase.
17.9.1. Study Completion	Text was added to indicate that the full study will end with the completion of the Extension Phase.
Synopsis (Overview of Study Design); Time and Events Schedule (Main Study); 3.1. Overview of Study Design; 9.1.1. Overview; 11.4. Efficacy Analyses; 17.4. Source Documentation; 17.9.1. Study Completion	Clarification was added to distinguish between the main study and the full study. The full study includes the Extension Phase.
Rationale: Sufficient data will have been collected at the time of Amendment 3 to allow the final study analysis to occur; therefore, the scope of data collected during the Extension Phase has been reduced.	
Time and Events Schedule (Extension Phase)	A new Time and Events Schedule was added for the Extension Phase.
Synopsis (Safety Evaluations); 9.1.1. Overview; 12.3.4. Pregnancy	The scope of data collection during the Extension Phase was described.
12.3.1. All Adverse Events	As of Amendment 3, only serious adverse event will be reported using the Serious Adverse Event Form.
17.4. Source Documentation	Text was added to describe requirements for source documentation during the Extension Phase.
Rationale: The sponsor's commitment to provide continued treatment beyond the 1-year Extension Phase has been restated.	

Applicable Section(s)	Description of Change(s)
17.9.1. Study Completion	The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue ~~treatment after the end of the study~~ their assigned treatment.
Rationale: Enhanced data collection is required to help characterize serious hemorrhagic adverse events and serious hepatic adverse events.	
12.3.2. Serious Adverse Events	A subsection was added to guide collection of additional data for subjects who experience serious hemorrhagic adverse events or serious hepatic adverse events.
Rationale: A description of the analysis planned for data collected during the Extension Phase is required.	
Synopsis (Statistical Methods); 11.4. Efficacy Analyses	The last 2 planned efficacy analyses include: (4) the final analysis at the end of the main study, which is defined as 18 months after the last subject is enrolled or when the sponsor terminates the study~~, whichever comes first~~; and (5) OS-related analysis will be performed or updated when the Extension Phase has ended.
Rationale: Updated information regarding hematologic toxicity, non-hematologic toxicity, and hepatotoxicity is available.	
1.1.5.3.1. Hematologic Toxicity; 1.1.5.3.2. Non-hematologic Toxicity; 1.1.5.3.3. Hepatotoxicity	Text was added directing investigators to the current Investigator's Brochure for the latest description of hematologic, non-hematologic, and hepatic safety information. The information retained in Section 1 support the design of the main study.
Rationale: Progressive disease of myelofibrosis was incorrectly identified as an anticipated event rather than a study endpoint.	
12.3.1. All Adverse Events	Text was corrected to indicate that progressive disease of myelofibrosis is not an anticipated event, but rather a study endpoint.
Rationale: A later version of the Investigator's Brochure is available.	
References	Reference 21 was updated to the current version of the Investigator's Brochure.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (29 September 2016)

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: Changes to study conduct are required following the first interim review, which included data for 40 subjects (20 subjects per treatment arm) followed-up for at least 12 weeks.

Applicable Section(s)	Description of Change(s)
Rationale: [redacted]	

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design); 3.1. Overview of Study Design 11.2. Sample Size Determination	Text was added to acknowledge that the original study design allowed for enrollment of approximately 200 subjects; however, following the first interim review of data, and in line with Protocol Amendment 2, enrollment of new subjects into Arm A was suspended and enrollment into Arm B was permanently closed. Therefore, total enrollment in the study may be approximately 160 subjects if enrollment in Arm A is resumed after the second interim review.
Synopsis (Overview of Study Design); 3.1. Overview of Study Design 5. Treatment Allocation and Blinding 9.1.2. Screening Phase 9.1.3. Single-Blind Treatment Phase	Text was modified where appropriate to indicate that randomization is no longer part of the study design. References to "randomization" have been changed to "randomization/registration" to accurately reflect that subjects in the Screening Phase at the time randomization was stopped may enter the study through registration rather than randomization.
Synopsis (Overview of Study Design); 3.1. Overview of Study Design 5. Treatment Allocation and Blinding 9.1.3. Single-Blind Treatment Phase 16.1. Study-Specific Design Considerations	Beginning with Protocol Amendment 2, neither subjects nor investigators will be blinded to subject treatment assignment.
Synopsis (Dosage and Administration); 3.1. Overview of Study Design; 5. Treatment Allocation and Blinding	Beginning with Protocol Amendment 2, enrollment of new subjects into Arm A (9.4 mg/kg) is suspended and enrollment into Arm B (4.7 mg/kg) is permanently closed. Subjects in Arm B may continue their current treatment or have their dose increased to 9.4 mg/kg at the investigator's discretion according to the guidance provided in Section 6. Subjects in Arm A may continue treatment at the investigator's discretion. Subjects in either arm who discontinue treatment will continue in the Posttreatment Follow-up Phase.
Synopsis (Dosage and Administration); Time and Events Schedule (footnote 'a') 3.1. Overview of Study Design 5. Treatment Allocation and Blinding	Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the 9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification.

Applicable Section(s)	Description of Change(s)
Synopsis (Interim Review); 3.1. Overview of Study Design; 11.10. Interim Review	Text was added to clarify that the first interim review has occurred but was designed prospectively.
Figure 1, Schematic Overview of the Study	The study schematic diagram was updated to show suspension of enrollment and the option for eligible subjects to have their dose increased from 4.7 mg/kg to 9.4 mg/kg.
Synopsis (Interim Review); Synopsis (Statistical Methods) 3.1. Overview of Study Design 11.4. Efficacy Analyses 11.10. Interim Review	Text was added describing the timing of a new, second planned interim review, data to be assessed in the second interim review, and guidelines for interpretation of results.
3.2.1. Rationale for Protocol Changes Following First Interim Review	A new section was added to describe the results of the first interim data review and the resulting changes to study conduct.
Rationale: Subjects in the 4.7 mg/kg arm should only be escalated to the 9.4 mg/kg dose if their current status supports administration of the higher dose.	
6.0. Dosage and Administration (Dose Escalation Following Amendment 2)	Beginning with Protocol Amendment 2, subjects in Arm B may continue to receive their current dose of imetelstat or, at the discretion of the investigator, have their dose increased to 9.4 mg/kg. Subjects being considered for dose escalation from 4.7 mg/kg to 9.4 mg/kg must meet the eligibility criteria for hematologic laboratory values (inclusion criterion 8.1) and biochemical laboratory values (inclusion criterion 9.1). In addition, these subjects cannot meet any threshold for dose modification, nor can they have had an earlier imetelstat dose reduction.
Rationale: Additional study procedures are required for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg so that the effect of dose escalation on safety, efficacy (including spleen volume), PK exposure, and target inhibition can be assessed.	
Time and Events Schedule; Time and Events Schedule (PK Sampling)	Columns have been added to the Time and Events Schedules to show study procedures required for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg. Footnote ‘w’ was added to the Time and Events Schedule.
Synopsis (Statistical Methods); 11.4. Efficacy Analyses (Secondary Endpoint Analyses); 11.9. Safety Analyses	Additional safety and efficacy analyses will be performed for subjects initially treated with imetelstat 4.7 mg/kg who had their dose increased to 9.4 mg/kg.
Time and Events Schedule (footnote ‘h’)	Subjects whose dose is increased from 4.7 mg/kg to 9.4 mg/kg must have an abdominal MRI within approximately 14 days before starting treatment at the 9.4 mg/kg dose.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (footnote 'i')	Subjects whose dose is increased from 4.7 mg/kg to 9.4 mg/kg must have spleen palpation performed within approximately 14 days before starting treatment at the 9.4 mg/kg dose.
Time and Events Schedule (footnote 'r'); Time and Events Schedule (PK Sampling, footnote 'e')	Subjects whose dose is increased from 4.7 mg/kg to 9.4 mg/kg will have sparse PK blood samples collected during the first cycle of treatment at the 9.4 mg/kg dose.
Time and Events Schedule (footnote 'v'); 9.4. Pharmaco-dynamic Evaluations	Subjects whose dose is increased from 4.7 mg/kg to 9.4 mg/kg will have additional samples collected for assessment of TA, TL, and hTERT during the first 2 cycles of treatment at the 9.4 mg/kg dose.
9.1.1. Study Evaluations Overview 16.1. Study-Specific Design Considerations	The total blood volume to be collected was increased from 508.5 mL to 604 mL. Table 8 was updated to reconcile with study procedures and current requirements for sample volumes by the central laboratory. PK blood samples will be collected at the 2 hour post-infusion time point for all subjects until the sponsor notifies investigators that this collection can stop. Additional blood samples for PD and PK analyses are required only for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg, or who have bone marrow aspirate collected for PK analysis (Table 8 footnotes 'f' and 'g').
Rationale: Changes or clarification to study procedures were required to improve quality of the data record.	
Synopsis (Statistical Methods) 11.4. Efficacy Analyses	Clarification was made that the spleen response data reviewed by the IRC will be used for the primary analysis, the interim data reviews, and the final analysis.
Time and Events Schedule (Abdominal MRI; footnote 'h'); 9.1.4. Posttreatment Phase (Follow-Up)	Two abdominal MRIs were added. The first, which will be performed within 30 days after the last dose of imetelstat, was added as an End-of Treatment Visit procedure. This MRI is not required if one already exists confirming disease progression or otherwise demonstrating cause for treatment discontinuation. The second added MRI will be performed during the Posttreatment Follow-up Phase, 3 months after the subject's last dose of study drug, if feasible.
Time and Events Schedule (Spleen palpation; footnote 'i'); 9.2.1. Evaluations (Spleen Length Measurement)	Spleen palpation during the Posttreatment Follow-up Phase was added at 3 months after the subject's last dose of study drug, if feasible. Assessment time points were specified in Section 9.2.1.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (Bone marrow aspirate and biopsy; footnote 'j'); Time and Events Schedule (PK samples; footnote 'f') 9.1.1. Overview 9.3.1. Sample Collection and Handling; 9.3.2. Analytical Procedures	A sample of bone marrow aspirate and a time-matched plasma sample will be collected, if feasible, 24-48 hours after imetelstat dosing at Weeks 24 and 48 for evaluation of imetelstat concentration.
Time and Events Schedule (PK samples; footnote 'r'); Time and Events Schedule (PK Sampling, footnote 'f')	For each administration of imetelstat starting at Cycle 3, all subjects will have a 2-hour postdose (immediately before the end of infusion) PK blood sample collected. This will continue until the sponsor notifies investigators that the collection can stop.
4.2. Exclusion Criteria; 6.0. Dosage and Administration	Clarification was added that if a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all hematologic eligibility criteria, the decision to administer study drug on Cycle 1 Day 1 is at the discretion of the investigator provided that the subject does not meet any threshold for dose ~~delay~~ modification.
9.1.4. Posttreatment Phase (Follow-Up)	Clarification was added that a plasma sample for immunogenicity testing should be collected at the first follow-up visit.
9.2.1. Evaluations (Imaging)	Clarification was added that there will be local MRI review in addition to central MRI review by the IRC. Text referring to MRI interpretation by the central imaging vendor was deleted. Text was added to emphasize that treatment decisions following spleen volume assessment will be based on the IRC assessment.
Rationale: Janssen Research & Development standard protocol text has been updated.	
Title Page	Janssen Infectious Diseases BVBA was deleted as one of the legal entities comprising Janssen Research & Development.
12.3.1. All Adverse Events	Additional text was added describing Anticipated Events and the reporting process for serious Anticipated Events.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (23 November 2015)

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: This amendment makes revisions to study eligibility criteria based on feedback from investigators and discussion with the Independent Hepatic Expert Committee, and clarifies some aspects of study conduct.

Applicable Section(s)	Description of Change(s)
Rationale: Additional clarification was required for the definition of disease progression during or after JAK inhibitor therapy. In addition, because MRI or palpation measurement may not always be considered routine standard of care, eligibility may be demonstrated using CT or ultrasound measurements.	
4.1. Inclusion Criteria (criterion 6.1)	Subjects are required to have worsening of splenomegaly-related abdominal pain in conjunction with either no reduction in spleen volume or size after 12 weeks of JAK inhibitor therapy; or documented worsening splenomegaly from nadir at any time after the start of JAK inhibitor therapy. For documentation of splenomegaly, CT was added as an accepted imaging modality by which to demonstrate increase in spleen volume. CT and ultrasound were added as accepted imaging modalities to demonstrate increase in spleen size.
Rationale: Redundant information deleted. All screening procedures are to be completed within 21 days before randomization.	
4.1. Inclusion Criteria (criterion 8.1)	Reference to the 21-day period before randomization for absolute neutrophil count and platelet count was deleted.
Rationale: Criteria for liver function test values did not account for the high prevalence of elevated ALP and bilirubin abnormalities in the target population, which reflect disease course rather than presence of liver damage.	
4.1. Inclusion Criteria (criterion 9.1)	ALP criteria changed from ≤2.5 x ULN to ≤5 x ULN. Criteria for bilirubin changed from direct bilirubin ≤1.5 x ULN to total bilirubin ≤3 x ULN and direct bilirubin ≤ 2 x ULN.
Rationale: Clarification of exclusion criterion required.	
4.2. Exclusion Criteria (criterion 3.1)	Clarification added that subjects are excluded if they experienced major surgery prior to randomization.
Rationale: Subjects must be free from the effects of all prior MF therapy to prevent confounding of the imetelstat treatment effect. [redacted]	
4.2. Exclusion Criteria (criterion 4.1)	Any MF-directed therapy was added categorically as a possible prior therapy requiring washout before study entry. Reference to prior treatment with growth factors was removed, as independence from growth factor support is addressed in inclusion criterion 8.1. [redacted].
9.1.2. Screening Phase	[redacted].
Time and Events Schedule (footnotes e, h)	Collection of screening symptoms using the Screening Myelofibrosis Symptom Form (footnote “e”) and the screening abdominal MRI (footnote “h”) must be performed after [redacted].

Applicable Section(s)	Description of Change(s)
Rationale: Subjects with hepatitis infections that are unlikely to cause long-term liver damage may be included without additional risk.	
4.2. Exclusion Criteria (criterion 9.1)	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: To allow for investigator discretion regarding continued subject eligibility given the labile clinical course of this patient population.	
4.2. Exclusion Criteria; 6. Dosage and Administration	Text was added to the note below the list of exclusion criteria. If a subject's status changes after screening but before the first dose of study drug is given, such that he or she no longer meets all eligibility criteria, the decision to administer study drug on Cycle 1 Day 1 is at the discretion of the investigator provided that the subject does not meet any threshold for dose delay.
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.	
Synopsis (Efficacy Evaluations); Time and Events Schedule (footnote t); 9.1.2. Screening Phase; 9.2.1. Evaluations (Bone marrow); 9.6. Biomarkers	Text was added emphasizing that bone marrow aspirate is preferred over peripheral blood for cytogenetic analyses. However, a peripheral blood sample may replace bone marrow aspirate for cytogenetic analysis when collection of aspirate is not clinically feasible.
9.6. Biomarkers; Time and Events Schedule (footnote t)	Text added that every effort should be made to continue collecting the same type of sample (bone marrow aspirate or peripheral blood) at screening and subsequent time points when possible.
Rationale: Revisions or clarifications to study procedures facilitate assessment of study data.	
Time and Events Schedule (Expanded LFT, footnote p); 9.8. Safety Evaluations (Clinical Laboratory)	An expanded liver function panel was added as a Screening Phase evaluation for all subjects. In the Time and Events Schedule, an expanded LFT panel was added to the End-of-Treatment Visit and Posttreatment Follow-up Phase for subjects with an ongoing adverse event of interest (consistent with Section 9.8, Safety Evaluations).
Time and Events Schedule (Chemistry)	Clinical chemistry was added as a Posttreatment Follow-up Phase evaluation for subjects being followed-up for elevated LFT values (consistent with Section 9.8, Safety Evaluations). Footnote "o" was applied to the End-of- Treatment Visit time point.
Time and Events (footnote d) 9.8. Safety Evaluations (Viral hepatitis)	Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg).

Applicable Section(s)	Description of Change(s)
Time and Events Schedule (footnotes e, i, o); Section 9.1.2. Screening Phase	Clarification was added that the MFSAF v2.0 e-diary (footnote "e"), spleen palpation (footnote "i"), and hematology assessment for eligibility (footnote "o") must be started or performed after [redacted].
Time and Events Schedule (footnote h)	Clarified that abdominal MRI will be read locally for volume measurement.
Time and Events Schedule (footnote h); 9.1.2. Screening Phase	Clarified that the abdominal MRI may include a portion of the pelvis in cases where the spleen protrudes into the pelvic cavity.
Time and Events Schedule (PK Sampling, footnote a)	Footnote "a" was added to clarify that all sampling times are relative to the start of imetelstat infusion.
9.8. Safety Evaluations (Clinical Laboratory)	Text was added to the serum chemistry panel stating that bilirubin fractionation is required at screening. The presentation of the expanded LFT panel was changed to match that used for the hematology and serum chemistry panels. Text was added to state that the expanded LFT panel is required at screening.
Rationale: Text was updated to address the situation at some centers where imetelstat dose cannot be accurately measured out and administered to the nearest 0.1 mg by study personnel.	
6. Dosage and Administration	The instruction to calculate the dose of imetelstat to the nearest 0.1 mg has been deleted.
Rationale: Blood volumes to be collected from subjects during the study have changed.	
9.1.1. Procedures Overview; 16.1. Study-Specific Design Considerations	In Table 8, the blood volume collected for hepatitis serology was increased from 3 mL to 7.5 mL. Footnote "d" was added to explain that 2.5 mL of this sample will be used for PCR testing, when required. The blood volume for each biomarker (mutational analysis) sample was increased from 5 mL to 6 mL (subtotal volume increased from 20 mL to 24 mL). The total volume of blood to be collected increased from approximately 500 mL to approximately 508.5 mL. Text was added below Table 8 noting that some subjects may have additional 4-mL blood samples collected if peripheral blood is used for cytogenetic analysis in place of bone marrow aspirate.
Rationale: Study drug presentation may change during the study. Updated study drug information became available and was included in the Investigational Product Preparation Instructions (IPPI).	
14.1. Physical Description of Study Drug	The precise size (10 mL) was deleted from description of the single-dose imetelstat vial. Each vial will deliver a minimum of 200 mg of reconstituted Imetelstat Sodium for Injection. The concentration of reconstituted Imetelstat Sodium for Injection was changed from 20 mg/mL to 33.33 mg/mL.
14.2. Packaging	Text was revised to state that imetelstat vials are provided in a protective carton and that all packaging will meet applicable regulatory requirements. Redundant information regarding the concentration of reconstituted imetelstat was deleted.
14.4. Preparation, Handling, Storage	Text stating that the product must be protected from light was deleted. The specific period of time following imetelstat reconstitution when the study drug can be used was deleted, and investigators are directed to the IPPI for this information.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification added to aid interpretation or for consistency with other parts of the protocol.	
Synopsis (Efficacy Evaluations); Time and Events Schedule (physical examination)	Clarification was made that physical examination includes spleen palpation, as specified in other parts of the protocol.
Time and Events Schedule (footnote o); 9.8. Safety Evaluations (Clinical Laboratory Tests)	Text was aligned between Section 9.8, Safety Evaluations, and footnote "o" of the Time and Events Schedule, regarding requirements for follow-up of bilirubin, AST, ALT, and ALP after Grade ≥3, and Grade 1 and 2, treatment-emergent elevations are reported.
4.2. Exclusion Criteria	A sentence was added to the note following the final exclusion criterion specifying that the last laboratory result obtained before randomization will be used to establish eligibility.
6.1. Dose Modifications for Hematologic Toxicities (Table 2, Table 3)	Table footnotes were revised to state that dose modifications in response to Grade 3 and Grade 4 hematologic malignancies are at the investigator's discretion.
6.3. Dose Modifications for Hepatic Toxicities (Table 6)	A footnote was added to the table providing guidance for handling hepatic abnormalities not addressed in the table.
8. Prestudy and Concomitant Therapy	MF-directed therapy added as a prohibited medication during the study, consistent with exclusion criterion 4.1.
9.1.2. Screening	Consistent with other sections of the protocol, text was added stating that the sponsor will inform the sites which subjects have a cytogenetic abnormality based on the baseline analysis and who will need to have subsequent samples collected for cytogenetic analysis. Clarification was added that bone marrow aspirate and biopsy used for disease assessment must be performed up to 60 days before randomization.
9.2.1. Evaluations (Bone marrow)	Clarification was added that bone marrow biopsy and aspirate samples must be collected according to the Time and Events Schedule. Central review of bone marrow aspirate for efficacy analysis was deleted. Central review of bone marrow biopsy will be used to assess response to imetelstat for the efficacy analysis.
9.2.1. Evaluations (MFSAF Diary)	Unnecessary text "(prior to randomization)" describing the Day -7 time point was deleted.
9.2.1. Evaluations (Table 9)	Footnote "a" was added to Table 9. For all response categories, benefit must last 12 weeks. This applies to clinical improvement, anemia response, spleen response, and symptoms response.
Rationale: Janssen Research & Development standard protocol text has been updated.	
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.
16.2.2. IEC or IEB	Clarification was made that IEC/IRB annual approval of the protocol will be obtained, where required.

