Official Title: **A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and Other Myeloid Malignancies**

NCT Number: NCT01731951

Document Date: Clinical Study Protocol: 05 October 2015

CLINICAL STUDY PROTOCOL

TITLE:	A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and other Myeloid Malignancies
PROTOCOL NUMBER:	CP14B019 (formerly MC1285)
IND:	116129
EUDRACT NUMBER:	N/A
STUDY DRUG:	JNJ-63935937 (Imetelstat Sodium for Injection) (formerly GRN163L for Injection)
SPONSOR:	Janssen Research & Development
Document History	**(Effective Date)**
Activation	October 26, 2012
Mayo Add1	April 12, 2013
Mayo Add2	June 7, 2013
Mayo Add3	August 8, 2013
Mayo Add4	August 29, 2013
Mayo Add5	December 4, 2013
Mayo Add6	Protocol changes not approved
Mayo Add7	December 30, 2013
Mayo Add8	February 18, 2014
Mayo Add 9	March 3, 2014
Mayo Add 10	April 7, 2014
Geron Document History	**(Protocol Finalization Date)**
Amendment 11	July 31, 2014
Janssen Research & Development Document History	**(Approval Date)**
Amendment 12	21 January 2015
Amendment 13	5 October 2015

EDMS number: EDMS-ERI-98370922, 2.0

PROTOCOL FINALIZATION SIGNATURE PAGE

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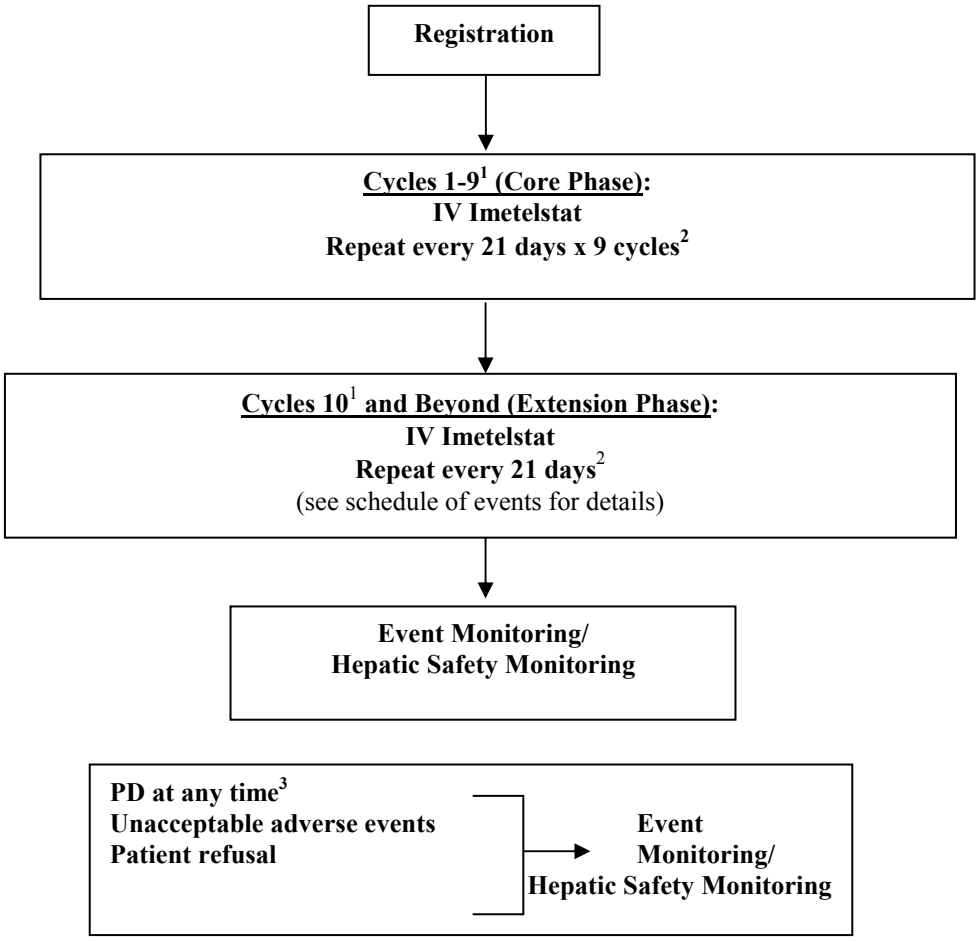
Note: All Study Arms (A, B, C, D, E, F, and G) are now permanently closed to accrual