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

Myelofibrosis (MF) is classified as one of the myeloproliferative neoplasms (MPN), a group of related clonal diseases that includes polycythemia vera (PV) and essential thrombocythemia (ET). Allogeneic stem cell transplantation is the only treatment that can induce long-term remissions in patients with MF. Hydroxyurea, interferon, and, more recently, Janus kinase (JAK) inhibitors have been evaluated in clinical studies. Imetelstat, a first-in-class telomerase inhibitor, may provide clinical benefit to MF patients previously treated with a JAK inhibitor primarily due to its novel mechanism of action compared with available therapies.

OBJECTIVES AND HYPOTHESISES

Primary Objectives

The primary objectives of this study are to evaluate spleen response rate and symptom response rate of 2 dose regimens of imetelstat (9.4 mg/kg and 4.7 mg/kg imetelstat given intravenous [IV] every 3 weeks) in subjects with intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.

Secondary Objectives

The secondary objectives are to assess the safety of imetelstat; to assess complete remission (CR) or partial remission (PR), clinical improvement (CI), spleen response, symptoms response and anemia response per modified 2013 International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, duration of responses, and overall survival (OS); to evaluate the pharmacokinetics (PK) of imetelstat; to evaluate the PK/response and pharmacodynamic (PD) relationships with factors that include hemoglobin concentration, spleen size, and platelet count; to evaluate the immunogenicity of imetelstat; and to assess the effect of treatment on patient-reported outcomes (PROs).

Exploratory Objectives

The exploratory objectives are to assess the PK relationship with telomerase activity (TA), telomere length (TL) or human telomerase reverse transcriptase (hTERT), to characterize the baseline cytogenetic and mutational status for their association with clinical response, and to evaluate the change of cytogenetic abnormalities or mutant allele burden for assessing cytogenetic and molecular responses.

Hypothesis

The primary hypothesis of the study is that treatment with the selected dose of imetelstat will result in a [redacted] with intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.

OVERVIEW OF STUDY DESIGN

This was originally designed as a randomized (1:1), single-blind, multicenter, Phase 2 study of 2 dosing regimens of single-agent imetelstat in approximately 200 subjects with intermediate-2 or high risk MF (primary MF [PMF], post-ET-MF [PET-MF], or post-PV-MF [PPV-MF]) who are relapsed after or refractory to JAK inhibitor treatment. When the randomization was in effect, eligible subjects were stratified based on a) spleen size ≥ 15 cm below the left costal margin by palpation (yes vs. no) and b) platelet count at study entry (platelets ≥75 x 10^9/L and < 150 x 10^9/L vs. ≥ 150 x 10^9/L). Study treatment will be administered on a 21-day cycle. The main study will have 3 phases: a screening phase of up to 21 days before randomization/registration during which subject eligibility will be reviewed and approved

by the sponsor prior to randomization/registration; a treatment phase will extend from randomization/registration until study drug discontinuation; and a posttreatment follow-up phase that begins when the subject discontinues imetelstat. The posttreatment follow-up phase will continue until death, lost to follow-up, withdrawal of consent or study end, whichever occurs first. The end of the main study is defined as 18 months after the last subject is enrolled or when the sponsor terminates the study, whichever comes first.

The original study design allowed for enrollment of approximately 200 subjects; however, following the first interim review of data, and in line with Protocol Amendment 2, enrollment of new subjects into Arm A was suspended and enrollment into Arm B was permanently closed. Therefore, total enrollment in the study may be approximately 160 subjects if enrollment in Arm A is resumed after the second interim review. In addition, neither subjects nor investigators will be blinded to subject treatment assignment.

The co-primary endpoints of this study are spleen response rate and symptom response rate. Spleen response rate is defined as the proportion of subjects who achieve ≥35% reduction in spleen volume at Week 24 from baseline as measured by imaging scans. Symptom response rate is defined as the proportion of subjects who have ≥50% reduction in total symptom score at Week 24 from baseline as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary.

With Protocol Amendment 3, the study is closed to further subject enrollment. Subjects in the Treatment Phase who are benefiting from study treatment may enter an Extension Phase and continue to receive imetelstat until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. Subjects in the Posttreatment Follow-up Phase will enter the Extension Phase to continue follow-up for survival status. In line with Protocol Amendment 4, the Extension Phase will end approximately 2 years after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first.

SUBJECT POPULATION

Key eligibility criteria include the following: ≥18 years of age; diagnosis of PMF per the revised World Health Organization (WHO) criteria, or PET-MF or PPV-MF per the IWG-MRT criteria; Dynamic International Prognostic Scoring System (DIPSS) intermediate-2 or high risk MF; measurable splenomegaly prior to study entry; active symptoms of MF; documented progressive disease during or after JAK inhibitor therapy; and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2.

DOSAGE AND ADMINISTRATION

Imetelstat will be administered as a 2-hour IV infusion. Subjects in Arm A will receive imetelstat 9.4 mg/kg every 3 weeks and subjects in Arm B will receive 4.7 mg/kg every 3 weeks. Subjects may receive treatment until disease progression or unacceptable toxicity.

Subjects in Arm B may continue with their current imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion according to the guidance provided in Section 6 (Dosage and Administration) of the protocol. Subjects in Arm A may continue treatment at the investigator's discretion. Subjects in either arm who discontinue treatment will continue in the Posttreatment Follow-up Phase.

Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the 9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification.

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

EFFICACY EVALUATIONS

Efficacy evaluations will include magnetic resonance imaging (MRI) scans, laboratory testing, limited physical examinations (including spleen palpation), bone marrow biopsy and aspirate for disease assessment, peripheral blood smears, and symptom assessment. Bone marrow aspirate for cytogenetic testing must be submitted for all subjects when clinically feasible. Peripheral blood may be submitted in place of an aspirate only if a bone marrow aspirate cannot be obtained.

PHARMACOKINETIC EVALUATIONS

Sparse PK samples will be obtained from all subjects and the derived PK parameters will provide information about the determinants of inter-subject variability in this population. In addition, for a subset of subjects at selected sites, serial PK sampling will be performed in both treatment arms to increase the robustness of the population PK model. Samples may also be used to evaluate the formation of metabolites of imetelstat.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected from all subjects to determine immunogenicity to imetelstat (anti-drug antibody generation).

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Different PK/PD models will be built to understand and characterize the exposure-response relationship for key efficacy and safety parameters, to detect the influence of covariates, and identify inter-individual variability in response.

BIOMARKER EVALUATIONS

Blood and bone marrow samples will be collected to evaluate the pharmacodynamic effects of imetelstat and to determine cytogenetic and molecular response rates. 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.

PATIENT REPORTED OUTCOMES

Patient-reported outcome questionnaires and an e-diary will be collected to provide an assessment of the subject's functional status, well-being, and MF 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, physical examinations, clinical laboratory parameters, vital sign measurements, ECOG performance status, and concomitant medication usage.

A Sponsor Committee will review all the safety data on a quarterly basis, or more frequently, if needed. The study will have enhanced reporting for adverse events of interest, which include Grade 3 or greater elevations of AST, ALT, ALP and bilirubin, and all hepatic adverse events. Additionally, all hepatic adverse events and LFT abnormalities will be reviewed at least on a quarterly basis, or as needed, by an Independent Hepatic Expert Committee.

During the Extension Phase, serious adverse events will be collected for subjects receiving imetelstat, and all subjects will be followed-up for overall survival and reported pregnancy. The Hepatic Expert Committee and Sponsor Committee will continue to review study data collected during the Extension Phase.

INTERIM REVIEW

The first interim data review was designed as follows: The interim data review will be performed by the sponsor after approximately 20 subjects have been randomized in each arm and followed for at least 12 weeks. At this time, the sponsor will assess all available data (eg, PK, safety, efficacy, PD biomarkers: TA, TL or hTERT), and conduct integrated exposure-response analyses with PK/PD, safety and efficacy modeling. Based on these analyses, the sponsor will determine if enrollment in one or both treatment arms should continue, or if an alternative dose should be selected for further development. Enrollment will continue during this time and response data assessed by the investigator will be used for the interim review.

[redacted]

STATISTICAL METHODS

The study was originally designed to enroll approximately 200 subjects (approximately 100/arm). For each treatment arm, the sample size is calculated based on the following assumptions:

1) null hypothesis: [redacted]

2) alternative hypothesis: [redacted]

3) the null hypothesis is tested by the intersection-union test. Each of the co-primary endpoints is tested at one sided α=0.025, and the maximum Type I error rate for testing co-primary endpoints is the same as one sided α=0.025.

[redacted]

Planned efficacy analyses are as follows: (1) a first interim review after approximately 20 subjects in each arm have been followed for at least 12 weeks; (2) a second interim review with a clinical cutoff that is 6 months after the clinical cutoff used for the first interim review; (3) the primary efficacy analysis after all subjects have been followed for at least 24 weeks; (4) the final analysis at the end of the main study, which is defined as 18 months after the last subject is enrolled or when the sponsor terminates the study; and (5) OS-related analysis will be performed or updated when the Extension Phase has ended.

The analysis for the co-primary endpoints (spleen response rate and symptom response rate) will be based on the Treated Population. For each treatment arm, spleen response rate and symptom response rate will be presented along with their 95% 2-sided exact confidence interval. The spleen response data reviewed by the Independent Review Committee (IRC) will be used for the primary analysis, the interim data reviews, and the final analysis. The symptom response data measured by the modified MFSAF v2.0 Total Symptom Score (TSS) will be calculated as the 7-day average of daily TSS, which is the summation of 6 individual symptom scores. Additional analyses will be performed for subjects initially treated with imetelstat 4.7 mg/kg who had their dose increased to 9.4 mg/kg as described in Section 6 (Dosage and Administration) of the protocol.

EudraCT NUMBER: 2015-000946-41

TIME AND EVENTS SCHEDULE (MAIN STUDY)

Beginning with Amendment 3, follow the Time and Events Schedule for the Extension Phase.

PHASE	Screening Phase	Treatment Phase[a] (21-day treatment cycle)						Posttreatment Follow-up Phase[b]
		Cycle 1	Cycle 1	Cycle 2	Cycle 3 until End-of-Treatment	Dose Escalation[w] (4.7 to 9.4 mg/kg)	End-of-Treatment Visit	
	Day -21 to -1	Day 1	Day 8, 15	Day 1, 8, 15	Day 1		Within 30 days after last dose	Every 16 weeks
Study Procedures								
Screening/Administrative								
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history and demographics	X							
ECOG performance status	X	X		X (D1 only)	X		X	
Transfusion history and status[c]	X	X	X	X	X			
Hepatitis serologies[d]	X							
Pregnancy test	X							
Screening Myelofibrosis Symptom Form[e]	X							
Study Drug Administration								
Randomization		X[a]						
Dispense/administer study drug		X		X (D1 only)	X			
Safety Assessments								
Physical examination including spleen palpation[f]	X	X		X (D1 only)	X		X	
Vital signs[g]	X	X		X (D1 only)				
12-lead ECG	X							
Efficacy Assessments								
Abdominal MRI[h]	X	Every 12 weeks up to Week 48 then every 24 weeks and at time of CR/PR				X[h]	X	3 months posttreatment
Spleen palpation[i]	X	Every 12 weeks up to Week 48 then every 24 weeks and at time of CR/PR				X[i]	X	3 months posttreatment
BM aspirate and biopsy[j]	X	Every 24 weeks and at time of CR/PR					X (if feasible)	
Peripheral blood smear[k]	X	Every 12 weeks up to Week 48 then every 24 weeks and at time of CR/PR					X	
Response assessment per modified 2013 IWG-MRT		Every 12 weeks up to Week 48 then every 24 weeks						
Modified MFSAF v2.0 e-diary[e]	To be completed each evening from Day -7 through Week 48							
MF Symptom Recall Form					X (After Week 48)[l]			

PHASE	Screening Phase	Treatment Phase[a] (21-day treatment cycle)						Posttreatment Follow-up Phase[b]
		Cycle 1	Cycle 1	Cycle 2	Cycle 3 until End-of-Treatment	Dose Escalation[w] (4.7 to 9.4 mg/kg)	End-of-Treatment Visit	
	Day -21 to -1	Day 1	Day 8, 15	Day 1, 8, 15	Day 1		Within 30 days after last dose	Every 16 weeks
Study Procedures								
EORTC QLQ-C30 questionnaire		X[m]	X (D8 only)	X (D1 only)	X and also at Week 24[n]		X	X
EQ-5D-5L questionnaire		X[m]		X(D1 only)	X and also at Week 24[n]		X	X
BPI questionnaire		X[m]	X (D8 only)	X(D1 only)	X and also at Week 24[n]		X	X
PGIC questionnaire			X (D8 only)		Only at Week 24[n]		X	
Survival status								X
Clinical Laboratory Assessments								
Hematology[o]	X	X	X	X	X	X	X	
Expanded liver function panel[p]	X	If adverse event of interest occurs					X[p]	X[p]
Chemistry[o]	X	X	X	X	X	X	X[o]	X[o]
INR (or PT) and aPTT[q]	X	X		X (D1 only)	X		X	
Pharmacokinetics								
PK samples[r]		X		X (D1 only)	X[r]	X[r]		
Immunogenicity samples		X (pre-dose)			X (pre-dose D1)		X	X (first visit if feasible)
Pharmacodynamics								
TA, TL and hTERT		X[s]	X (D8 only)	X (D1 only)	At time of CR/PR	X[v]	X (at progression)	
Biomarkers								
Blood samples for mutation analysis	X	At time of CR/PR and every 12 weeks thereafter					X (at progression)	
BM aspirate/peripheral blood for cytogenetics[t]	X	For subjects with baseline cytogenetic abnormalities at time of CR/PR and at each subsequent BM biopsy					X (at progression)	
Blood samples for immunophenotyping	X			X (D1 only)	At time of CR/PR		X (at progression)	
Ongoing Subject Review								
Concomitant therapy	X	Continuous					X	
Adverse events	X	Continuous					X	
Subsequent therapy							X	X[u]

Abbreviations: ALP=alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BM = bone marrow; BPI = Brief Pain Inventory (Short Form); CR = complete remission; D1 = Day 1; ECG=electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and treatment of Cancer (EORTC) QLQ-C30; EQ-5D-5L = EuroQol-EQ-5D; INR = international normalized ratio; IWG-MRT = International Working Group – Myeloproliferative Neoplasms Research and Treatment; JAK = Janus kinase; LFT=liver function test; MFSAF = Myelofibrosis Symptom Assessment Form; MRI

= magnetic resonance imaging; PGIC = Global Impression of Change; PK=pharmacokinetic; PR = partial remission; PT = prothrombin time; RBC = red blood cell; ULN = upper limit of normal; WBCs = white blood cells

Footnotes:

[a] A treatment cycle is defined as 21 days ± 3 days. Subjects should start study treatment within 72 hours after randomization. Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the 9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification.

[b] Post-treatment follow-up can be performed via a clinic visit or a phone call every 16 weeks ± 7 days.

[c] Assessment of RBC transfusion requirements 12 weeks prior to baseline and at each clinic visit.

[d] 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).

[e] Screening symptoms using the Screening Myelofibrosis Symptom Form must be completed [redacted] and as close as possible to Day -7, prior to the start of the modified MFSAF v2.0 e-diary. Subjects should start the MFSAF v2.0 e-diary [redacted]

[f] Only a limited symptom-directed physical examination including spleen palpation and measurement. Weight assessment is required on Day 1 of all cycles after baseline.

[g] Vital signs should be measured and recorded prior to imetelstat infusion and will include measurements of temperature, pulse/heart rate, and systolic and diastolic blood pressure, preferably while the subject is in a seated position.

[h] Abdominal MRIs will be performed on all subjects at baseline, then every 12 weeks up to Week 48, then every 24 weeks until disease progression or unacceptable toxicity, and at the time of CR/PR. MRIs are required within 30 days after last dose of study drug for the End-of-Treatment Visit, unless an MRI confirming disease progression or leading to treatment discontinuation was already performed. A follow-up MRI will be performed 3 months after the subject's last dose of study drug, if feasible. All scans will be read locally for volume measurement and by a central review facility. Abdominal MRI includes a portion of the pelvis when the spleen protrudes into the pelvic cavity. After baseline, scans can be performed with a window of ± 7 days. Abdominal MRI for spleen assessment at screening must be completed [redacted] and as close as possible to randomization. Subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg must have an abdominal MRI performed [redacted] with 9.4 mg/kg.

[i] The edge of the spleen shall be determined by palpation, and measured in centimeters from the costal margin to the point of greatest splenic protrusion. Assessments will be performed every 12 weeks up to Week 48, then every 24 weeks until disease progression or unacceptable toxicity, and at the time of CR/PR. Spleen palpation at screening must be completed [redacted]. Follow-up spleen palpation will be performed 3 months after the subject's last dose of study drug, if feasible. Subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg must have spleen palpation conducted within approximately 14 days before starting treatment with 9.4 mg/kg.

[j] Bone marrow aspirate (if clinically feasible) and biopsy must be performed during screening or up to 60 days before randomization. All subjects must have baseline bone marrow evaluation, and then repeat bone marrow evaluation every 24 weeks and at time of suspected CR/PR until disease progression. After CR/PR is observed a repeat bone marrow evaluation should be obtained 12 weeks later for response confirmation. Fibrosis assessment will be performed on the biopsy by a central pathologist. After baseline, bone marrow biopsy can be performed with a window of ± 7 days. A sample of bone marrow aspirate and a time-matched plasma sample will be collected, if feasible, 24-48 hours after imetelstat dosing at Weeks 24 and 48 for evaluation of imetelstat concentration.

[k] Peripheral blood smear will be performed every 12 weeks up to Week 48, then every 24 weeks until disease progression or unacceptable toxicity and at time of CR/PR. Peripheral blood smear review will be performed by a central pathologist.

[l] MF Symptom Recall Form will be completed starting after Week 48, on Day 1 of every cycle at time of other PROs, and at time of CR/PR if occurring after Week 48.

[m] EORTC QLQ-C30 questionnaire, EQ5D-5L, and BPI questionnaires on Cycle 1 Day 1 should be completed prior to the first dose of study treatment.

[n] Week 24 PRO questionnaires should be performed the same day as Week 24 MRI.

[o] Hematology and chemistry laboratory assessments to determine subject eligibility must be performed within 21 days prior to randomization. The last result obtained prior to randomization will be used to determine eligibility. Hematology assessment for eligibility must be completed [redacted]. For Cycle 1, Day 1 only, clinical laboratory hematology and chemistry assessments do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment. After Cycle 1, Day 1, required laboratory tests must be performed within 48 hours prior to the scheduled visit. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, laboratory assessments need be to repeated weekly until bilirubin with fractionation is <3 x ULN, and AST, ALT and ALP are <5 x ULN. Subjects with Grade 1 and Grade 2 treatment emergent elevations in AST, ALT, ALP or bilirubin at time of treatment discontinuation should continue to have laboratory assessments monthly until resolution to at least baseline. For further guidance on liver function tests, see section on laboratory evaluations in Section 9.8. Subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg must meet the eligibility criteria for hematologic laboratory values (inclusion criterion 8.1) and biochemical laboratory values (inclusion criterion 9.1) before starting treatment with 9.4 mg/kg.

[p] An expanded liver panel should be performed at screening. Thereafter, if an adverse event of interest is reported, then an expanded liver panel should be performed which should include GGT, chloride, bicarbonate, magnesium, and fractionated bilirubin. The expanded liver panel will need to be repeatedly weekly until adverse event of interest has resolved.

[q] Repeat INR (or PT) and aPTT during study if subject has a hemorrhagic event.

[r] Sparse PK sampling will be performed in all subjects. In a subset of subjects, intensive PK sampling will be performed for a maximum of 7 time points in approximately 10 subjects per treatment arm. Refer to the Time & Events Schedule (PK Sampling) for details. All subjects, regardless of imetelstat dose received, must have a 2-hour postdose (ie, immediately before the end of infusion) PK sample collected each time imetelstat is administered, beginning with Cycle 3 and continuing until the sponsor determines that the PK objective has been met and notifies investigators that blood collection for this PK analysis can stop. Sparse PK samples must be collected for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg during the first cycle at the higher dose. Refer to the Time and Events Schedule (PK Sampling) for details.

[s] A pre-dose and 24 hours post-dose blood sample, if feasible, will be obtained for determination of TA, TL and hTERT.

[t] Where clinically feasible, bone marrow aspirates will be collected for cytogenetic testing. Peripheral blood may be submitted in place of an aspirate only if a bone marrow aspirate cannot be obtained. The same sample type collected at screening must be collected throughout the subject's participation in the study if possible. The sponsor will notify the sites to specify which subjects have a cytogenetic abnormality based on baseline analysis and will need to have subsequent BM aspirate samples collected.

[u] Subsequent anti-MF treatment to be collected throughout posttreatment follow-up phase.

[v] For subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg, 4 additional blood samples for PD analysis (TA, TL and hTERT) are required during the first 2 cycles receiving the 9.4 mg/kg dose at the following time points: first cycle at 9.4 mg/kg Day 1 predose and 24 hr postdose (if feasible); first cycle at 9.4 mg/kg Day 8; and second cycle at 9.4 mg/kg Day 1 pre-dose.

[w] Beginning with Protocol Amendment 2, subjects in Arm B (4.7 mg/kg) may continue to receive their current imetelstat dose or have the dose increased to 9.4 mg/kg at the investigator's discretion and according to the guidance provided in Section 6. Dose escalation for these subjects may occur at any cycle of the Treatment Phase. Subjects who have their dose increased will have additional MRI and spleen assessments before receiving the first dose of imetelstat 9.4 mg/kg. Additional blood samples will be collected for biomarker assessments before and after the first dose of imetelstat 9.4 mg/kg, and blood samples for PK assessment will be collected after receiving the first dose of imetelstat 9.4 mg/kg.

TIME AND EVENTS SCHEDULE (EXTENSION PHASE)

Use this Time and Events Schedule after local IEC/IRB approval of Amendment 3.

Study Procedures	All Subjects	Extended Treatment (21-day treatment cycle)	Extended Follow-up (Every 16 weeks ± 7 days)
Informed consent	X[a]		
Dispense/administer study drug		X (Day 1)	
Serious adverse event monitoring[b]		X[b]	
Survival status			X[c]

a 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.

b Submit a Serious Adverse Event Form to the sponsor within 24 hours of awareness of the event for all serious adverse events. If the subject has a hemorrhagic serious adverse event, INR (or PT), aPTT, and platelet count will be assessed and reported in the serious adverse event report. If the subject experiences a hepatic serious adverse event, serum chemistry and an expanded liver panel will be assessed and reported; if the event includes Grade 3 or 4 ALP elevation, ALP fractionation or 5'neucleotidase will also be assessed and reported. Serious adverse events will be reported from the time the Extension Phase ICF is signed and dated until 30 days after the last dose of imetelstat.

c Assessment of survival status is required for all subjects who enter the Extension Phase, including those who discontinued treatment during the main study.

TIME AND EVENTS SCHEDULE (PK SAMPLING)

Study Day	PK Blood Sampling Time[a]	Serial (Intense) PK Blood Sampling[b]	Sparse PK Blood Sampling[b]	Sparse PK Blood Sampling Dose Escalation (4.7 to 9.4 mg/kg)[e]
Cycle 1, Day 1	0 (before start of infusion)	X		
Cycle 1, Day 1	1 h	X		
Cycle 1, Day 1	2 h[c]	X		
Cycle 1, Day 1	3h-5h	X		
Cycle 1, Day 1	6h-10h	X		
Cycle 1, Day 1	12h-16h	X		
Cycle 1, Day 1	18h-24h	X		
Cycle 1, Day 1	0 (before start of infusion)			
Cycle 1, Day 1	2 h[c]		X	
Cycle 1, Day 1	3h-6h		X	
Cycle 1, Day 1	8h-12h		X	
Cycle 1, Day 1	16-24h[d]		X	
Cycle 2, Day 1	0 (before start of infusion)			
Cycle 2, Day 1	2 h[c]		X	
Cycle 2, Day 1	3h-6h		X	
Cycle 2, Day 1	8h-12h[d]		X	
First Cycle 9.4 mg/kg, Day 1	0 (before start of infusion)			
First Cycle 9.4 mg/kg, Day 1	2 h[c]			X
First Cycle 9.4 mg/kg, Day 1	3h-6h			X
First Cycle 9.4 mg/kg, Day 1	8h-12h			X
First Cycle 9.4 mg/kg, Day 1	16-24h[d]			X
Every cycle starting from Cycle 3[f]	2 h[c]	X	X	X

[a] All sampling times are relative to the start of the imetelstat infusion.
[b] Of the subjects who participate in the study and receive imetelstat, approximately 10 subjects per arm will undergo serial PK blood sample collections, with the remaining subjects undergoing sparse PK sampling.
[c] Immediately before end of the infusion.
[d] If feasible.
[e] Subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg will have sparse PK samples collected during the first cycle receiving 9.4 mg/kg.
[f] All subjects, regardless of imetelstat dose received, must have a 2-hour postdose (ie, immediately before the end of infusion) PK sample collected each time imetelstat is administered, beginning with Cycle 3 and continuing until the sponsor determines that the PK objective has been met and notifies investigators that blood collection for this PK analysis can stop. In addition, time-matched plasma PK samples will be collected for subjects with bone marrow aspirate (if feasible) at Weeks 24 and 48.

ABBREVIATIONS

ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BAT	best available therapy
βhCG	beta human chorionic gonadotropin
BM	bone marrow
BPI	Brief Pain Inventory (Short Form)
CFU-Meg	megakaryocyte colony-forming unit
CFU-MK	malignant megakaryocyte colony-forming unit
CI	clinical improvement
CL	clearance
C_{max}	maximum plasma concentration
CR	complete remission
CRF	case report form
CSC	circulating stem cells
DCF	data clarification form
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
E_{max}	maximum efficacy
EMH	extramedullary hematopoiesis
EORTC QLQ-C30	European Organization for Research and treatment of Cancer (EORTC) QLQ-C30
EQ-5D-5L	EuroQol-EQ-5D
ET	essential thrombocythemia
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HEENT	head, eye, ear, nose, and throat
HIV	human immunodeficiency virus
HR	heart rate
hTERT	human telomerase reverse transcriptase
IAC	Interim Analysis Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous
IVRS	interactive voice response system
IWG-MRT	International Working Group – Myeloproliferative Neoplasms Research and Treatment
IWRS	interactive web response system

JAK	Janus kinase
LCM	left costal margin
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactic acid dehydrogenase
LFT	liver function test
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MM	multiple myeloma
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NONMEM	nonlinear mixed effects modeling
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia-myelofibrosis
PGIC	Global Impression of Change
PK	pharmacokinetic(s)
PMF	primary myelofibrosis
PPV-MF	post-polycythemia vera-myelofibrosis
PQC	product quality complaint
PR	partial remission
PRO	patient-reported outcome(s)
PT	prothrombin time
PV	polycythemia vera
QRS	part of electrocardiographic wave representing ventricular depolarization
RBC	red blood cell
RNA	ribonucleic acid
SD	standard deviation
SIPM	Site Investigational Product Manual
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
SVR	spleen volume reduction
TA	telomerase activity
TI	transfusion independence
TIC	tumor inducing cell
TGI	tumor growth inhibition
TIW	3 times per week
TL	telomere length
TRAP	telomere repeat amplification protocol
TSS	Total Symptom Score
ULN	upper limit of normal
USP	United States Pharmacopeia
V	volume of distribution
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

For the most comprehensive nonclinical and clinical information regarding imetelstat, refer to the latest version of the Investigator's Brochure (IB) and IB Addenda for imetelstat.[21] 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. Imetelstat

Imetelstat 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, 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.[3,19] 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.[14,16]

1.1.2. Myelofibrosis

Myelofibrosis (MF) is classified as one of the myeloproliferative neoplasms (MPN), a group of related clonal diseases that includes polycythemia vera (PV) and essential thrombocythemia (ET). MF can arise on its own (primary myelofibrosis, [PMF]), or as a progression of polycythemia vera (post-PV-MF) or essential thrombocythemia (post-ET-MF). The manifestations of PMF, post-PV-MF and post-ET-MF are virtually identical and treatment is generally the same for all 3 (World Health Organization [WHO] classification 2008). The disease is characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow stromal changes, hepatosplenic extramedullary hematopoiesis and aberrant cytokine expression.[30] Patients present with splenomegaly, constitutional symptoms, moderate to severe anemia, thrombocytopenia and leukocytosis.

There is a strong association between survival after the diagnosis of MF and the Dynamic International Prognostic Scoring System (DIPSS) risk category. Patients in the low risk category have more than 15 years median survival. Patients with intermediate risk-1, intermediate risk-2 or high risk have median survivals of 14.2, 4, and 1.5 years, respectively.[27] Approximately 70% of individuals with MF are in the intermediate-2 or high-risk categories,[15] representing the greatest unmet medical need. Symptomatic enlargement of the spleen and liver, the necessity for red cell transfusions, cachexia, and the other MF-associated symptoms result in compromised quality of life for these patients.[26]

1.1.3. Treatment Options for Myelofibrosis

Allogeneic stem cell transplantation is the only treatment that can induce long-term remission of MF. However, many patients will not be transplanted because of the advanced age at which MF is

diagnosed (mean=65 years). Hydroxyurea, interferon, and, more recently, Janus kinase (JAK) inhibitors have been evaluated in clinical studies. Treatment with these agents may result in a spleen volume reduction (SVR), alleviation of discomfort due to splenomegaly, and improvement in anemia, but not in an anti-clonal effect.

In recent years, the understanding of MPNs in general and the molecular mechanisms of these diseases, including MF, has improved. In 2005, the JAK2V617F mutation was discovered. This mutation is observed in approximately 50% to 60% of patients with PMF and ET, and in 90% to 95% of patients with PV. This discovery, and the observation of other mutations that activate the JAK/signal transducers and activators of transcription (STAT) pathway established dysregulation of the JAK signaling pathway as the major contributor to the pathogenesis of MPNs. It also led to the development of small-molecule JAK inhibitors.

The JAK1/2 inhibitor ruxolitinib currently is the only approved therapy for MF. Two randomized, controlled studies (COMFORT-I and COMFORT-II) compared ruxolitinib to placebo and to the best available therapy (BAT), respectively. The studies demonstrated benefit, with a significantly higher proportion of subjects in the ruxolitinib arms exhibiting a ≥35% reduction in spleen volume as measured by magnetic resonance imaging at 24 weeks in COMFORT-I (41.9% ruxolitinib vs. 0.7% placebo) and at 48 weeks in COMFORT-II (28.5% ruxolitinib vs. 0% BAT).[33,17] In COMFORT-I there was >50% improvement in the Total Symptom Score (TSS) measured by the Myelofibrosis Symptom Assessment Form (MFSAF) at 24 weeks in 45.9% of ruxolitinib subjects compared with 5.3% of placebo subjects. In COMFORT-II, 2 quality of life measures were used to assess symptom improvement, and both demonstrated a significant response in the ruxolitinib treated group. Improvement in survival among patients treated with ruxolitinib was demonstrated in COMFORT-I (8.4% mortality vs. 15.6% with BAT) and in a 3-year follow-up of the COMFORT-II study. The median survival at the time of publication had not yet been reached; however, treatment with ruxolitinib led to a 52% risk of death reduction as compared with BAT.[9]

The benefit of ruxolitinib therapy in terms of spleen response and constitutional symptoms is associated with a lower rate of treatment-associated anemia (40.4% vs. 12.3% for BAT) and thrombocytopenia (44.5% vs. 9.65% for BAT).[18] The 1-, 2-, and 3-year discontinuation rates are 49%, 71% and 86%, respectively. Major reasons for discontinuation are loss of therapeutic effect, lack of response and drug-induced cytopenias. Based on the 2013 International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) response criteria for efficacy in patients with MF,[28] no subjects achieved complete remission (CR) or partial remission (PR) on treatment with ruxolitinib,[2] suggesting that ruxolitinib does not affect the underlying neoplastic process.

Responses to ruxolitinib are typically observed within the first 3 to 6 months after therapy initiation.[33,17] It has been suggested that for patients who have not had a reduction in spleen size or improvement in symptoms after that period, alternative therapies should be considered.[23] The median survival for patients who relapse after treatment with or are refractory to ruxolitinib is

6 months.[22] Therefore, there remains a need for effective treatments for the patients who have been treated previously with a JAK inhibitor.

Imetelstat, a first-in-class telomerase inhibitor, may provide clinical benefit to MF patients. In patients previously treated with a JAK inhibitor, imetelstat may improve clinical signs and symptoms and may induce CR and PR including normalization of fibrotic bone marrow.[29] This is likely due to its novel mechanism of action compared with available therapies, such as JAK inhibitors.

1.1.4. Rationale for Use of Imetelstat in Myeloproliferative Neoplasm (MPNs)

Myelofibrosis 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.[16] Telomerase activity (as measured in granulocytes) is high in patients with myeloproliferative neoplasms.[12] Telomere length (TL) in patients with myeloproliferative neoplasms is short, regardless of JAK2 mutational status. Therefore, telomerase inhibition may be effective in both JAK2V617F and JAK2 wild-type MF.[31,13,7]

Emerging data suggest that malignant hematopoietic progenitor cells are more susceptible than normal progenitor cells to telomerase inhibition, which results in telomere shortening and apoptotic cell death. Several preclinical studies have shown that imetelstat is an effective inhibitor of clonogenicity and proliferation of malignant progenitor cells derived from primary patient samples with myeloproliferative neoplasms such as MF. A study of CD34+ progenitor cells isolated from either normal cord blood or from MF patients treated with imetelstat ex vivo showed that the drug had minimal effect on proliferation and apoptosis of normal CD34+ cells but a profound effect on CD34+ cells from MF patients, which leads to reduction of colony formation and depletion of malignant progenitor cells.[34]

In vitro studies have demonstrated that imetelstat selectively inhibits spontaneous megakaryocytic colony-forming unit (CFU-Meg) growth from the blood of patients with MPNs such as ET, but not from healthy individuals. Inhibition of neoplastic progenitor cell growth was observed ex-vivo.[5] Furthermore, imetelstat demonstrated the ability to reduce selectively the malignant megakaryocyte colony-forming unit (CFU-MK) from patients with MF and ET, but had a minimal effect on clonogenicity of normal MK progenitors.[20]

In the Phase 2 Study CP14B015 in ET, which is the first proof of concept study in hematological malignancies, patients 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 complete response. Ten of 18 (56%) patients remain on maintenance therapy (median duration of treatment is 18 months; range 7.5–34.5 months) and

continue to be responsive to imetelstat. Importantly, 7 of 8 subjects with the JAK2V617F mutation achieved partial molecular response with 72% to 96% reduction in allele burden.[4] In addition, imetelstat accumulates in bone marrow, has the ability to target circulating stem cells (CSCs) and tumor inducing cells (TICs), inhibits CFU-MK in vitro, and targets diseases with short TL. All such properties are relevant to patients with MF and myelodysplastic syndrome (MDS)/MPN, which arise from malignant progenitor cell clones, have short TLs, and highly active telomerase. These data suggest that imetelstat can selectively inhibit neoplastic clonal proliferation in patients with ET, and provided the rationale for evaluating imetelstat in patients with other MPNs, such as MF.

1.1.5. Study CP14B019 With Imetelstat in Myelofibrosis

An open-label, Phase 2 (Study CP14B019) study was conducted to evaluate the safety and efficacy of single-agent imetelstat in patients with DIPSS-plus intermediate-2 or high-risk PMF, PPV-MF, or PET-MF, blast phase MF, and MDS patients. The primary endpoint for the MF cohorts of the study was overall response rate, defined as clinical improvement (CI), PR, or CR, consistent with IWG-MRT criteria.[28] Secondary endpoints included safety, reduction of spleen size by palpation, improvement in anemia, or achievement of red blood cell transfusion independence.

As of December 2014, preliminary data from 33 subjects with MF are available. Subjects in Arm A (n=19) received imetelstat 9.4 mg/kg on Day 1 every 21 days. Subjects in Arm B (n=14) received 9.4 mg/kg imetelstat on Days 1, 8 and 15 of Cycle 1, followed by 9.4 mg/kg on Day 1 every 21 days for subsequent cycles.

The median age of the eligible subjects was 67 years. Eighteen (54.5%) subjects had primary MF, 5 (15.2%) subjects had post-ET MF, and 10 (30.3%) subjects had post-PV MF. Sixteen (48.5%) subjects had intermediate-2 risk MF and 17 (51.5%) subjects had high risk MF. Thirteen (39.4%) subjects were transfusion dependent at entry; 23 (69.7%) subjects had a palpable spleen (median spleen size=15 cm below the costal margin) and 21 (63.6%) had symptoms at baseline. The majority of the subjects (26 [78.8%]) had prior treatment including 16 (48.5%) who had received a prior JAK inhibitor.

1.1.5.1. Clinical Efficacy Results

Twelve of the 33 subjects (36.4%) achieved a response (CR+PR+CI) as defined by 2013 IWG-MRT criteria. In Arm A, 7 (36.8%) of 19 subjects achieved a response and in Arm B, 5 (35.7%) of 14 subjects achieved a response. Seven (7) subjects (4 in Arm A and 3 in Arm B) had a CR or PR, and 4 of these subjects (3 in Arm A and 1 in Arm B) had a CR. Five (5) subjects (15.2%) had CI, 4 (12.1%) by spleen reduction (3 subjects in Arm A and 1 subject in Arm B) and 1 (3%) by anemia improvement (in Arm B).[29]

All 4 of the subjects who had CR had reversal of bone marrow fibrosis and 3 of the 4 achieved a molecular response. Four subjects who initially achieved PR converted to CR with continued treatment. The median time to onset of response was 1.6 months (range 0.7 to 5.6 months) and the responses were durable with a median of 14 months (range 4.4-18.9 months).[29]

1.1.5.1.1. Spleen and Anemia Response

Spleen and anemia responses were assessed according to the 2013 IWG-MRT criteria. Eight (34.8%) of 23 subjects with baseline splenomegaly had a spleen response (5 of 14 subjects in Arm A and 3 of 9 subjects in Arm B) defined as ≥50% spleen size reduction by palpation lasting at least 12 weeks. Four (4) of 13 (30.8%) subjects who were transfusion dependent at baseline (3 of 8 subjects in Arm A and 1 of 5 subjects in Arm B) became transfusion independent during the study.[29] Among 7 subjects who had CR or PR, 4 subjects with splenomegaly at baseline also achieved splenic response, and 3 subjects who were transfusion dependent at baseline became transfusion independent. Additional analysis of spleen response, defined as ≥50% spleen size reduction by palpation at 24 weeks from treatment initiation, were performed and 9 (39.1%) of 23 evaluable subjects (6 subjects in Arm A and 3 subjects in Arm B) had a response.