Figure 1: Schema – Arm A

(Note: Arm A permanently closed to accrual)



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

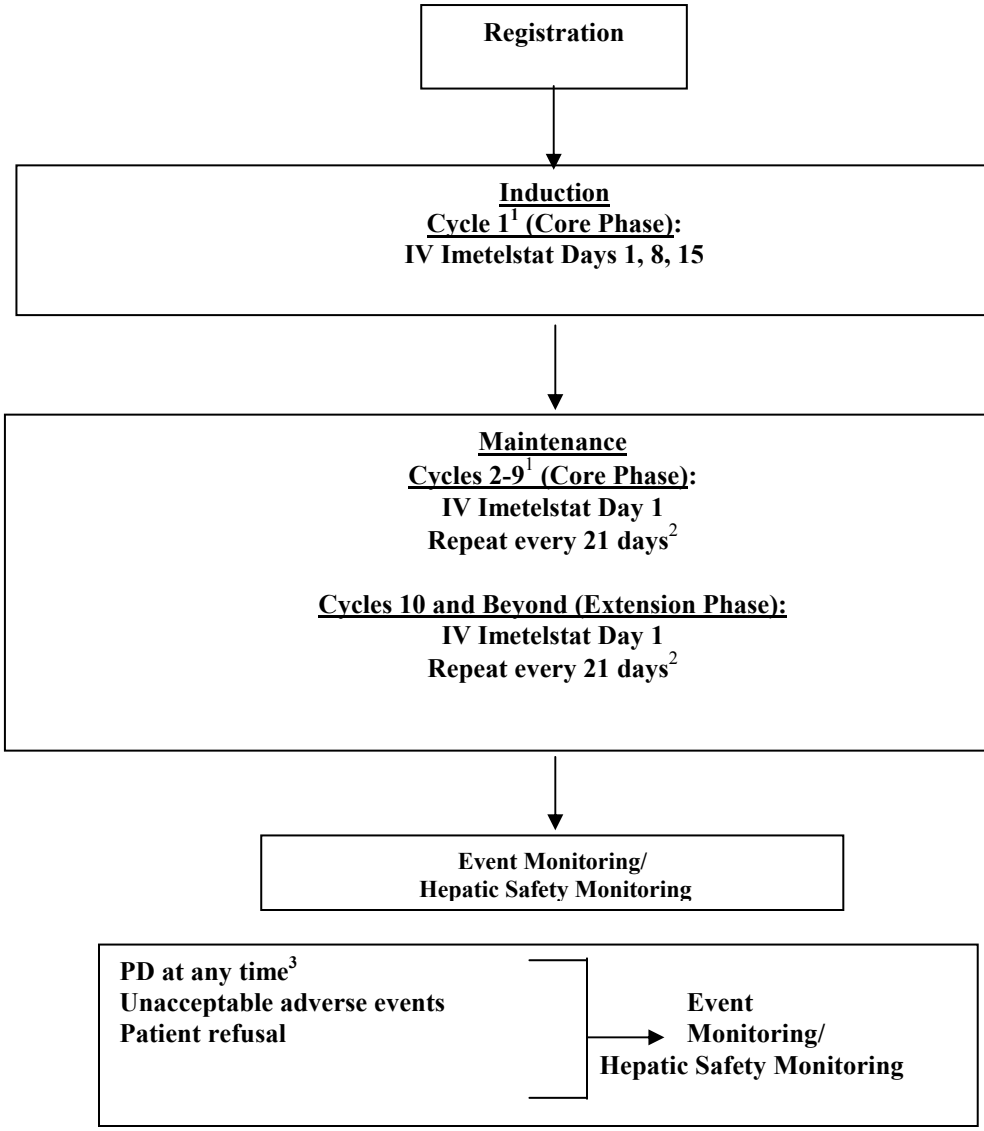
[1] Cycle length = 21 days. For patients who do not achieve a CR or PR by the end of Cycle 6, the frequency of dosing may be increased and the cycle length will be 21-28 days. For patients whose response has plateaued for a minimum of 3 months, the dose frequency may be reduced, or treatment may be interrupted until relapse then restarted, and the cycle length will be the length of the dosing interval. See Section 7.1. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥ 3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[3] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