1.1.5.1.2. Constitutional Symptoms

Study CP14B019 did not use a patient-reported outcomes (PROs) instrument to assess symptoms. However, the presence of constitutional symptoms such as fever, weight loss, night sweats, and bone pain were documented at baseline and assessed by physicians during the study. Among the subjects who achieved CR and PR in both Arms A and B, 4 of 7 had constitutional symptoms at baseline and all demonstrated resolution of symptoms by the onset of the response.

1.1.5.1.3. Subject Status and Time on Treatment

The median duration of treatment was 8.6 months (range 1.4 to 21.7 months) for all 33 subjects in Arms A and B. The median duration of treatment was 15.5 months (range 6.5 to 21.7 months) for the subjects with CR, PR, or CI, 15.5 months (range 14.0 to 21.7 months) for subjects with CR or PR, and 6.9 months (range 1.4 to 19.3 months) for subjects with stable disease. Subjects who did not have CR, PR, CI, or evidence and maintenance of clinical benefit (defined as ≥50% improvement in leukocytosis, a ≥50% improvement in thrombocytosis, a ≥50% decrease in palpable splenomegaly, or a ≥50% improvement in RBC transfusion requirement) were discontinued from treatment even if they did not meet criteria for progression. Of the 33 subjects, 25 (75.8%) discontinued treatment, 16 (48.5%) of whom discontinued due to insufficient response or the start of alternative therapy. Two (2) subjects progressed and 1 subject relapsed while on treatment. Two (2) subjects (6.1%) discontinued due to an adverse event. As of the cut-off date (December 2014) for this analysis, 8 subjects are still on treatment, 6 of them with ongoing CR, PR, or CI.

1.1.5.1.4. Efficacy Data in Subjects Previously Treated With a JAK Inhibitor

The data from this study suggest that treatment with imetelstat may provide benefit to patients previously treated with a JAK inhibitor. Among the 16 subjects who were previously treated with a JAK inhibitor, 5 (31.3%) achieved a response (CR+PR+CI; as defined by the 2013 IWG-MRT criteria). Two (2) subjects had CR and 1 had PR. In addition, 2 subjects had CI, 1 subject by improvement in spleen volume and 1 subject by improvement in anemia. Three (3) of 11 subjects (27.3%) evaluable for spleen response had a spleen response that was durable for at least 12 weeks and 3 of 7 (42.9%) transfusion-dependent subjects became transfusion independent during the

study. Additional analysis of spleen response, defined as ≥50% spleen size reduction by palpation at 24 weeks from treatment initiation, was performed: 3 of 11 (27.3%) evaluable subjects had a response.

1.1.5.2. Clinical Pharmacology of Imetelstat

Single-dose kinetics showed dose dependent increases in exposure 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. Drug interaction potential has not been tested clinically.

1.1.5.3. Clinical Safety of Imetelstat in Myelofibrosis

1.1.5.3.1. 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 patients had been exposed, and low marrow reserve.

In Study CP14B019, the incidence of treatment-emergent Grade 3 and 4 thrombocytopenia in Arm A was 42.1% and 10.5% respectively. Seven (7; 36.8%) subjects from this arm required dose reduction, and 2 discontinued following these events. No major bleeding events or deaths due to thrombocytopenia were reported in this arm. There appeared to be more pronounced toxicity for Arm B: treatment-emergent Grade 3 thrombocytopenia was 7.1% and Grade 4 was 35.7%. Five (5; 35.7%) subjects in this arm required dose reduction, but none discontinued due to thrombocytopenia. One subject (1) 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 Arm A was 21.1% and 10.5%, respectively. Three (3) subjects from this arm required dose reduction following Grade 3 or 4 neutropenia, but none discontinued due to this event. Again, there appeared to be more pronounced toxicity for Arm B: treatment-emergent Grade 3 and Grade 4 neutropenia were reported for 14.3% and 28.6% of subjects, respectively. Four (4) subjects in this arm required dose reduction, but none discontinued due to this event. No Grade 4 treatment-related anemia was reported. A higher number of Grade 3 events was reported in Arm B than in Arm A (64.3% vs. 42.1%). In conclusion, hematologic toxicities were less pronounced in Arm A and, from a safety perspective, this dose and regimen warrants further investigation.

Refer to the latest version of the Investigator's Brochure[21] for updated information regarding hematologic toxicity.

1.1.5.3.2. Non-Hematologic Toxicities

In Study CP14B019, the incidence of severe (Grade 3 or greater) non-hematologic adverse events was low. Events that happened in more than 1 subject are as follows: fatigue in 3 patients, and 2 patients each who had a prolonged activated partial thromboplastin time (aPTT), atrial fibrillation, heart failure, hyperuricemia, and hyperkalemia.

Refer to the latest version of the Investigator's Brochure[21] for updated information regarding non-hematologic toxicity.

1.1.5.3.3. Hepatotoxicity

The adverse events of concern in the clinical studies thus far have been liver function test (LFT) abnormalities or clinical hepatic adverse events. In Study CP14B019, in Arms A and B, worsening in aspartate aminotransferase (AST) (60.6%) is the most commonly reported treatment-emergent LFT parameter, followed by alkaline phosphatase (ALP) (57.4%), total bilirubin (48.5%), and alanine aminotransferase (ALT) (42.4%). Worsening is defined as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade elevated after baseline OR if baseline result was > upper limit of normal (ULN) and on-study result elevated to $\geq$ 1.5 x baseline. Most LFT abnormalities were Grade 1 and Grade 2, with only 3 subjects experiencing Grade 3 events (2 with ALP and 1 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. The CP14B-019 study is ongoing and LFT monitoring continues.

Reversibility of liver function test abnormalities was demonstrated. Following cessation of imetelstat in the ET/PV and multiple myeloma study patients, there were no new liver-related adverse events and the LFT abnormalities resolved in the majority of the patients 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.

Refer to the latest version of the Investigator's Brochure[21] for updated information regarding hepatotoxicity.

1.1.6. Target Engagement With Imetelstat

Preclinical and clinical target engagement data suggest that $\geq$30% inhibition of telomerase is required to exert a measurable pharmacological effect. In the Phase 1 Study CP05-101, inhibition of telomerase activity (TA) in peripheral blood mononuclear cells (PBMC) was measured 24 hours after a single dose of imetelstat (ranging from 4.8 mg/kg to 11.7 mg/kg) in 23 subjects. Telomerase activity was analyzed using the telomere repeat amplification protocol (TRAP) assay. Measurable inhibition of telomerase was observed across different doses. A maximum efficacy (E_{max}) model was constructed to relate percent of TA change to the observed C_{max}. [redacted]

[redacted]

1.1.7. Differentiation of Response by Exposure

A dose of 4.7 mg/kg every 3 weeks was the minimum dose that engages the target, as demonstrated by telomerase inhibition. To evaluate the pharmacokinetic (PK) overlap between the lower dose of 4.7 mg/kg and 9.4 mg/kg given every 3 weeks, a population PK model was developed for imetelstat using a 2-compartment target-mediated drug disposition model with saturable binding. The PK simulation results showed minimal overlap of exposure range (90% confidence interval of both area under the curve (AUC) and maximum plasma concentration [C_{max}]) associated with the 9.4 mg/kg dose and 4.7 mg/kg, thus theoretically allowing for a differentiated response.

The data summarized above provide support for 9.4 mg/kg every 3 weeks as an effective and tolerable dosing regimen. A dose of 4.7 mg/kg is anticipated to be the lowest dose associated with a measurable level of target engagement. Exposures associated with the 4.7 and 9.4 mg/kg doses show minimal overlap. Therefore, these are rational choices to cover the potential therapeutic range.

In conclusion, data to date from Study CP14B019 show the overall response rate (CR+PR+CI, 2013 IWG-MRT criteria) was 36.4%. Durable remissions (CR+PR) evaluated per modified 2013 IWG-MRT criteria were also seen. In addition, 34.8% of subjects had a spleen response (by palpation, lasting ≥ 12 weeks) and 30.8% of subjects who were transfusion dependent at baseline became transfusion independent during the study. Thirty-nine point one percent (39.1%) of subjects had a spleen response (50% reduction by palpation at 24 weeks), including subjects who were previously treated with a JAK inhibitor.

The safety profile of imetelstat is consistent with its mechanism of action. The safety profile of Arm A (9.4 mg/kg every 21 days) is acceptable in the setting of patients with relapsed/refractory MF. Treatment-related cytopenias are expected in this population given their compromised bone marrow reserve and reliance on extramedullary hematopoiesis. These events can be managed by rigorous safety monitoring, timely dose modifications, transfusions and immediate treatment of patients with fever and neutropenia or other signs of infections. Liver function test abnormalities were mainly Grade 1 and 2 and were reversible. However, they remain adverse events of special interest that will be closely monitored. Given the efficacy and safety findings from Study CP14B019, imetelstat 9.4 mg/kg every 21 days appears to have an acceptable balance of benefit and risk in this patient population.

1.2. Overall Rationale for the Study

Myelofibrosis, particularly intermediate-2 or high risk disease, is a fatal condition. Ruxolitinib, a JAK inhibitor, is the only drug approved for the treatment of patients with intermediate or high risk MF. Several other JAK inhibitors such as pacritinib and momelotinib are currently in Phase 3 development. For patients who have been previously treated with a JAK inhibitor, there is no

approved therapy and the prognosis is very poor. Despite the demonstrated clinical activity of JAK inhibitor in MF, many subjects discontinued treatment. For example, the 3-year discontinuation rates after treatment with ruxolitinib have been reported to be approximately 50%, with major reasons for discontinuation being loss of therapeutic effect and lack of response.[30] The median survival of patients with relapsed and refractory MF who discontinued ruxolitinib has been reported to be 6 months.[22] Therefore, there remains great unmet need for the patients who have been treated previously with a JAK inhibitor.

Imetelstat, a first-in-class telomerase inhibitor, with its novel mechanism of action, may provide clinical benefit to MF patients. In addition to reduction in palpable splenomegaly in subjects previously treated with a JAK inhibitor, treatment with imetelstat has induced CR and PR in subjects with MF, including improvement of bone marrow fibrosis.[29] Imetelstat has also demonstrated an acceptable and manageable safety profile.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

The primary objectives of this study are to evaluate spleen response rate and symptom response rate of 2 dose regimens of imetelstat (9.4 mg/kg and 4.7 mg/kg imetelstat given intravenous [IV] every 3 weeks) in subjects with intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.

Secondary Objectives

The secondary objectives are:

- To assess the safety of imetelstat
- To assess CR or PR, CI, spleen response, symptoms response, and anemia response per modified 2013 IWG-MRT criteria, duration of responses, and overall survival (OS).
- To evaluate the pharmacokinetics of imetelstat
- To evaluate the PK/response and pharmacodynamic (PD) relationships with factors that include hemoglobin concentration, spleen size, and platelet count
- To evaluate the immunogenicity of imetelstat
- To assess the effect of treatment on PROs (patient-reported outcomes)

Exploratory Objectives

The exploratory objectives are:

- To assess the pharmacokinetic relationship with TA, TL or hTERT

- To characterize the baseline cytogenetic and mutational status for their association with clinical response, and to evaluate the change of cytogenetic abnormalities or mutant allele burden for assessing cytogenetic and molecular responses.

2.2. Hypothesis

The primary hypothesis of the study is that treatment with the selected dose of imetelstat will result in a [redacted] in subjects with intermediate-2 or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This was originally designed as a randomized, single-blind, multicenter, Phase 2 study of 2 dosing regimens (treatment arms) of single-agent imetelstat in subjects with intermediate-2 or high risk MF (PMF, PET-MF, or PPV-MF) whose disease is relapsed after or refractory to JAK inhibitor treatment. Approximately 200 subjects were to be enrolled in this study with approximately 100 subjects per treatment arm.

The original study design allowed for enrollment of approximately 200 subjects; however, following the first interim review of data, and in line with Protocol Amendment 2, enrollment of new subjects into Arm A was suspended and enrollment into Arm B was permanently closed. Therefore, total enrollment in the study may be approximately 160 subjects if enrollment in Arm A is resumed after the second interim review. In addition, neither subjects nor investigators will be blinded to subject treatment assignment.

The main study will have 3 phases: a screening phase of up to 21 days before randomization/registration during which subject eligibility will be reviewed and approved by the sponsor prior to randomization/registration; a treatment phase will extend from randomization/registration until study drug discontinuation; and a posttreatment follow-up phase that begins when the subject discontinues imetelstat. The posttreatment follow-up phase will continue until death, lost to follow-up, withdrawal of consent or study end, whichever occurs first. The end of the main study is defined as 18 months after the last subject is enrolled or when the sponsor terminates the study, whichever comes first.

Study treatment will be administered on a 21-day cycle. When the randomization was in effect, eligible subjects were stratified based on a) spleen size ≥15 cm below the left costal margin by palpation (yes vs. no) and b) platelet count at study entry (platelets ≥75 x 10^9/L [ie, ≥75,000/mm^3] and <150 x 10^9/L [ie, <150,000/mm^3] vs. ≥150 x 10^9/L [ie, ≥150,000/mm^3]). Subjects were then randomized within each stratum in a 1:1 ratio to one of the treatment arms. Subjects on Arm A received 9.4 mg/kg every 3 weeks and subjects on Arm B received 4.7 mg/kg every 3 weeks. Study drug will be administered intravenously (IV) until disease progression, unacceptable toxicity, or study end.

Subjects in Arm B may continue with their current imetelstat dose or have it increased to 9.4 mg/kg at the investigator's discretion according to the guidance provided in Section 6. Subjects in Arm A may continue treatment at the investigator's discretion. Subjects in either arm who discontinue treatment will continue in the Posttreatment Follow-up Phase. Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the 9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification.

The co-primary endpoints of this study are spleen response rate and symptom response rate. Spleen response rate is defined as the proportion of subjects who achieve ≥35% reduction in spleen volume at Week 24 from baseline as measured by imaging scans. Symptom response rate is defined as the proportion of subjects who have ≥50% reduction in TSS at Week 24 from baseline as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 (Attachment 1) diary. The selected dose of imetelstat will be considered effective if both of the endpoints pass the defined lower rate threshold. Secondary efficacy endpoints include CR or PR, CI, spleen response, symptoms response, and anemia response per modified 2013 IWG-MRT criteria, duration of responses, and OS.

Assessment of disease response and disease progression will be conducted based on modified 2013 IWG-MRT response criteria[28] at the time points specified in the Time and Events Schedule. Safety evaluations will include adverse event monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, Eastern Cooperative Oncology Group (ECOG) performance status, and concomitant medication usage. All study evaluations will be conducted according to the Time and Events Schedule.

The first interim data review was designed as follows: The interim data review will be performed by the sponsor after approximately 20 subjects have been randomized in each arm and followed for at least 12 weeks. At this time, the sponsor will assess all available data (eg, PK, safety, efficacy, PD biomarkers: TA, TL or hTERT), and conduct integrated exposure-response analyses with PK/PD, safety and efficacy modeling. Based on these analyses, the sponsor will determine if enrollment in one or both treatment arms should continue, or if an alternative dose should be selected for further development. Enrollment will continue during this time and response data assessed by the investigator will be used for the interim review.

At the time of Protocol Amendment 2, enrollment of new subjects in this study is suspended. A second interim review will be performed with a clinical cutoff that is 6 months after the clinical cutoff used for the first interim review. IRC assessment of SVR will be used for efficacy evaluation. [redacted]

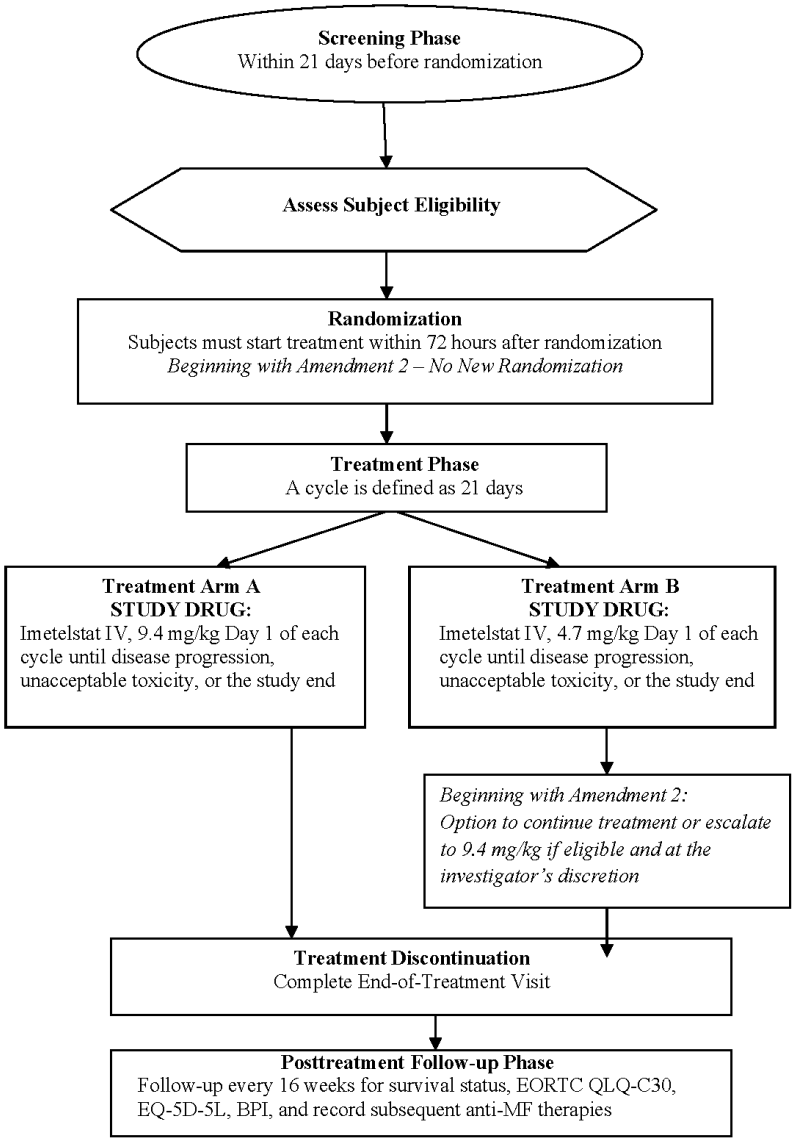
The Sponsor Committee will review all the safety data on a quarterly basis, or more frequently, as needed. The study will have enhanced reporting for adverse events of interest, which includes

Grade 3 or greater elevations of AST, ALT, ALP and bilirubin, and all hepatic adverse events. Additional details can be found in Sections 9.8 (Safety Evaluations) and 12.3.3 (Adverse Events of Interest). Additionally, all hepatic adverse events and LFT abnormalities will be reviewed at least on a quarterly basis, or as needed, by an Independent Hepatic Expert Committee.

With Protocol Amendment 3, the study is closed to further subject enrollment. Subjects in the Treatment Phase who are benefiting from study treatment may enter an Extension Phase and continue to receive imetelstat until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. Subjects in the Posttreatment Follow-up Phase will enter the Extension Phase to continue follow-up for survival status. In line with Protocol Amendment 4, the Extension Phase will end approximately 2 years after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first. The Hepatic Expert Committee and Sponsor Committee will continue to review study data collected during the Extension Phase.

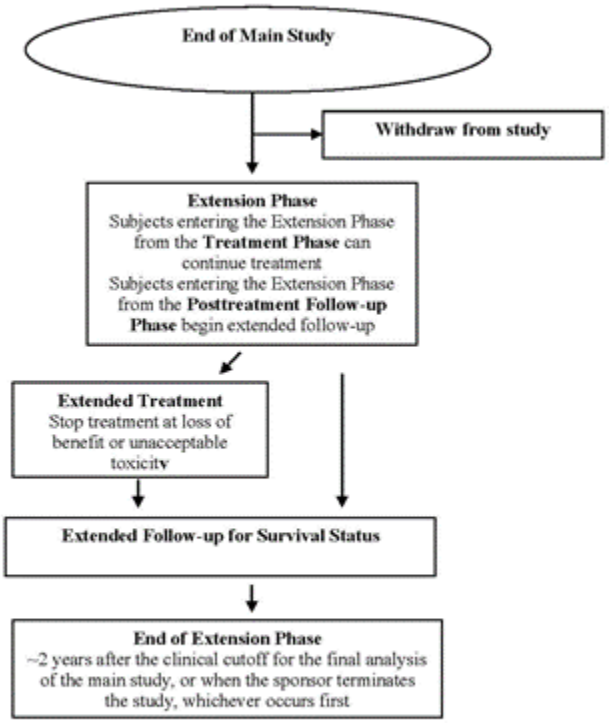
A diagram of the study design following Amendment 2 is provided below in Figure 1. Figure 2 presents the design of the Extension Phase following Amendment 4.