Figure 2: Schema – Arm B

(Note: Arm B permanently closed to accrual)



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

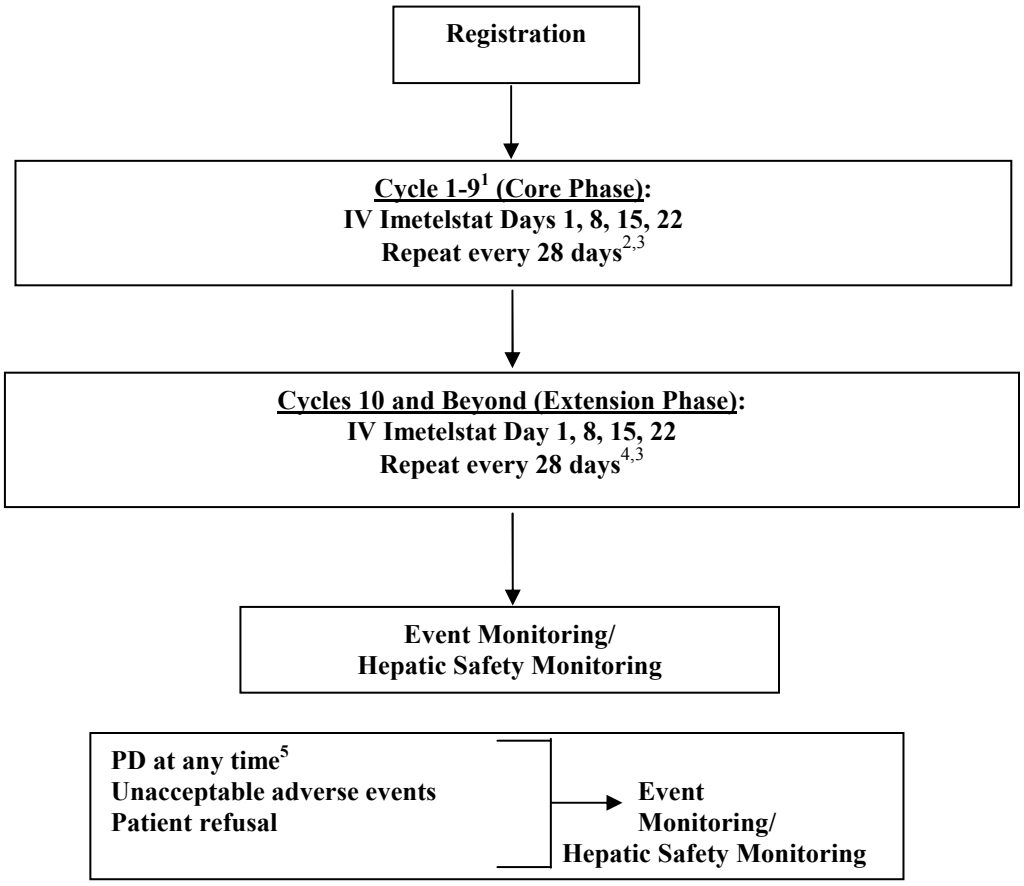
[1] Cycle length = 21 days. For patients who do not achieve a CR or PR by the end of Cycle 6, the frequency of dosing may be increased and the cycle length will be 21-28 days. For patients whose response has plateaued for a minimum of 3 months, the dose frequency may be reduced, or treatment may be interrupted until relapse then restarted, and the cycle length will be the length of the dosing interval. See Section 7.1. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[3] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

Figure 3: Schema – Arms C and D

(Note: Arms C and D permanently closed to accrual)



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥ 3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] For patients without response after the first two cycles, dosing might be increased to either Days 1, 3, 5 or Days 1, 3 every 2 to 4 weeks, per physician discretion. See Section 7.1.

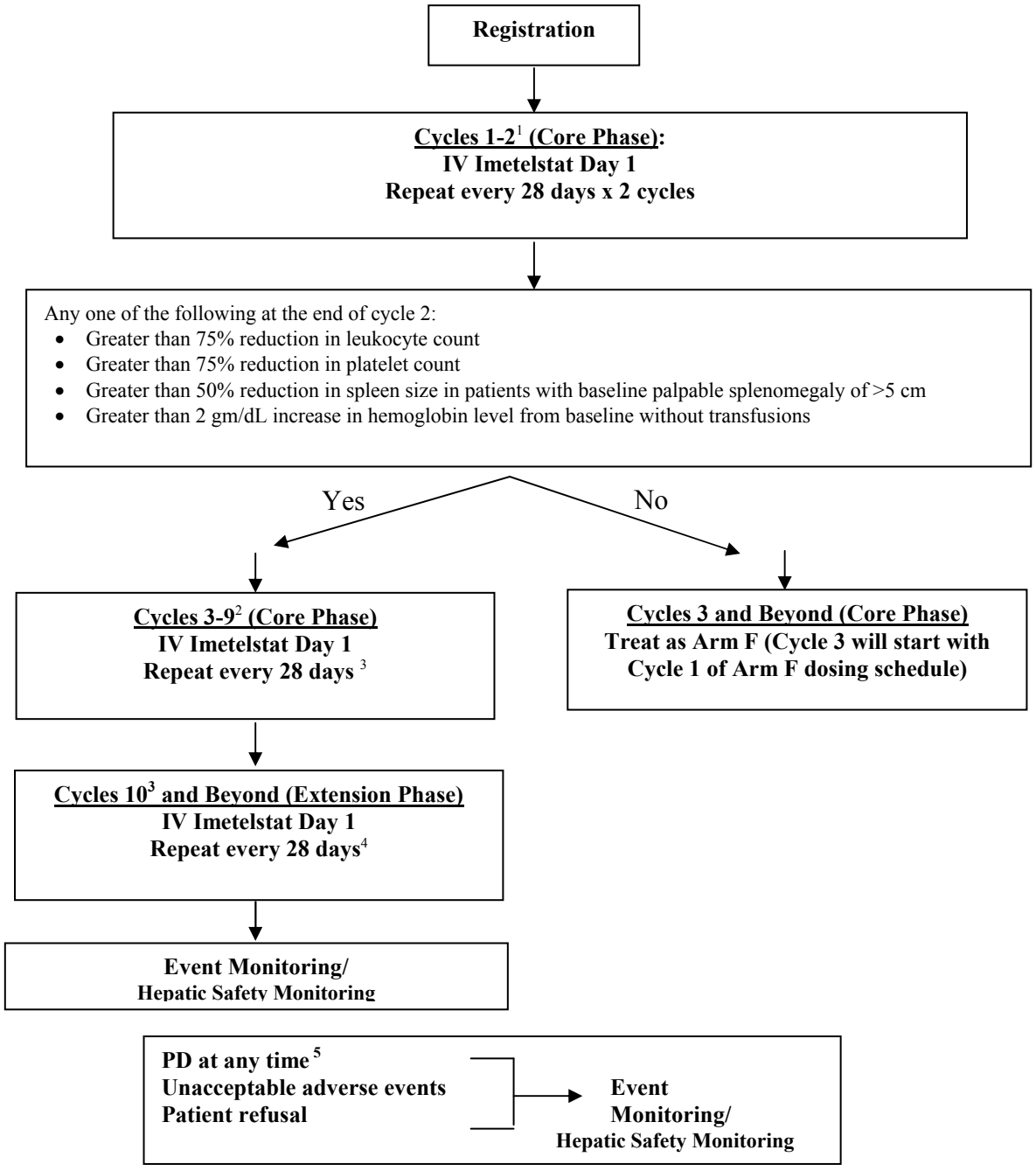
[3] For patients whose response has plateaued for a minimum of 3 months, the dose frequency may be reduced, or treatment may be interrupted until relapse then restarted, at the physician's discretion. See Section 7.1.

[4] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[5] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

Figure 4: Schema – Arm E

(Note: Arm E permanently closed to accrual) (myelofibrosis patients with spliceosome mutations or ring sideroblasts)



[1] Cycle length = 28 days. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥ 3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] In patients who do not achieve CR or PR, by the end of Cycle 4, the frequency of dosing may be increased to every week or every 2 weeks, at the physician's discretion.