Figure 1: Schematic Overview of the Study Following Amendment 2



Note: Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the 9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification.

Figure 2: Schematic Overview of the Extension Phase Following Amendment 4



3.2. Study Design Rationale

Study Population

Treatment options for patients with advanced MF who are not allogeneic stem cell transplant candidates are limited to hydroxyurea, interferon, and JAK inhibitors. The effectiveness of these treatments mainly is limited to symptom burden relief and reduction in splenomegaly. Current therapies have not been shown to induce remissions or change the natural history of MF and result in high discontinuation rates and a lack of durable responses. Survival for patients whose disease has relapsed or is refractory to ruxolitinib is approximately 6 months.[22] Therefore, there remains a highly unmet need for effective treatments for the patients who have been treated previously with a JAK inhibitor.

Primary Endpoints

The co-primary endpoints of this study are spleen response rate and symptom response rate. Spleen response rate is defined as the proportion of subjects achieving a ≥35% reduction in spleen volume at Week 24 from baseline as measured by imaging scans. Symptom response rate is defined as the proportion of subjects who have ≥50% reduction in TSS at Week 24 from baseline as measured by the modified MFSAF v2.0 diary.

Splenomegaly is a cardinal feature of MF and is linked to abdominal pain and impairment of quality of life. Therefore, spleen volume reduction (SVR) by ≥35% has been shown to be a valid endpoint that predicts clinical benefit. Recent data by Vannucchi[32] suggests positive correlation of on-treatment SVR at Week 24 with a reduced risk of death.

As was seen in COMFORT-I and COMFORT-II, treatment of MF with ruxolitinib led to a significant reduction in spleen volume as well as improvement in clinical symptom burden (using the MFSAF TSS in COMFORT-I). Notably, some patients without SVR demonstrated symptom improvement in these studies. Mature data from both studies also have demonstrated significant improvements in OS.[33,9]

Secondary Endpoints

The depth of the response will be captured by assessment of CR and PR. The data from Study CP14B019 suggest the potential for disease modification (eg, reversal of bone marrow fibrosis, resolution of leukoerythroblastosis, blast count reduction) and long-term benefit to patients that has not been observed with current therapies. Duration of responses will be assessed. Subjects will be followed for OS.

Dose and Regimen Selection

Based on data from the MF CP14B019 study, 9.4 mg/kg given on a 3-week cycle has an acceptable safety profile and favorable efficacy. Therefore, this is one of the doses to be used in the study.

In Phase 1 and 2 studies in various solid tumor types, lower as well as higher doses of imetelstat were explored allowing for the derivation of dose and exposure-response relationships. [redacted]

Pharmacokinetic and Immunogenicity Evaluations

The PK data from this study will be used for PK/PD modeling to aid in the selection of a development dose. Therefore, PK samples will be obtained from all subjects and the derived PK parameters will provide information about the determinants of inter-subject variability in this population. Samples may also be used to evaluate the formation of metabolites of imetelstat.

Immunogenicity to imetelstat has not been studied in preclinical or clinical studies. Therefore, samples to determine the presence of antibodies to imetelstat (immunogenicity) will be collected from all subjects.

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 to evaluate TA, TL, or hTERT RNA level changes as PD

biomarkers. Karyotyping on bone marrow samples will be performed to evaluate cytogenetic response by assessing the reduction or depletion of clones with cytogenetic abnormalities. Blood samples will be analyzed to characterize mutation status and decrease or eradication of specific mutation burden, for determining molecular response. Other biomarker goals include evaluation of potential inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to imetelstat.

Patient-reported Outcomes

The purpose of the PRO questionnaires, EORTC QLQ-C30 (Attachment 2), Brief Pain Inventory (Short Form) (BPI) (Attachment 3) and The Patient Global Impression of Change (PGIC) (Attachment 4), is to provide an assessment of the subject's functional status, well-being, and MF symptoms over time and will be used to further validate the modified MFSAF v2.0. The EuroQol-EQ-5D (EQ-5D-5L) (Attachment 5) assessment will provide estimates of utility to include in future cost effectiveness models.

3.2.1. Rationale for Protocol Changes Following the First Interim Review

The first interim data review to assess safety and early efficacy, and to perform comprehensive exposure-response analyses was performed after approximately 20 subjects in each arm were followed-up for at least 12 weeks. The safety analysis for this interim review included data for 79 subjects (40 in the 4.7 mg/kg arm; 39 in the 9.4 mg/kg arm) who received at least 1 dose of study drug. The efficacy analysis included 40 evaluable subjects (20 in 4.7 mg/kg arm; 20 in the 9.4 mg/kg arm) who received at least 1 dose of study drug, had a baseline MRI, and at least 1 post-baseline MRI assessed by investigator.

First Interim Review of Safety

The patient populations enrolled into each arm were balanced in terms of type of myelofibrosis (primary-MF, PPV-MF, or PET-MF) and DIPSS prognostic risk.

With a median treatment duration of 4 cycles (range 1-15 cycles), both the 4.7 mg/kg and 9.4 mg/kg arms were found to have an acceptable safety profile consistent with that observed in prior studies with imetelstat. [redacted]

First Interim Review of Efficacy

The landmark analysis of spleen response demonstrated that at Week 12, [redacted]

First Interim Review of PK

No prior PK data were available from subjects with myelofibrosis. [redacted]

Summary

Data from the first interim review indicate that [redacted]

[redacted]

Consequently, the following protocol changes will be implemented with Protocol Amendment 2:

- Enrollment of new subjects was suspended for Arm A (9.4 mg/kg) and permanently closed for Arm B (4.7 mg/kg).
- Subjects currently in the 9.4 mg/kg arm may continue treatment at the investigator's discretion.
- Subjects in the 4.7 mg/kg arm may continue to receive treatment and may have their dose escalated to 9.4 mg/kg if pre-defined safety parameters are met and at the investigator's discretion (see Section 6). Subjects who have clinical benefit per investigator assessment but do not meet eligibility for dose escalation may choose to continue to be treated with the 4.7 mg/kg dose and continue assessments per protocol.
- PK sampling will continue for all subjects to allow further characterization of the imetelstat exposure-response relationship in patients with MF until the PK/PD objectives are met.

The determination of whether a subject is to continue on treatment is to be made by the investigator in consultation with the subject and will be based on the assessment of benefit-risk for each individual subject.

3.2.2. 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, if considered to be in the subject's interest, until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. The addition of an Extension Phase allows this unmet-need population to continue treatment with imetelstat for approximately 2 years after the clinical cutoff for the final analysis of the main study, or until the sponsor terminates the study, whichever occurs first. It is anticipated that 2 years will allow sufficient time for all subjects to receive adequate treatment and allow additional maturity of the survival data and a more precise estimate of overall survival. [redacted] Because sufficient data will have been collected during the main study to allow the planned final analysis, data collection during the Extension Phase is limited to imetelstat treatment information, survival status, pregnancy, and serious adverse event reporting. Data review by the Hepatic Expert Committee and Sponsor Committee during the Extension Phase provides continued independent oversight of subject safety.

4. SUBJECT POPULATION

Subject eligibility will be reviewed and approved by the sponsor prior to randomization. Screening for eligible subjects will be performed within 21 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. ≥18 years of age

2. Diagnosis of PMF according to the revised WHO criteria (Attachment 6); or PET-MF or PPV-MF according to the IWG-MRT criteria (Attachment 7). A report from the local laboratory for diagnosis of MF must be reviewed and approved by the sponsor.

3. DIPSS intermediate-2 or high risk MF (Attachment 8)

4. Measurable splenomegaly prior to study entry as demonstrated by:

   - palpable spleen measuring ≥5 cm below the left costal margin. The edge of the spleen should be measured in centimeters from the mid-clavicular line on the left side of the abdomen to the point of greatest splenic protrusion.

   OR

   - spleen volume of ≥ 450 cm^3 measured by magnetic resonance imaging (MRI)

5. Active symptoms of MF as demonstrated by a symptom score of at least 5 points (on a 0 to 10 scale) on at least one of the symptoms or a score of 3 or greater on at least 2 of the following symptoms: night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, bone or muscle pain, and inactivity.

6. Criterion modified per Amendment 1.

6.1 Documented progressive disease during or after JAK inhibitor therapy defined as worsening of splenomegaly-related abdominal pain at any time after the start of JAK inhibitor therapy, and

   EITHER

   - no reduction in spleen volume or size after 12 weeks of JAK inhibitor therapy

   OR

   - worsening splenomegaly at any time after the start of JAK inhibitor therapy documented by:
     - increase in spleen volume from nadir by 25% measured by MRI or computed tomography (CT), or
     - increase in spleen size by palpation, CT, or ultrasound
       - for splenomegaly of 5-10 cm at the start of JAK inhibitor treatment, at least 100% increase in palpable spleen size from nadir is required;

- for splenomegaly of >10 cm at the start of JAK inhibitor treatment, at least 50% increase in palpable spleen size from nadir is required;
- new splenomegaly must measure at least 5 cm.

7. ECOG performance status 0, 1 or 2 (Attachment 9)

8. Criterion modified per Amendment 1.

8.1 Hematology laboratory test values within the following limits:

- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (ie, ≥1,500/mm^3) independent of growth factor support
- Platelets ≥75 x 10^9/L (ie, ≥75,000/mm^3) independent of platelet transfusion support

9. Criterion modified per Amendment 1.

9.1 Biochemical laboratory test values must be within the following limits

- AST and ALT ≤2.5 x ULN
- ALP ≤5 x ULN
- Serum creatinine ≤2 x ULN
- Total bilirubin ≤3 x ULN and direct bilirubin ≤2 x ULN

10. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not father a child or donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

11. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening.

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.

4.2. Exclusion Criteria

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

1. Peripheral blood blast count of ≥10% or bone marrow blast count of ≥10%

2. Prior treatment with imetelstat

3. Criterion modified per Amendment 1.

3.1 Major surgery within 4 weeks prior to randomization

4. Criterion modified per Amendment 1.

4.1 Any chemotherapy or MF-directed therapy, investigational drug regardless of class or mechanism of action, hydroxyurea, immunomodulatory or immunosuppressive therapy, corticosteroids >30 mg/day prednisone or equivalent, or JAK inhibitor therapy ≤14 days prior to randomization.

5. Prior history of hematopoietic stem cell transplant

6. Diagnosis or treatment for malignancy other than MF, except

- Malignancy treated with curative intent and with no known active disease present for ≥3 years before randomization
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease

7. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

8. Known history of human immunodeficiency virus (HIV) or any uncontrolled active systemic infection requiring IV antibiotics

9. Criterion modified per Amendment 1.

9.1. Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or any type or known acute or chronic liver disease including cirrhosis

10. Females who are pregnant or currently breastfeeding

11. 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. The last laboratory result obtained prior to 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 the first dose of study drug is given such that he or she no longer meets all hematologic eligibility criteria, the decision to administer study drug on Cycle 1 Day 1 is at the discretion of the investigator provided that the subject does not meet any threshold for dose modification (per Section 6, Dosage and Administration). Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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 and for 1 month after the last dose of study drug.

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 and for 3 months after receiving the last dose of study drug.

3. Section 8 details prestudy and concomitant therapies used in this study.

5. TREATMENT ALLOCATION AND BLINDING

This was originally designed as a single-blind study, in which subjects will be blinded to the treatment arms. This was to reduce potential bias during data collection, eg, modified MFSAF v2.0 diary and PROs, which may be subject to self-assessment bias. Central randomization was implemented in this study. Subjects were assigned randomly to 1 of 2 treatment arms in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization was stratified by a) spleen size ≥15 cm below the left costal margin by palpation (yes vs. no) and b) platelet count (≥75 x 10^9/L and <150 x 10^9/L vs. ≥150 x 10^9/L) and balanced by using randomly permuted blocks. The interactive web response system (IWRS) assigned a unique treatment code that dictated the treatment assignment and matching study drug kit for the subject. The requestor must use his or her user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to identify the subject.

Beginning with Protocol Amendment 2, enrollment of new subjects into Arm A (9.4 mg/kg) is suspended and enrollment into Arm B (4.7 mg/kg) is permanently closed. Any subject already in the Screening Phase at the time study enrollment was suspended, and who was subsequently determined to be eligible for the study, was allowed to proceed with treatment assignment to the

9.4 mg/kg arm per investigator discretion, subject agreement, and IRB/IEC notification. In addition, neither subjects nor investigators will be blinded to treatment assignment.

6. DOSAGE AND ADMINISTRATION

Imetelstat Sodium (GRN163L) for Injection (imetelstat) is the investigational product in this study and will be provided by the sponsor. Imetelstat will be administered as a 2-hour IV infusion (± 10 minutes) at a constant rate using a programmable volumetric infusion pump. The baseline weight will be used to calculate the dose of imetelstat. The dose should be recalculated if there is a ≥ 10% weight change from baseline. Subjects in Arm A will receive imetelstat 9.4 mg/kg every 3 weeks and subjects in Arm B will receive 4.7 mg/kg every 3 weeks. Subjects may receive treatment until disease progression or unacceptable toxicity. Study drug may be held for up to 21 days from the expected start date of the scheduled cycle; a hold >21 days must be reviewed and approved by the sponsor. Imetelstat should be discontinued permanently if it cannot be restarted within 21 days due to toxicity, unless approved by the sponsor. For treatment of hematologic toxicities, granulocyte colony stimulating factors (G-CSF) are permitted for neutropenia as well as blood transfusions for anemia or thrombocytopenia.

If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all hematologic eligibility criteria, the decision to administer study drug on Cycle 1 Day 1 is at the discretion of the investigator provided that the subject does not meet any threshold for dose modification.

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

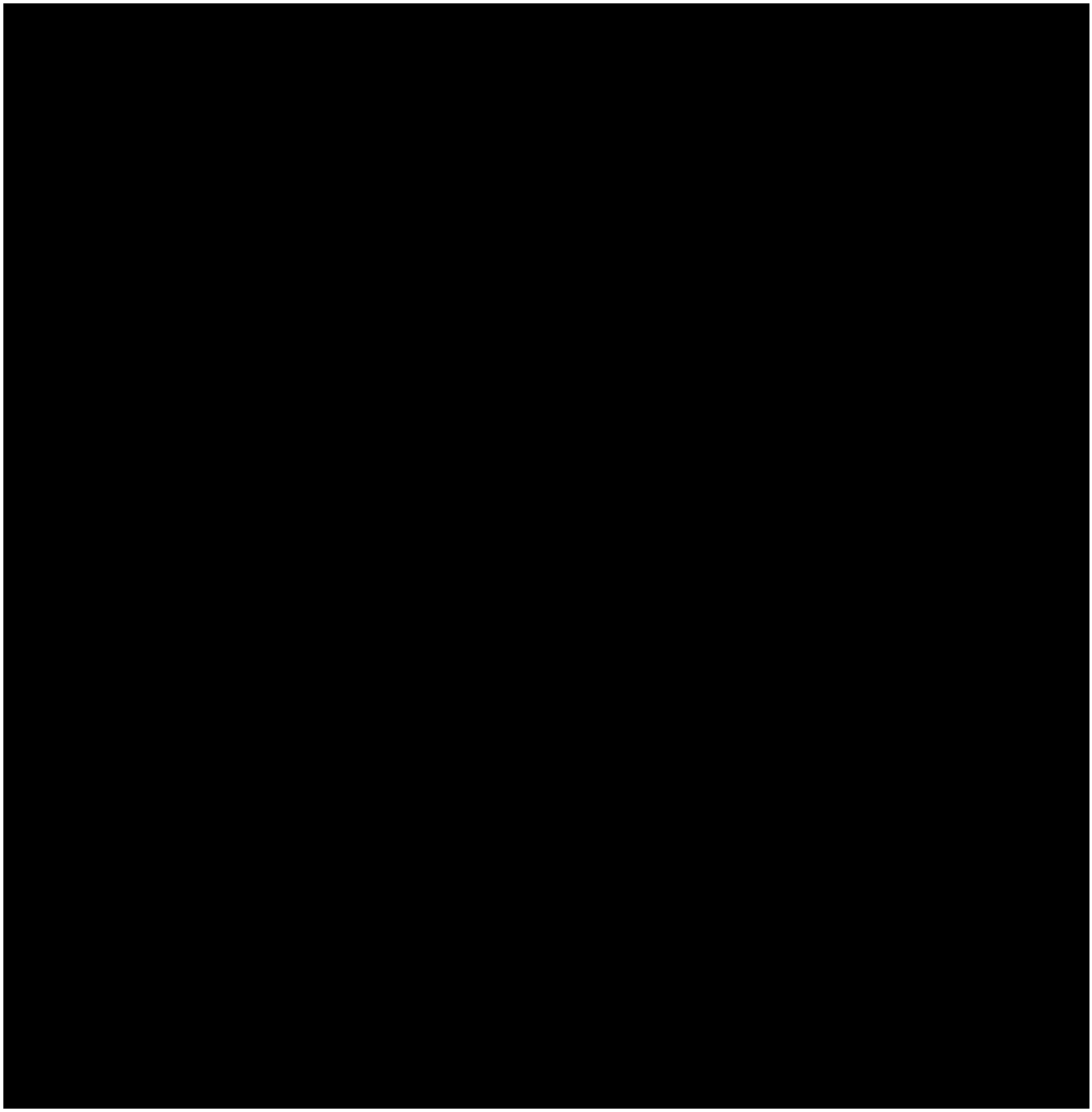
Dose Escalation Following Amendment 2

Beginning with Protocol Amendment 2, subjects in Arm B (4.7 mg/kg) may continue to receive their current dose of imetelstat or, at the discretion of the investigator, have their dose increased to 9.4 mg/kg. To be eligible for this dose escalation, a subject must meet study eligibility criteria for hematology laboratory values (inclusion criterion 8.1; ie, ANC ≥1.5 x 10^9/L; platelets ≥75 x 10^9/L) and biochemical laboratory values (inclusion criterion 9.1; ie, AST and ALT ≤2.5 x ULN, ALP ≤5 x ULN, serum creatinine ≤2 x ULN, total bilirubin ≤3 x ULN, direct bilirubin ≤2 x ULN). In addition, subjects may not meet any threshold for dose modification for hematologic toxicity

(Section 6.1), non-hematologic toxicity (Section 6.2), or hepatic toxicity (Section 6.3). A subject who had a dose reduction at any time during the study is not permitted to dose escalate.

Treatment During the Extension Phase

Once the end of the main study has been reached, subjects who are receiving benefit from study treatment may continue to receive imetelstat 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.



[redacted]

6.4. Infusion-Related Reactions

Subjects should be observed carefully during imetelstat infusions. Trained study staff at the clinic should be prepared to intervene in case of an infusion-related reaction. If an infusion-related

reaction develops, then the infusion should be interrupted temporarily and the actions in Table 7 should be taken.

Table 7: Management of Infusion-related Reactions

Severity	Recommended action
Grade 1	• Evaluate and manage symptomatically as needed. • May complete infusion if reaction remains mild, with stable vital signs and does not worsen to Grade 2.
Grade 2	• Stop infusion • Manage symptomatically as needed • After recovery, resume infusion at half the previous rate for 30 minutes – If no further symptoms occur, complete the infusion at the full dose rate – If symptoms recur, discontinue infusion for that cycle
Grade 3	• Stop infusion • Administer supportive care as indicated • 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. – 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	• Stop infusion • Administer supportive care as indicated • Discontinue imetelstat

7. TREATMENT COMPLIANCE

Study drug (imetelstat) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (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

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

All subjects receiving imetelstat must be premedicated with diphenhydramine (25 to 50 mg) and hydrocortisone (100 to 200 mg), or equivalent. It is recommended that subjects are monitored for at least 1 hour after the infusion has been completed.