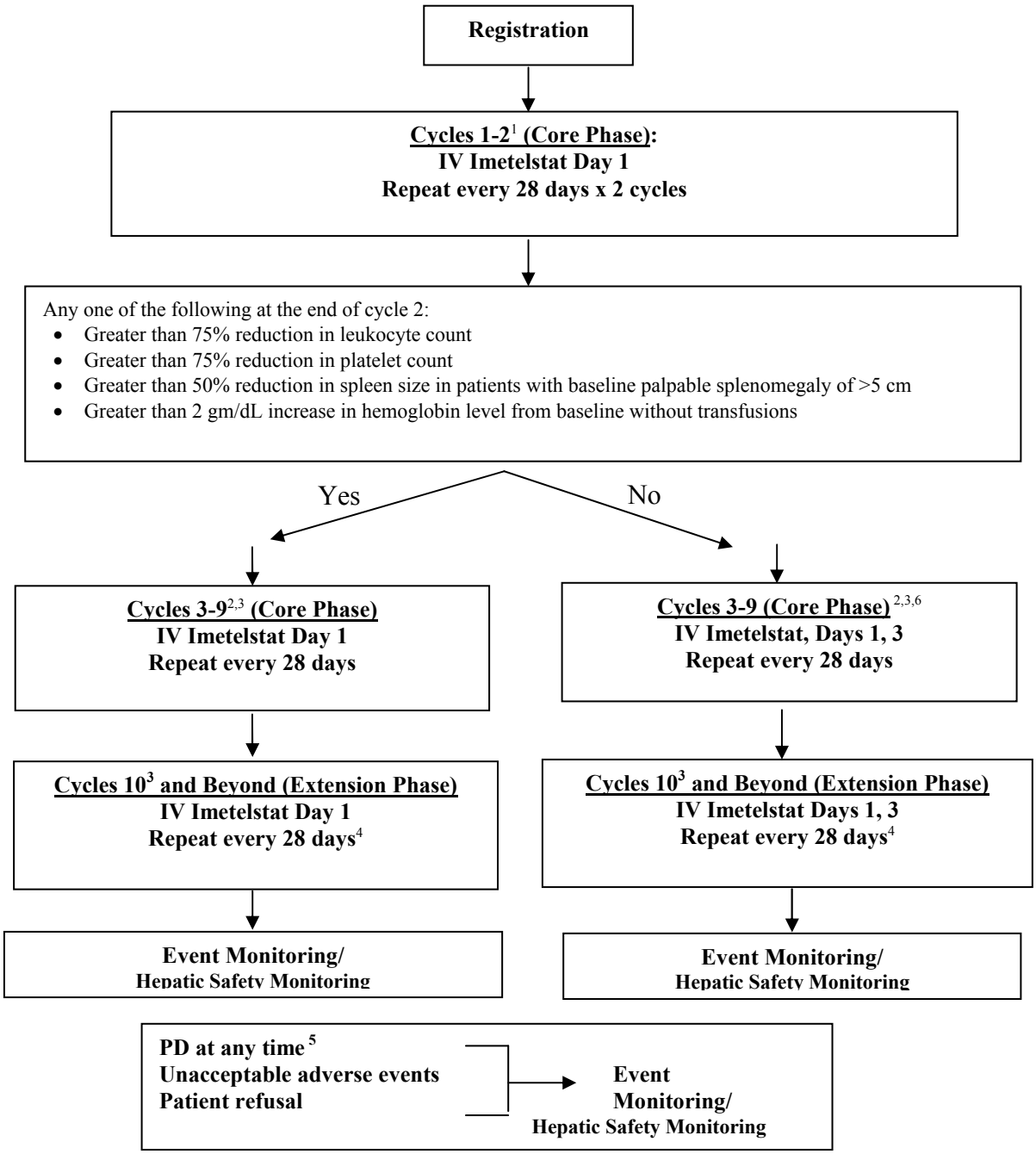
[3] For patients whose response has plateaued, without signs of further improvement, for a minimum of 3 months, dosing frequency may be reduced to every 2 to 3 months, or treatment may be interrupted until relapse then restarted, at the physician's discretion.

[4] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[5] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

Figure 5: Schema – Arm F

(Note: Arm F permanently closed to accrual) (myelofibrosis patients without spliceosome mutations or ring sideroblasts)



[1] Cycle length = 28 days. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥ 3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] In patients who do not achieve CR or PR, by the end of Cycle 4, the frequency of dosing may be increased to every two weeks, at the physician's discretion.

[3] For patients whose response has plateaued, without signs of further improvement, for a minimum of 3 months, dosing may be reduced to Day 1 every 28 days or Days 1 and 3 every 2 to 3 months or treatment may be interrupted until relapse then restarted, all at the physician's discretion.