Subjects may receive supportive care as clinically indicated. This includes blood product support (blood transfusions and the use of granulocyte colony stimulating growth factors), anti-diarrheals, anti-emetics, analgesics, antibiotic treatment, and treatment of other medical conditions.

The following medications are prohibited during the study: chemotherapy (anticancer) or MF-directed therapy, 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 also should 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.

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded at screening. Transfusions up to 12 weeks prior to baseline also must be recorded at screening.

Concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements), including growth factors, transfusions, 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 last dose of study drug or until the start of subsequent anticancer treatment, if earlier. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study. 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.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of efficacy, pharmacokinetic, immunogenicity, pharmacodynamic, biomarker, and safety measurements applicable to the main study and to the Extension Phase. As of Amendment 3, subjects will follow the Time and Events Schedule for the Extension Phase. Additional detail is provided in Section 9.1.5.

The total blood volume for the study is approximately 604 mL (Table 8).

Table 8: Volume of Blood to be Collected From Each Subject

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 including efficacy	5	19	95
- PT/INR and aPTT	5	15	75
- Serum chemistry and expanded liver panel[c]	10	20	200
- Hepatitis Serology[d]	13	1	13
- Serum β-hCG pregnancy tests	2	1	2
Pharmacokinetic samples (intensive or sparse)[g]	2	22	44
Immunogenicity	2	14	28
Pharmacodynamic samples[f]	14.5	6	87
Biomarkers (Mutation analysis)[e]	6	4	24
Peripheral blood for cytogenetics (if required)	4	5	20
Biomarkers (Immunophenotyping)	4	4	16
Approximate Total			604

a. Volumes below derived for median 12 cycle duration and includes end of study 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 is required at screening and may also be required for safety reasons.
d. Includes 2.5 mL of blood for hepatitis PCR testing when required to confirm study eligibility.
e. Samples will be collected every 12 weeks until disease progression.
f. Four additional 14.5-mL blood samples (58 mL total) for pharmacodynamic analysis are required for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg.
g. Up to 4 additional 2-mL blood samples (up to 8 mL total) for sparse PK analysis are required for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg; and up to two, 2-mL time-matched blood PK samples are required for subjects who have bone marrow aspirate collected for PK analysis at Weeks 24 and 48.

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

The total blood volume to be collected from each subject will be approximately 604 mL, including additional samples to be collected for subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg for pharmacodynamic analysis (58 mL) and PK analysis (up to 12 mL). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Additional 4-mL blood samples may be required for subjects who have peripheral blood collected for cytogenetic testing in place of bone marrow aspirate.

Additional serum or urine pregnancy tests may be performed, 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. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

9.1.2. Screening Phase

All subjects must sign an ICF prior to the conduct of any study-related procedures. Screening procedures will be performed up to 21 days before randomization/registration. Screening symptoms using the Screening Myelofibrosis Symptom Form must be completed after [redacted] and as close as possible to Day -7. An abdominal MRI for spleen assessment (including a portion of the pelvis when the spleen protrudes into pelvic cavity) must be completed [redacted] and as close as possible to randomization. Screening spleen palpation and hematology must also be completed

[redacted]. The bone marrow aspirate (if clinically feasible) and biopsy must be performed for disease assessment up to 60 days before randomization. Additionally, where clinically feasible, a bone marrow aspirate will be collected prior to randomization for cytogenetic assessment. Peripheral blood may be submitted in place of an aspirate only if a bone marrow aspirate cannot be obtained. The sponsor will inform the sites which subjects have a cytogenetic abnormality based on the baseline analysis and will need to have subsequent samples collected for cytogenetic analysis.

Laboratory tests noted in the inclusion criteria must be performed and the results within the limits specified in the inclusion criteria. Testing may be repeated for this purpose and can be repeated if needed to fall within the screening period. The last result obtained prior to randomization will be used to determine eligibility. 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 randomization.

Diagnosis of MF must be confirmed by the sponsor. A laboratory report from the local laboratory and supporting documentation consistent with a diagnosis of MF must be made available to the sponsor prior to randomization. The sponsor will review eligibility criteria and approve enrollment of each subject into the study.

The modified MFSAF v2.0 e-diary will be completed each evening starting on Day -7 ([redacted]) and will continue to be completed each evening through Week 48. The first EORTC QLQ-C30, EQ-5D-5L and BPI assessments will be administered prior to the first dose of study treatment. Subjects should be provided a private, quiet area to complete the questionnaires. 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 determined their study eligibility.

9.1.3. Single-Blind Treatment Phase

Day 1/Day of Randomization/Registration

This was originally a single-blind study, in which subjects were blinded to the treatment arms. Beginning with Protocol Amendment 2, neither subjects nor investigators will be blinded to subject treatment assignment. The Treatment Phase will begin at randomization/registration and will continue until study drug discontinuation. Subjects should start study treatment within 72 hours after randomization/registration in the IWRS.

Treatment Phase

A cycle is defined as 21 days. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. A window of ±3 days is allowed for visits to the clinic. Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical

response. It is recommended that the EORTC QLQ-C30, EQ-5D-5L, BPI, PGIC, and MF Symptom Recall Form are administered before any tests, procedures, or other consultations. After the PRO questionnaires have been administered, a symptom-directed physical examination including spleen palpation will be conducted (see Section 9.2.1). Laboratory test results must be reviewed prior to administering study treatment. Adverse events and changes to concomitant medications will be recorded (see Section 17.5). Dose modifications will be made according to criteria described in Sections 6.1, 6.2, and 6.3. The investigator will assess subject response to therapy using the efficacy measurements and disease response criteria according to the schedule described in Section 9.2.1.

Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If a subject develops features of response (eg, improvement in palpable or radiographic splenomegaly, improvement of symptoms, resolution of leukoerythroblastosis, decreased transfusion requirements, etc.) and CR or PR are clinically suspected at a time not specified on the Time and Events Schedule then all required disease assessments should be performed. In order to confirm a CR or PR per modified IWG-MRT criteria, all disease assessments should be repeated 12 weeks from time of CR or PR. If progressive disease is diagnosed, or the subject discontinues study treatment for other reasons, then the subject will complete the End-of-Treatment Visit within 30 days after the last dose of study treatment, and enter the Posttreatment Follow-up Phase.

End-of-Treatment/Early Withdrawal

An End-of-Treatment Visit will be scheduled within 30 days after the last dose of the last study treatment for all subjects, including those discontinuing treatment for any reason, except for lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinued from treatment due to disease progression, adverse event, or other reasons and enter the Posttreatment Follow-up Phase should have the End-of-Treatment Visit completed before starting any subsequent anti-MF 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 treatment. Additional information on reporting adverse events may be found in Section 12. The PGIC questionnaire and MF Symptom Recall Form should also be completed at the End-of-Treatment Visit. If the PGIC assessment is 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 assessment during the Posttreatment Follow-up Phase, then the reason for not completing the questionnaire will be documented (ie, too ill, subject refused).

9.1.4. 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 to determine survival status, and subsequent anti-MF treatment every 16 weeks ± 7 days until study end. 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 CRF. Where allowed by local law, public records may be used to document death for the purpose of obtaining survival status.

During the Posttreatment Phase, sites should attempt to administer the EORTC QLQ-C30, EQ-5D-5L and BPI assessments every 16 weeks ± 7 days, unless death or study end occurs first. 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 (ie, too ill, subject refused).

Note that a plasma sample for immunogenicity testing should be collected at the first follow-up visit, and a posttreatment MRI is required 3 months after the last dose of study drug. Refer to the Time and Events Schedule for the timing of all Post-treatment Follow-up Phase procedures.

9.1.5. Extension Phase

Once the end of the main study has been reached, subjects in the Treatment Phase who are benefiting from study treatment may enter the Extension Phase and continue to receive imetelstat. Treatment may continue until there is loss of benefit or unacceptable toxicity, as determined by the investigator according to local standard of care. Subjects in the Posttreatment Follow-up Phase of the main study will enter the Extension Phase for continued follow-up of survival status.

Subjects entering the Extension Phase must sign and date an updated ICF, at which time they will begin following the Time and Events Schedule for the Extension Phase. 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.

Subjects who discontinue imetelstat during the Extension Phase, or who have already discontinued imetelstat before entering the Extension Phase, will be contacted to determine survival status every 16 weeks ±7 days until the Extension Phase ends. Procedures for documentation of survival follow-up are described in Section 9.1.4.

Data collection in the eCRF during the Extension Phase will be limited to imetelstat treatment information and survival status. Serious adverse events will be collected using the Serious Adverse Event Form (see Section 12.3.2) from the time the subject signs and dates the ICF for the Extension Phase until 30 days after the subject's last dose of imetelstat. All serious adverse event information including information on concomitant medication, diagnostic procedures, and imetelstat administration associated with the serious adverse event will be collected using the Serious Adverse Event Form and entered into the Global Safety database for imetelstat only, and not into the clinical database. Pregnancy will be reported using the pregnancy notification form.

The Extension Phase will end approximately 2 years after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first. The full study will end at that time.

9.2. Efficacy

9.2.1. Evaluations

Imaging

MRI of the abdomen will be performed to assess spleen volume. MRI will be performed at the time points specified in the Time and Events Schedule for disease evaluation. The scans will be reviewed locally and also sent to and read by the Independent Review Committee (IRC). Treatment decisions following any spleen volume assessments will be based on the IRC assessment.

Spleen Length Measurement

Spleen length measurement in centimeters will be assesed by manual palpation at every physical examination, disease evaluation study visit, end-of-treatment visit, and at the 3-month posttreatment follow-up (if feasible) as noted in the Time and Events Schedule. Subjects who have their dose increased from 4.7 mg/kg to 9.4 mg/kg will have an additional spleen assessment before starting the higher dose. The edge of the spleen should be determined by palpation from the mid-clavicular line at the costal margin on the left side of the abdomen to the point of greatest splenic protrusion.

Bone Marrow Assessment

Bone marrow biopsy and aspirate samples must be collected at the time points specified in the Time and Events Schedule for disease assessment and must be sent to the sponsor's approved central laboratory. Where clinically feasible, bone marrow aspirate should also be collected at the time points specified and sent to the central laboratory for cytogenetic assessment. In cases where it is not clinically feasible to collect an aspirate for cytogenetics, a peripheral blood sample will be collected for this testing. Central review of the bone marrow biopsy will be used to assess response to imetelstat for the efficacy analysis.

Peripheral Blood Analysis

Peripheral blood will be collected at the time points specified in the Time and Events Schedule for disease assessment and evaluated for hemoglobin, neutrophils and immature myeloid cells. Central review of the peripheral smear will be used to assess response to imetelstat for the efficacy analysis.

Screening Myelofibrosis (MF) Symptom Form

The Screening MF Symptom Form (Attachment 10) should be completed during Screening so that eligibility (Inclusion Criteria #5) may be determined. The Screening MF Symptom Form is a single-use, paper version of the modified MFSAF v2.0 diary that will be implemented in the study

using a hand-held device, and is adapted from the published modified MFSAF v2.0 questionnaire published by Mesa.[25]

Modified Myelofibrosis Symptom Assessment Form (MFSAF) Diary

Once eligibility has been confirmed via the Screening MF Symptom Form, subjects will be issued a hand-held electronic device to record answers to queries regarding MF symptoms. Questions on these symptoms are from the modified MFSAF v2.0 questionnaire[25] and will be completed by subjects each night beginning at Day -7, and continuing to the Week 48 visit. Symptoms will be assessed including night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, bone or muscle pain, and inactivity. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. Detailed directions for the administration of the modified MFSAF v2.0 diary will be provided in a Reference Manual.

Myelofibrosis (MF) Symptom Recall Form

The MF Symptom Recall Form (Attachment 11) should be completed, starting after Week 48, at the time points specified in the Time and Events Schedule. The MF Symptom Recall Form is a paper questionnaire adapted from the modified MFSAF v2.0 diary, and includes a modified recall period of the average of the prior 7 days.

Efficacy Response Assessment

Response assessment for the response categories in Table 9 will be done per the modified 2013 IWG-MRT criteria. Assessment of response should include radiographic imaging, evaluation of blood and bone marrow (if applicable), and modified MFSAF v2.0 diary.

Table 9: Response Categories

Response Category	Required Criteria
	For all response categories, benefit must last for >12 weeks[a] to qualify as a response
Clinical Improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia[b]
Anemia Response	Subjects with baseline Hb <10 g/dL but not meeting strict criteria for transfusion dependency: a ≥ 2 g/dL increase in Hb[c] Transfusion dependent subjects at baseline: becoming transfusion independent. Transfusion independence is defined as absence of any pRBC transfusions for at least 12 "rolling" weeks[c]
Spleen Response	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable or A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50% A spleen response requires confirmation by MRI showing ≥35% SVR
Symptoms Response	A ≥50% reduction in the modified MFSAF v2.0 TSS[d]
Progressive Disease	Splenomegaly requires MRI showing a ≥25% increase in spleen volume from baseline or Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 X 10^9/L that lasts for at least 2 weeks
Stable Disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month

[a] Benefit must last 12 weeks. This applies to clinical improvement, anemia response, spleen response, and symptoms response.

[b] Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥2.0 g/dL decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or ANC, according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. In addition, assignment to CI requires a minimum platelet count of ≥25,000 X 10^9/L and ANC of ≥0.5 x 10^9/L.

[c] Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <8.5 g/dL, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥8.5 g/dL.

[d] Symptoms are evaluated by the modified MFSAF v2.0 TSS. The modified MFSAF v2.0 TSS is assessed by the patients themselves and this includes night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, bone or muscle pain, and inactivity. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The modified MFSAF v2.0 TSS is the summation of all the individual scores, excluding inactivity (0-60 scale). Symptoms response requires ≥50% reduction in the modified MFSAF v2.0 TSS. After Week 48 symptom response will be assessed by the MF Symptom Recall Form.

For the response categories of CR and PR the criteria in Table 10 will be used.

Table 10: Remission Parameters

Parameters	Complete Remission (CR)	Partial Remission (PR) (Scenario 1)	Partial Remission (PR) (Scenario 2)
	For all response categories, benefit must last for >12 weeks to qualify as a response		
Bone marrow	Normocellular, <5% blasts, ≤ Grade 1 fibrosis	Normocellular, <5% blasts, ≤ Grade 1 fibrosis	Not meeting bone marrow remission criteria
Immature myeloid cells in PB	<2%	<2%	<2%
Hemoglobin	10 g/dL – ULN	8.5 – <10 g/dL	10 g/dL – ULN
Neutrophils	1 x 10^9/L – ULN	1 x 10^9/L – ULN	1 x 10^9/L – ULN
Platelets	100 x 10^9/L – ULN	50 - <100 x 10^9/L	100 x 10^9/L – ULN
Spleen	Not palpable and ≤350ml volume	≥35% splenic volumetric reduction by MRI or not palpable	≥35% splenic volumetric reduction by MRI or not palpable
EMH	No non-hepato-splenic EMH	No non-hepato-splenic EMH	No non-hepato-splenic EMH
Symptoms	>70% improvement in symptom score per modified MFSAF v2.0 TSS	>50% improvement in symptom score per modified MFSAF v2.0 TSS	>50% improvement in symptom score per modified MFSAF v2.0 TSS

CR=complete remission; EMH=extramedullary hematopoiesis; MFSAF TSS= Modified Myelofibrosis Symptom Assessment Form Total Symptom Score; MRI=magnetic resonance imaging; PR=partial remission; ULN=upper limit of normal

Radiographic evaluations will be assessed by an independent radiologist, and bone marrow fibrosis and peripheral blood smear assessments will be performed by an independent pathologist. Detailed procedures will be described in a separate IRC charter.

9.2.2. Endpoints

Primary Endpoints

The co-primary endpoints of this study are spleen response rate and symptom response rate. Spleen response rate is defined as the proportion of subjects who achieve ≥35% reduction in spleen volume at Week 24 from baseline as measured by imaging scans. Symptom response rate is defined as the proportion of subjects who have ≥50% reduction in TSS at Week 24 from baseline as measured by the modified MFSAF v2.0 diary.

Secondary Endpoints

- CR or PR per modified 2013 IWG-MRT criteria
- CI per modified 2013 IWG-MRT criteria
- Spleen response, symptoms response, and anemia response per modified 2013 IWG-MRT criteria

- Duration of spleen response, duration of symptoms response, duration of CR or PR, duration of CI, and duration of anemia response
- OS
- Patient reported outcomes including EORTC QLQ-C30, EQ-5D-5L, BPI, and PGIC
- Safety profile of imetelstat
- PK profile of imetelstat

Exploratory Endpoints

- TA, TL and hTERT at baseline and the change from baseline
- Cytogenetic response and molecular response
- Leukemia free survival

9.3. Pharmacokinetic and Immunogenicity Evaluations

9.3.1. Sample Collection and Handling

Plasma samples will be collected from all subjects for measurement of plasma concentrations of imetelstat and the generation of antibodies to imetelstat the time points specified in the Time and Events Schedule for PK Sampling. An optional bone marrow sample will be collected for measurement of concentration of imetelstat in the bone marrow.

Samples will be used to evaluate the pharmacokinetics as well as the immunogenicity of imetelstat (antibodies to imetelstat). Plasma samples will be divided into 2 aliquots for pharmacokinetics analysis: 1 for testing and 1 for back-up. Plasma samples will be tested for anti-drug antibodies. Samples collected for analyses of imetelstat plasma concentration and antibody 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. At visits where plasma concentration and antibodies to imetelstat will be evaluated, 1 blood sample can be used.

The exact dates and times of blood sampling and bone marrow 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.

Collection of plasma and/or bone marrow samples may be deferred or suspended during the study if the objectives of PK/PD analysis are met.

9.3.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of imetelstat using a validated, specific, and sensitive hybridization ELISA method by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a research characterization method. In addition, plasma PK samples may be stored for future analysis.

Bone marrow samples will be analyzed to determine concentrations of imetelstat using a qualified method.

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.

9.3.3. Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the sponsor in accordance with the sponsor's current Clinical Pharmacokinetics Guideline. For all subjects who have serial pharmacokinetic blood samples collected, based on the individual plasma concentration-time data, using actual sampling times, the following plasma pharmacokinetic parameters of imetelstat will be determined via non-compartmental analysis with validated Phoenix™ WinNonlin® software (Pharsight Corporation, Certara, L.P., St. Louis, MO):

C_{max}	maximum observed plasma concentration
t_{max}	time to reach the maximum observed plasma concentration
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time 0 to 24 hours postdose
$t_{1/2}$	elimination half-life associated with the terminal slope (λ_z) of the semi-logarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$

Additional pharmacokinetic parameters may be determined as appropriate.

Sparse Pharmacokinetic Blood Sample Collection

Model-derived exposure parameters (eg, C_{max} or AUC) may be selected to further explore pharmacokinetic/pharmacodynamic correlation between exposure with relevant clinical, pharmacodynamic, or biomarker information imetelstat.

9.3.4. Immunogenicity Assessments

Antibodies to imetelstat (anti-drug antibodies [ADA]) will be evaluated in plasma samples collected from all subjects according to the Time and Events Schedule. Additionally, plasma samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. 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 or to further characterize the immunogenicity of imetelstat.

9.4. Pharmacodynamic Evaluations

Blood samples for PD analysis will be collected as outlined in the Time and Events Schedule to evaluate the target engagement by examining the change in TA, TL and hTERT RNA expression levels.

Additional blood samples will be collected per the Time and Events Schedule to assess target inhibition after dose escalation for subjects initially treated with 4.7 mg/kg who were subsequently dose escalated to 9.4 mg/kg.

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

A nonlinear mixed effects PK model will be built to characterize and predict the overall exposure of imetelstat in MF subjects and determine different PK parameters, such as, clearance (CL), volume of distribution (V), and metrics of systemic exposure AUC and C_{max}. PK/PD models will be constructed to describe and understand the relationship between imetelstat exposure and hematological effects (hemoglobin concentrations in blood and platelets count) as well as efficacy (spleen volume and response). The immunogenicity effects on imetelstat pharmacokinetics and exposure–response relationships for efficacy and safety will be assessed. Model-based simulations will be conducted to optimize the dose and to help guide the design of future studies. If sufficient data are available, PK/PD modeling may be performed to explore the relationship between pharmacokinetic parameters (eg, C_{max} or AUC) and pharmacodynamic biomarkers (eg, change of TA, TL or hTERT from baselines after treatment).

9.6. Biomarkers

Blood samples will be collected as outlined in the Time and Events Schedule for mutational analysis. Genomic DNA will be prepared from isolated granulocytes to characterize the mutation status on a panel of myeloid related genes by next-generation sequencing (NGS) or other methodology where necessary to evaluate the association with clinical response.

Additional blood samples will be collected as outlined in the Time and Events Schedule 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,

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.

Where clinically feasible, bone marrow aspirates will be collected as outlined in the Time and Events Schedule. Peripheral blood may be submitted in place of an aspirate only in cases where a bone marrow aspirate cannot be obtained. Every effort should be made to continue collecting the same type of sample (bone marrow aspirate or peripheral blood) at screening and subsequent time points when possible. Karyotype testing may be performed to characterize cytogenetic abnormalities at screening to correlate to clinical response; and to evaluate eradication or reduction of a preexisting abnormality to assess the rate of cytogenetic response as defined by modified 2013 IWG-MRT response criteria for MF.[28] Sites will be notified if a subject's baseline bone marrow aspirate does not show an abnormality and collection of samples for cytogenetics will cease for these subjects. Subjects who show a cytogenetic abnormality at baseline will continue to have samples collected.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. 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.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded (FFPE) bone marrow sample for the successful completion of the protocol-specified analyses, then the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected bone marrow samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

9.7. Patient Reported Outcomes

Additional PROs including health-related quality of life, pain, and overall change in patient's health will be assessed using the EORTC QLQ-C30, EQ5D, the BPI and the PGIC at certain visits as indicated in the Time and Event Schedule. The EORTC QLQ-C30 and instructions will be provided as separate documents. It is preferred that the paper PRO assessment questionnaires are administered before any tests, procedures, or other consultations and they should be done in the same order at each visit for each subject to ensure that the subject is answering these as consistently as possible. These PRO data will be used to further validate the modified MFSAF v2.0.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been used widely among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11 minutes. Reliability, validity, and clinically meaningful change have been demonstrated in patients with multiple myeloma.[8,1] The focus of the PRO assessment will be the global health scale which is designated as a secondary endpoint. The remaining domains are included as exploratory endpoints.

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective 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).[11,24] The scores for the 5 separate questions are categorical and are 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 BPI has become one of the most widely used measurement tools for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions.[10] The BPI is a 9-item measure that captures both pain intensity (severity) and the impact of pain on functioning (interference).

The PGIC is used to capture the patient perspective of improvement or decline in MF symptoms over time. The PGIC has a 7–point response scale ranging from 1 (very much improved) to 7 (very much worse), with 4 representing no change.

9.8. Safety Evaluations

All subjects who receive treatment will be considered evaluable for toxicity. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. 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 Sponsor's Committee will review all the safety data on a quarterly basis, or ad hoc, as needed. The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

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

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 nonserious adverse events) following the procedure described in the protocol for serious adverse events and will require enhanced data collection. For this study the adverse events of special interest include:

- 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

For these events laboratory assessments should be repeated weekly until bilirubin with fractionation is <3x ULN, and ALT, AST and ALP is <5 x ULN. 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. All hepatic adverse events and LFT abnormalities will be reviewed by an Independent Hepatic Expert Committee, at least quarterly, or as needed.

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, then 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.

Blood samples for serum chemistry and hematology to assess the safety of study treatment will be collected. Required laboratory tests must be performed within 48 hours prior to the scheduled visit. For Cycle 1, Day 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days of the first dose of study treatment.

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 CRF. For example,

laboratory abnormalities leading to an action regarding any study treatment (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 CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the adverse event, 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 the Time and Events Schedule:

- Hematology Panel

  -hemoglobin
  -absolute neutrophil count (ANC)
  -manual percent immature myeloid cells (blasts, promyelocytes, myelocytes, metamyelocytes and nucleated RBC)
  -white blood cell (WBC) count
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -blood urea nitrogen (BUN)
  -creatinine
  -alanine aminotransferase (ALT)
  - total bilirubin (with fractionation at screening; with fractionation post-screening if total bilirubin is abnormal)
  -alkaline phosphatase (ALP)
  -lactic acid dehydrogenase (LDH)
  -albumin
  -serum ferritin
  -aspartate aminotransferase (AST)

- INR (or PT) and aPTT
- Expanded LFT Panel

  - gamma-glutamyl transpeptidase (GGT)
  - chloride
  - bicarbonate
  - magnesium
  - fractionated bilirubin

  An expanded LFT panel is required for all subjects at screening and if an adverse event of interest is reported. For subjects with AST, ALT, ALP or bilirubin Grade ≥3, LFT laboratory assessments need to be repeated weekly until bilirubin with fractionation is <3x ULN, and AST, ALT and ALP are <5 x ULN. Additionally, subjects with Grade 1 and Grade 2 treatment emergent elevations in AST, ALT, ALP or bilirubin at the time of treatment discontinuation should continue to have laboratory assessments monthly until resolution to at least baseline.

- Viral hepatitis: Screening for hepatitis should include hepatitis serology panel A through E. Hepatitis D serology is only required if the subject tests positive for the hepatitis B surface antigen (HBsAg).

- Peripheral Blood Smear: A peripheral blood smear should be performed at the time points shown in the Time and Events Schedule.

Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening. During the collection of ECGs, 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. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Temperature, pulse/heart rate, and blood pressure will be recorded, preferably while the subject is seated, at the time points specified in the Time and Events Schedule. Vital signs that are considered to be clinically relevant by the investigator are to be documented as adverse events.

Physical Examination

Screening physical examination should include body weight, height, and the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Only a limited symptom-directed physical examination including spleen palpation 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.

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 CRF or laboratory requisition form. Refer to the Time and Events Schedule 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 finished all protocol-specified procedures before the end of the study, 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

Investigators are encouraged to keep a subject experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject's study treatment must be discontinued before the end of the treatment regimen, then this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) 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 experiences unacceptable toxicity
- 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 CRF.

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, then 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 CRF 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, then end-of-treatment and posttreatment assessments should be obtained.

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

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Analysis Set

The Treated Population will consist of all subjects who receive at least 1 dose of study drug. Primary efficacy and safety analyses will be performed using the Treated Population. The intent-to-treat (ITT) population will consist of all subjects who are randomized.

The PK/PD Population will consist of all subjects who received at least 1 dose of study drug and had at least 1 sample collected during treatment to determine the drug concentration or pharmacodynamic biomarker response.

The treatment arms will be evaluated independently. Continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation (SD), $25^{th}/75^{th}$ 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.

11.2. Sample Size Determination

The study was originally designed to enroll approximately 200 subjects (approximately 100/arm). On the basis of historical data, the outcomes are poor for patients whose disease is relapsed after or refractory to JAK inhibitor therapy. The expected spleen response rate (proportion of subjects who achieve ≥35% reduction in spleen volume at Week 24) and symptom response rate (proportion of subjects who have ≥50% reduction in TSS at Week 24) in patients with salvage therapy or without treatment [redacted].

For each treatment arm, the sample size is calculated based on the following assumptions:

1. null hypothesis: [redacted]
2. alternative hypothesis: [redacted]
3. the null hypothesis is tested by the intersection-union test.[6] Each of the co-primary endpoints is tested at one sided α=0.025, and the maximum Type I error rate for testing co-primary endpoints is the same as one sided α=0.025

[redacted]

[redacted]

The original study design allowed for enrollment of approximately 200 subjects; however, following the first interim review of data, and in line with Protocol Amendment 2, enrollment of new subjects into Arm A was suspended and enrollment into Arm B was permanently closed. Therefore, total enrollment in the study may be approximately 160 subjects if enrollment in Arm A is resumed after the second interim review.

11.3. Subject Information

The number of subjects enrolled, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation.

Demographic and baseline vital sign variables will include age, sex, race, ethnicity, height, weight, blood pressure, and weight. Baseline disease characteristics (documented in the source documents and CRFs) will be summarized.

11.4. Efficacy Analyses

Planned efficacy analyses are as follows: (1) a first interim review after approximately 20 subjects in each arm have been followed for at least 12 weeks; (2) a second interim review with a clinical cutoff that is 6 months after the clinical cutoff used for the first interim review; (3) the primary efficacy analysis after all subjects have been followed for at least 24 weeks; (4) the final analysis at the end of the main study, which is defined as 18 months after the last subject is enrolled or when the sponsor terminates the study; and (5) OS-related analysis will be performed or updated when the Extension Phase has ended.

Primary Endpoint Analyses

The analysis for the co-primary endpoints (spleen response rate and symptom response rate) will be based on the Treated Population. For each treatment arm, spleen response rate and symptom response rate will be presented along with their 95% 2-sided exact confidence interval. Sensitivity analysis may be performed on the intent-to-treat population and evaluable population in support of the primary analysis if deemed appropriate.

Spleen response rate is defined as the proportion of subjects who achieve ≥35% reduction in spleen volume at Week 24 from baseline as measured by imaging scans. The spleen response data reviewed by the IRC will be used for the interim data reviews, the primary analysis, and the final analysis. The response data assessed by the investigators will be used as a supportive analysis.

Symptom response rate is defined as the proportion of subjects who have ≥50% reduction in TSS at Week 24 from baseline as measured by the modified MFSAF v2.0 diary. The TSS will be calculated as the 7-day average of daily TSS, which is the summation of 6 individual symptom scores (night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, bone or muscle pain).

Secondary Endpoint Analyses

- Proportion of subjects with CR or PR, and proportion of subjects with CI will be evaluated using the same statistical methods as for the primary endpoints.
- Proportion of subjects with spleen response, symptoms response, and anemia response per modified 2013 IWG-MRT criteria will be reported along with a 95% confidence interval.
- The distributions of duration of spleen response and duration of symptom response will be summarized using Kaplan-Meier estimates based on responding subjects. The estimated median will also be reported along with a 95% confidence interval. Duration of CR or PR, CI, and anemia response will be provided descriptively using similar methods based on responding subjects.
- The distribution of OS will be summarized using similar Kaplan-Meier methods.
- Change in spleen volume, change in TSS, and change in PRO endpoints from baseline will be descriptively summarized over time.
- Additional analyses to be performed for the subjects who were initially treated with 4.7 mg/kg and subsequently dose escalated to 9.4 mg/kg per the guidance outlined in Section 6.

11.5. Pharmacokinetic Analyses

Pharmacokinetic Blood Sample Collection

Pharmacokinetic data collected from the sparse and intensive PK sampling will be pooled for the analysis. Nonlinear mixed effects modeling using NONMEM software will be used to develop the population PK model in MF subjects. Different structural and random effects models will be considered and compared. A stepwise covariate model building strategy will be adopted and covariate effects on PK parameters will be explored. Diagnostic plots, summary statistics, and a comparison of raw data to model predictions will be evaluated.

Serial Pharmacokinetic Blood Sample Collection

Data will be listed for all subjects with available plasma concentrations per treatment. Subjects will be excluded from the PK analysis in situations where extenuating factors preclude an accurate assessment of the PK parameters of interest (eg, incomplete administration of the study drug; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lowest quantifiable concentration will be treated as zero in the calculation of PK parameters and for the calculation of summary statistics of concentration-time data as per the PK analysis guideline. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Mean and individual plasma concentrations of imetelstat versus time profiles will be plotted. Descriptive statistics of imetelstat, including arithmetic mean, SD, coefficient of variation, geometric mean (PK parameters only), median, minimum, and maximum will be calculated for the imetelstat plasma concentrations at each sampling time for imetelstat and for all PK parameters of imetelstat.

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 one dose of imetelstat). The results will be summarized by treatment arm and subjects with appropriate samples for the detection of antibodies to imetelstat.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

Different PK/PD models will be built to understand and characterize the exposure-response relationship for key efficacy and safety parameters, to detect the influence of covariates, and identify inter-individual variability in response. The exposure-response analysis for efficacy parameters includes SVR from baseline at Week 12 and the proportion of subjects with response (≥35% SVR from baseline at Week 12). The exposure-response analysis for safety parameters will characterize the time course of platelet counts and hemoglobin. If sufficient data are available, then the immunogenicity effect on imetelstat PK and exposure–response relationships for efficacy and safety will be assessed and the correlation between the exposure and the change of biomarkers will be explored. The details will be given in the modeling analysis plan. If sufficient PD biomarker data are available, then the correlation between exposure and the change of PD will be explored.

11.8. Biomarker Analyses

Biomarker measures and the change from baseline will be listed, tabulated, and plotted where appropriate. Subjects may be grouped by dose, 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. Safety Analyses

Safety analyses will be performed using the Treated Population. Safety will be evaluated using the 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 treatment and reasons for discontinuation will be tabulated. Safety

variables are to be tabulated by descriptive statistics (n, mean, median, SD, minimum, and maximum; or n and percent).

Additional analyses will be performed for the subjects who were initially treated with imetelstat 4.7 mg/kg and subsequently dose escalated to 9.4 mg/kg per the guidance outlined in Section 6.

Adverse Events

Treatment-emergent adverse events are adverse events that occur after the first dose of study drug, through the Treatment Phase, and for 30 days following the last dose of study drug; any adverse event considered study drug-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 CRF 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 arm.

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 used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

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 experienced by the subject during treatment will be provided. The worst toxicity grade during the study will be tabulated.

Electrocardiogram (ECG)

Electrocardiogram data will be listed by ECG parameter at Screening.

Vital Signs

Descriptive statistics of temperature, heart rate, respiratory 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.

11.10. Interim Review

The first interim data review was designed as follows: The first interim review was performed after approximately 20 subjects were randomized in each arm and followed for at least 12 weeks. The goal of the interim review was to assess safety and early efficacy and perform comprehensive exposure-response analyses. Based on this analysis, if both doses were efficacious and had an acceptable safety profile, both arms will continue with enrollment until approximately 100 subjects per arm are enrolled. If only one dose was efficacious and had an acceptable safety profile, then that arm would continue enrollment, and enrollment would be stopped in the other arm. In the case that both arms were not efficacious and safe, an alternative dose may be selected based on the PK/PD exposure-response, efficacy, and safety analysis and a protocol amendment would be implemented to reflect this. Study enrollment continued at the time of interim review.

Safety was evaluated using the following parameters (including but not limited to): adverse events, serious adverse events, dose modifications and subject compliance. PK/PD exposure-response analyses for efficacy parameters (eg, SVR from baseline at Week 12), and for safety parameters (eg, platelets and hemoglobin) were be conducted. Biomarkers such as change in TA, TL and hTERT from baseline was evaluated for subjects with available data.

Early efficacy was evaluated by SVR by MRI and as assessed by the investigator. [redacted] Other efficacy data including symptoms, peripheral blood counts and bone marrow data up to interim was reviewed as well. This guideline was intended to inform the decision, which was expected to be multifactorial taking into consideration safety, tolerability, and PK/PD modeling.

At the time of Protocol Amendment 2, enrollment of new subjects in this study is suspended. A second interim review will be performed with a clinical cutoff that is 6 months after the clinical cutoff used for the first interim review. It is expected that approximately 35 subjects who were enrolled and treated in the 9.4 mg/kg arm will have been followed for at least 24 weeks. IRC assessment of SVR will be used for efficacy evaluation. [redacted]

11.11. Data Analysis Committees

A Sponsor Committee including the study physician, safety physician, study scientist and statistician will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study. The safety review will focus on, but will not be limited to, deaths,

treatment discontinuations, serious adverse events, Grade ≥ 3 events, and events of special interest. The Sponsor Committee responsibilities, authorities, and procedures will be documented in a charter.

Additionally, an Independent Hepatic Expert Committee consisting of 3 hepatologists will be established to monitor liver data on an ongoing basis. The Hepatic Expert Committee will review all hepatic adverse events and LFT abnormalities on at least a quarterly basis or as needed. The Hepatic Expert Committee responsibilities, authorities, and procedures will be documented in a charter.

The Hepatic Expert Committee will meet to review all hepatic serious adverse events reported during the Extension Phase, and the Sponsor Committee will continue to review study data.

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 or its affiliates 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 with 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 Union (EU) 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. These should usually be considered serious.

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 of an adverse event will be determined by 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

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events (with the exception of progression of MF) and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). 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 Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

As of Amendment 3, only serious adverse events will be reported from the time the ICF for the Extension Phase is signed and dated until 30 days after the last dose of imetelstat.

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. It is expected that subjects may experience progressive disease of MF during the study; however, disease progression will be documented as a study endpoint and NOT recorded and reported as an adverse event or anticipated event. 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.

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 CRF. 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 CRF 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 an expedited manner.

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.

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 appropriate sponsor contact person 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 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). 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 protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy 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 CRF). 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).

Serious Adverse Event Reporting Beginning With Amendment 3

Beginning with Amendment 3, only serious adverse event information will be collected. The reporting period extends from the time the ICF for the Extension Phase is signed and dated until 30 days after the subject’s last dose of imetelstat. Serious adverse event information will be provided to the sponsor via the Serious Adverse Event Form. The following information is requested for all reports of serious hemorrhagic adverse events and serious hepatic adverse events:

- Hemorrhagic serious adverse events: INR (or PT), aPTT, and platelet count should be assessed and reported in the serious adverse event report.
- Hepatic serious adverse events: serum chemistry and an expanded liver panel will be assessed and reported; if the event includes Grade 3 or 4 ALP elevation, ALP fractionation or 5’neucleotidase will also be assessed and reported.

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 will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

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)

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 Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

The effect of the study drug on sperm is unknown. Therefore, 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.

Pregnancy reporting, as described above, will continue during the Extension Phase.

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. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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, then the study-site personnel must report the PQC to the sponsor 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 individuals 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 vial contains 210 mg of imetelstat sodium and is designed to deliver a minimum of 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 Investigator's Brochure (IB) for a list of excipients.

14.2. Packaging

Imetelstat is supplied in glass vials in a protective carton. It will be supplied to the site/pharmacy as bulk supply. All packaging will meet applicable regulatory requirements.

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-46 F, refrigerated) and must not be utilized after the expiry date printed on the label. The product must not be frozen. Imetelstat does not contain preservatives; therefore any unused portion remaining in the vial must be discarded.

Imetelstat will be reconstituted with 0.9% Sodium Chloride. Refer to the Investigational Product Preparation Instructions (IPPI) and SIPM for details regarding dose preparation, storage, and handling of reconstituted and diluted solutions. Once reconstituted, imetelstat must be used within the time frame specified in the IPPI.

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 on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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 on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

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. Returned study drug must not be dispensed again, even to the same subject. 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
- Investigational Product Preparation Instructions
- Site Investigational Product Manual
- Central laboratory and central imaging manual and supplies
- NCI-CTCAE Version 4.03
- PRO questionnaires and user manuals
- Tablet devices for patient e-diary
- IWRS Manual and supplies
- eDC Manual and eCRF Completion Guidelines
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This was originally designed as a randomized, single-blind study to evaluate the efficacy and safety of 2 dose levels of imetelstat in subjects with intermediate-2 or high risk MF who were previously treated with a JAK inhibitor. For these patients previously treated with a JAK inhibitor there is no effective or approved therapy and the prognosis is very poor. All subjects will receive treatment with imetelstat.

Randomization was to be used to minimize bias in the assignment of subjects to each dose level, and treatment will be blinded to the subject to reduce potential bias during data collection (ie, symptom assessment and PROs). Beginning with Protocol Amendment 2 and suspension of new enrollment, neither subjects nor investigators will be blinded to subject treatment assignment.

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 according to modified 2013 IWG-MRT response criteria for MF. Safety assessments will occur through regular clinic visits including laboratory analyses. The sponsor will monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study.

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 604 mL. The total volume of blood includes laboratory assessments associated with screening and treatment including pharmacokinetic and biomarker samples. 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.

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 IB 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 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 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 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 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 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 pharmacodynamic biomarker PK 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 for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand imetelstat, to understand MF, to understand differential drug responders, and to develop tests/assays related to imetelstat and MF. The 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 for 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 CRF 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
- 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, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment 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 and enrollment 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 and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

For the main study, at a minimum, source documentation must be available for the following to confirm data collected in the CRF: 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; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

For the Extension Phase, at a minimum, source documentation must be available for the following: subject identification and study identification; discussion regarding closure of the main study and date of updated informed consent; dates of visits; drug dispensing records and study drug

administration information; and record of all serious adverse events and pregnancies and follow-up of serious adverse events and pregnancies.

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).

Subject-completed scales and assessments designated by the sponsor for the modified MFSAF v2.0 diary will be recorded directly into an electronic device and will be considered source data.

17.5. Case Report Form Completion

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

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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 CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF 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 CRFs are accurate and correct.

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

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

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- 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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

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

The sponsor 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 CRFs 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 CRF 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) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs 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.

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 main study is considered completed 18 months after the last subject is enrolled or anytime the sponsor terminates the study, whichever comes first. The full study, including the Extension Phase, will be completed approximately 2 years after the clinical cutoff for the final analysis of the main study, or when the sponsor terminates the study, whichever occurs first. The sponsor will ensure that subjects benefiting from treatment with imetelstat will be able to continue their assigned treatment. 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, provided there is reasonable cause and sufficient notice is given 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 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 CRFs. Subject privacy must, however, be respected. 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 and will contain CRF data from all study sites that participated in the study, direct transmission of

clinical laboratory data from a central laboratory and electronic diary data into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory or biomarker analyses performed after the Clinical Study Report has been issued will 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 will 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 60 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. 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 12 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 of and the results of clinical studies as required by law.

REFERENCES

1. Aaronson NK, Ahmedzai S, Bullinger M, et al. The EORTC core quality of life questionnaire: interim results of an international field study. In: Osoba, D, ed. *Effect of Cancer on Quality of Life.* Boca Raton: CRC Press Inc; 1991:185-203.
2. Abdelrahman RA, Begna KH, Al-Kali A, et al. Revised assessment of response and long-term discontinuation rates among 111 patients with myelofibrosis treated with momelotinib or ruxolitinib. *Leukemia*. 2014;doi:10.1038/leu.2014.286. Epub ahead of print.
3. Asai A, Oshima Y, Yamamoto Y, et al. A novel telomerase template antagonist (GRN163) as a potential anticancer agent. *Cancer Res*. 2003;63(14):3931–3939.
4. Baerlocher G, Leibundgut E, Spitzer G, et al. Imetelstat: a novel approach with robust hematologic and molecular responses in a phase 2 study in patients with essential thrombocythemia (ET) who are refractory or intolerant to prior therapy. [Abstract 4398]. EHA Annual Meeting, June 13-16, 2013.
5. Baerlocher GM, Leibundgut EO, Ayran C, et al. Imetelstat rapidly induces and maintains substantial hematologic and molecular responses in patients with essential thrombocythemia (ET) who are refractory or intolerant to prior therapy: preliminary Phase II results. *Blood*. 2012;120:179.
6. Berger, RL. Multiparameter hypothesis testing and acceptance sampling. *Technometrics*. 1982;24:295-300.
7. Bernard L, Belisle C, Mollica L, et al. Telomere length is severely and similarly reduced in JAK2V617F-positive and –negative myeloproliferative neoplasms. *Leukemia.* 2009;23:287–291.
8. Bjordal K, Kaasa S. Psychometric validation of the EORTC core quality of life questionnaire, 30 item version and a diagnosis specific module for head and neck cancer patients. *Acta Oncol.* 1992;31: 311-321.
9. Cervantes F, Vannucchi AM, Kiladjian JJ, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. *Blood*. 2013;122(25):4047-4053.
10. Cleeland C, Turk DC, Melzack R. Brief pain inventory. In: Cleeland C, Turk DC, Melzack R, eds. *Handbook of Pain Assessment.* New York: The Guilford Press; 1991:378–382.
11. De Charro F, Rabin R. EQ-5D-5L from the EuroQol group: an update. *QOL Newsletter.* 2000.
12. Ferraris AM, Mangerini R, Pujic N, et al. High telomerase activity in granulocytes from clonal polycythemia vera and essential thrombocythemia. *Blood*. 2005a;105(5):2138–2140.
13. Ferraris AM, Pujic N, Mongerini R, et al. Clonal granulocytes in polycythemia vera and essential thrombocythaemia have shortened telomeres. *Br J Haematology*. 2005b;130:391–393.
14. Frink R, Peyton, M, Sullivan J, et al. Sensitivity and resistance of non-small cell lung cancer to the telomerase inhibitor imetelstat. *Cancer Research.* 2010;70(8 Suppl):3577.
15. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol.* 2011;29(4):392–397.
16. Harley CB. Telomerase and cancer therapeutics. *Nat Rev*. 2008;8:167–179.
17. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787–798.
18. Harrison CN, Kiladjian J, Al-Ali, HK, et al. Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). *J Clin Oncol*. 2011;29(suppl):LBA6501.
19. Herbert B-S, Gellert GC, Hochreiter A, et al. Lipid modification of GRN163, an N3'-P5' thio-phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene*. 2005;24:5262–5268.

20. Iancu-Rubin C, Mosoyan G, Parker CC, et al. Imetelstat (GRN163L), a telomerase inhibitor selectively affects malignant megakaryopoiesis in myeloproliferative neoplasms (MPN). *Blood*. 2014;124(21):4582.

21. Investigator Brochure: JNJ-63935937 (imetelstat) Edition 14. Janssen Research & Development (30 Oct 2018).

22. Jabbour E, Hagop MK, Garcia-Manero G, et al. Outcome of patients (pts) with myelofibrosis (mf) after ruxolitinib (rux) therapy. *Blood*. 2013;122(21):1584.

23. Keohane C, Radia DH, Harrison CN. Treatment and management of myelofibrosis in the era of JAK inhibitors *Biologics: Targets and Therapy*. 2013;7:189–198.

24. Kind P, Dolan P, Gudex C, et al. Variations in population health status: results from a United Kingdom national questionnaire survey. *Brit Med J*. 1998;316(7133):736-741.

25. Mesa RA, Kantarjian H, Tefferi A, et al. Evaluating the serial use of the myelofibrosis symptom assessment form for measuring symptomatic improvement: performance in 87 myelofibrosis patients on a JAK1 and JAK2 inhibitor (INCB018424) clinical trial. *Cancer*. 2011;117:4869-4877.

26. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. *Cancer*. 2007;109:68-76.

27. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (international working group for myeloproliferative neoplasms research and treatment). *Blood*. 2010;115(9):1703–1708.

28. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: international working group-myeloproliferative neoplasms research and treatment (IWG-MRT) and European leukemia net (ELN) consensus report. *Blood*. 2013;122(8):1395–1398.

29. Tefferi A, LaPlant B, Begna K, et al. Imetelstat, a telomerase inhibitor, therapy for myelofibrosis: a pilot study. *Blood*. 2014;124(21): 634.

30. Tefferi A. How I treat myelofibrosis. Blood. 2011;117(13):3494–3504.

31. Terasaki Y, Okumura H, Ohtake S, et al. Accelerated telomere length shortening in granulocytes: a diagnostic marker for myeloproliferative diseases. *Exp Hematology.* 2002;30:1399–1404.

32. Vannucchi AM, Verstovsek S, Jones MM, et al. Efficacy of ruxolitinib by baseline spleen volume in patients with polycythemia vera resistant to or intolerant of hydroxyurea. *Blood*. 2014;124(21):1840.

33. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799–807.

34. Wang X, Hu CS, Li Y, et al. Effects of imetelstat on CD34+ cells of patients with myelofibrosis. *Blood*. 2014;124(21):1879.

Attachment 1: Modified Myelofibrosis Symptom Assessment Form v2.0 (modified MFSAF v2.0)

INSTRUCTIONS

Please complete this diary at night before bedtime. The diary asks about your myelofibrosis (MF) symptoms **during the past 24 hours.**

There is no right or wrong answer. Please give the answer that best reflects your opinion.

1. During the past 24 hours, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 24 hours, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 24 hours, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 24 hours, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 24 hours, what was the worst feeling of fullness (early satiety) you had after beginning to eat due to MF	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 24 hours, how severe was your worst bone or muscle pain due to MF (diffuse not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 24 hours, what was the worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Attachment 2: European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊⌋⌊⌋⌊⌋

Your birthdate (Day, Month, Year): ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋

Today's date (Day, Month, Year): 31 ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Attachment 3: Brief Pain Inventory (Short Form) (BPI)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date: ___/___/____ Time: _____

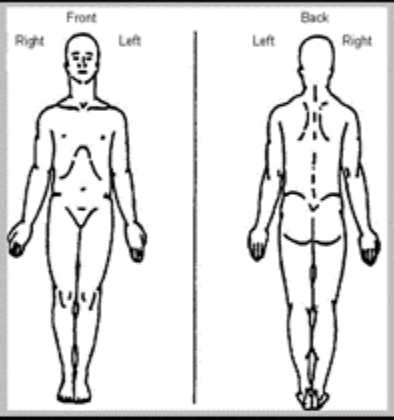
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

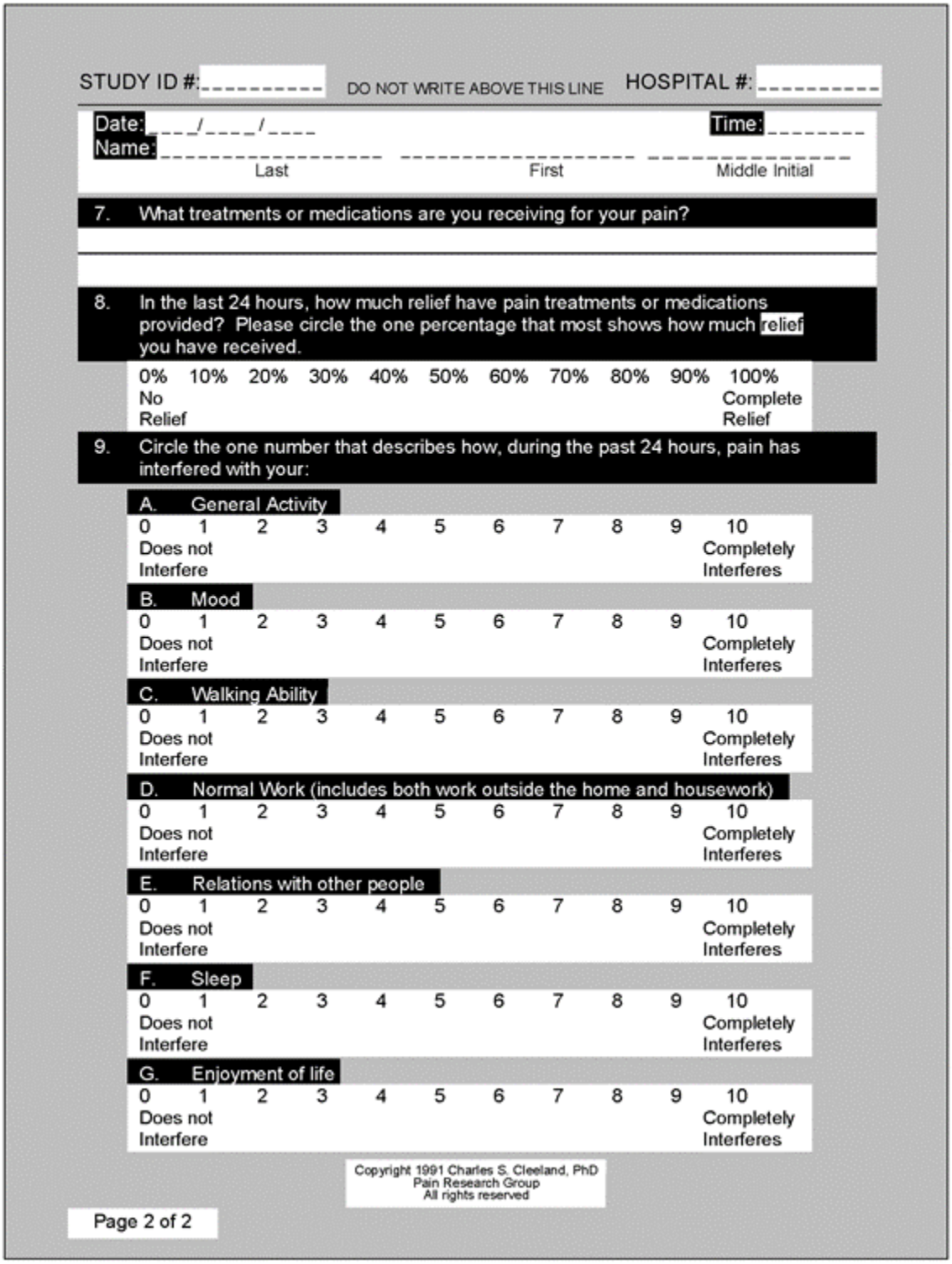
5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2



STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/___/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Page 2 of 2

Attachment 4: Patient's Global Impression of Change (PGIC)

Since the start of the treatment you've received in this study, your myelofibrosis symptoms 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 5: EuroQol-EQ-5D (EQ-5D-5L)

Health Questionnaire

English version for the USA

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 ❑

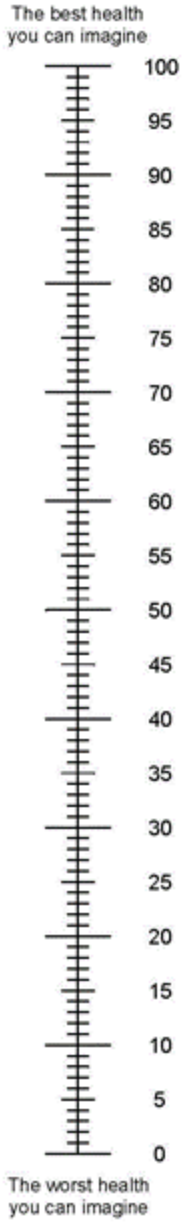
ANXIETY / DEPRESSION

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 ❑

2

- 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 = ☐



3

Attachment 6: World Health Organization (WHO) Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis

2008 WHO Diagnostic Criteria						
		Polycythemia Vera[1)]		Essential Thrombocythemia[1]		Primary Myelofibrosis[1]
Major criteria	1	Hgb > 18.5 g/dL (men) > 16.5 g/dL (women) or [2)]	1	Platelet count ≥ 450 x 10^9/L	1	Megakaryocyte proliferation and atypia[3)] accompanied by either reticulin and/or collagen fibrosis, or[4)]
	2	Presence of JAK2V617F or JAK2 exon 12 mutation	2	Megakaryocyte proliferation with large and mature morphology.	2	Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
			3	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
			4	Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis		
Minor criteria	1	BM trilineage myeloproliferation			1	Leukoerythroblastosis
	2	Subnormal serum Epo level			2	Increased serum LDH level
	3	EEC growth			3	Anemia
					4	Palpable splenomegaly

Key: BM, bone marrow; Hgb, hemoglobin; Hct, hematocrit; Epo, erythropoietin; EEC, endogenous erythroid colony; WHO, World Health Organization; CML, chronic myelogenous leukemia; PV, polycythemia vera; PMF, primary myelofibrosis; MDS, myelodysplastic syndromes; LDH, lactate dehydrogenase

[1] PV diagnosis requires meeting either both major criteria and one minor criterion **or** the first major criterion and 2 minor criteria. ET diagnosis requires meeting all 4 major criteria. PMF diagnosis requires meeting all 3 major criteria and 2 minor criteria.

[2] **Or** Hgb or Hct > 99th percentile of reference range for age, sex, or altitude of residence **or** red cell mass > 25% above mean normal predicted **or** Hgb > 17 g/dL (men)/ > 15 g/dL (women) if associated with a sustained increase of ≥ 2 g/dL from baseline that cannot be attributed to correction of iron deficiency

[3] Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

[4] In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (ie, pre-fibrotic PMF))

Attachment 7: International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Recommended Criteria for Post-Polycythemia Vera and Post-essential Thrombocythemia Myelofibrosis

Criteria for post-polycythemia vera-myelofibrosis	
Required criteria:	
1	Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2	Bone marrow fibrosis Grade 2–3 (on 0–3 scale) or Grade 3–4 (on 0–4 scale) (see footnote for details)
Additional criteria (2 are required):	
1	Anemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy
2	A leukoerythroblastic peripheral blood picture
3	Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4	Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)
Criteria for post-essential thrombocythemia myelofibrosis	
Required criteria:	
1	Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO
2	Bone marrow fibrosis Grade 2–3 (on 0–3 scale) or Grade 3–4 (on 0–4 scale) (see footnote for details)
Additional criteria (2 are required):	
1	Anemia and a ≥ 2 g/dL decrease from baseline hemoglobin level
2	A leukoerythroblastic peripheral blood picture
3	Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4	Increased lactate dehydrogenase
5	Development of ≥ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Note: Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Attachment 8: Dynamic International Prognostic Scoring System (DIPSS)

DIPSS (Dynamic International Prognostic Scoring System)

DIPSS Risk Factors	Adverse Points	Risk Category
Age > 65	1	0 → low risk 1-2 → Int-1 Risk 3-4 → Int-2 risk 5-6 → High risk
Hemoglobin < 10 g/dL	2	
Leukocytes > 25 10(9)/L	1	
Circulating blasts ≥1%	1	
Constitutional symptoms	1	

Passamonti Blood 2010

Attachment 9: Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Grade Scale (with Karnofsky conversion)

0	Fully active, able to carry on all predisease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg, light housework, office work. (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead. (Karnofsky 0)

Attachment 10: Screening Myelofibrosis (MF) Symptom Form

Instructions to Subjects: Please answer all questions to the best of your ability, based on your memory over the past 7 days (1 week). There is no right or wrong answer.

1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

2. During the past 7 days, how severe was your worst itchiness due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

5. During the past 7 days, at its worst, to what degree did you feel full quickly (early satiety) after beginning to eat due to MF?

0 (Not at all) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (diffuse, not joint or arthritis pain)?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

7. During the past 7 days, how severe was your worst inactivity (including work and social activities) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Attachment 11: Myelofibrosis (MF) Symptom Recall Form

Instructions: Please answer all questions to the best of your ability; circle the one number that describes the average of the worst level of each following symptoms on each day over the past week. There is no right or wrong answer.

1. During the past week, how severe were your worst night sweats (or feeling hot or flushed) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

2. During the past week, how severe was your worst itchiness due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

3. During the past week, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

4. During the past week, how severe was your worst pain under the ribs on the left side due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

5. During the past week, at its worst, to what degree did you feel full quickly (early satiety) after beginning to eat due to MF?

0 (Not at all) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

6. During the past week, how severe was your worst bone or muscle pain due to MF (diffuse, not joint or arthritis pain)?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

7. During the past week, how severe was your worst inactivity (including work and social activities) due to MF?

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

INVESTIGATOR AGREEMENT

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor
PROTOCOL:	63935937MYF2001, Amendment 5
IND:	N/A
EUDRACT NUMBER:	2015-000946-41
STUDY DRUG:	Imetelstat Sodium for Injection (GRN163L for Injection)
SPONSOR:	Geron Corporation 149 Commonwealth Drive Menlo Park, CA 94025 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
149 Commonwealth Drive
Menlo Park, CA 94025 USA

PROTOCOL FINALIZATION SIGNATURE PAGE

TITLE:	A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor
PROTOCOL:	63935937MYF2001, Amendment 5
IND:	N/A
EUDRACT NUMBER:	2015-000946-41
STUDY DRUG:	Imetelstat Sodium for Injection (GRN163L for Injection)
SPONSOR:	Geron Corporation 149 Commonwealth Drive Menlo Park, CA 94025 USA

[redacted] MD, PhD
Sponsor's Responsible Medical Officer

03/28/2019
Date