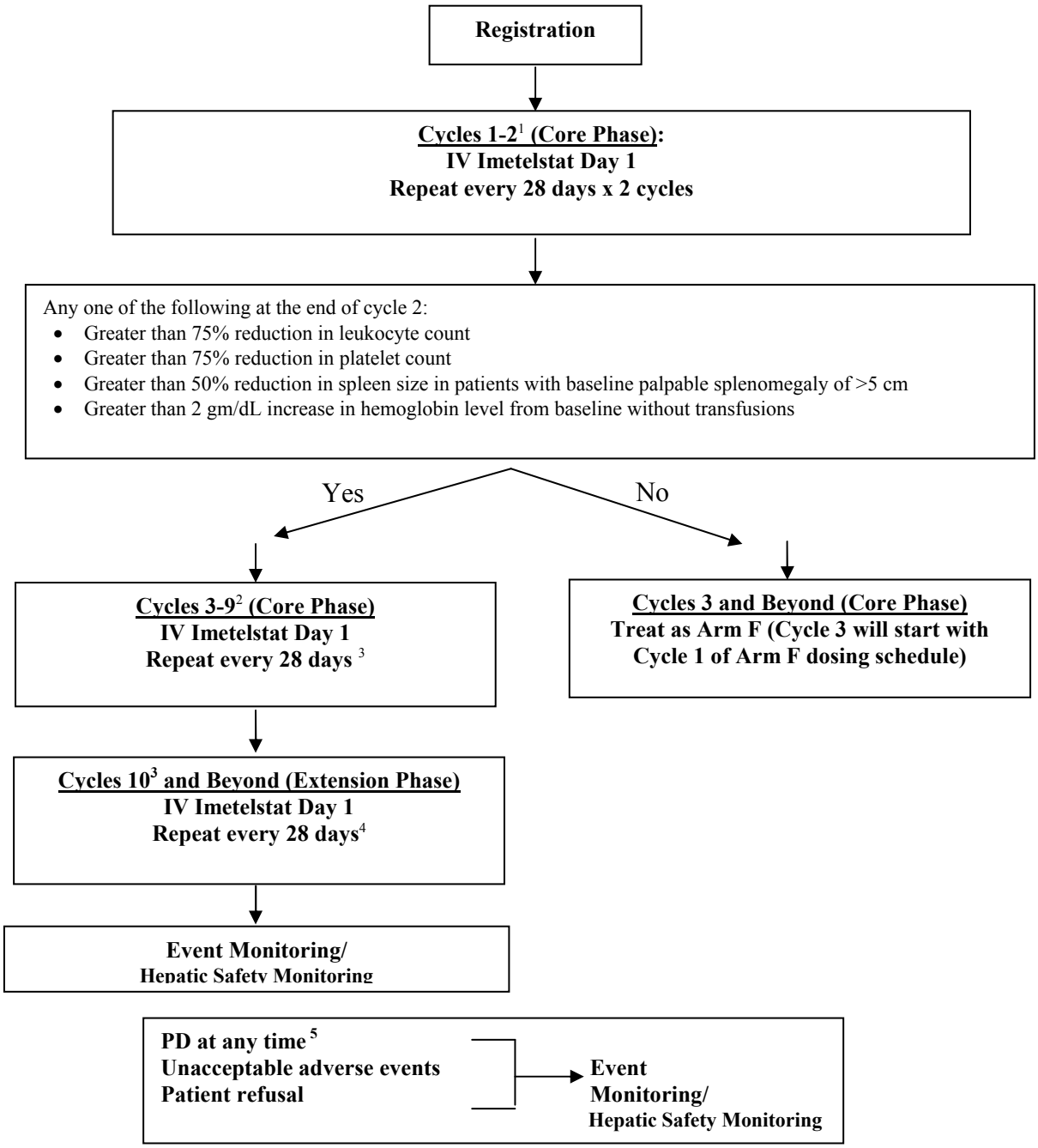
[4] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[5] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

[6] If criteria still not met after Cycles 3 and 4, at the physician's discretion, dosing might be increased to Days 1, 3, and 5 every 28 days.

Figure 6: Schema – Arm G

(Note: Arm G permanently closed to accrual) (MDS/MPN or MDS patients with spliceosome mutations or ring sideroblasts)



[1] Cycle length = 28 days. For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[2] In patients who do not achieve CR or PR, by the end of Cycle 4, the frequency of dosing may be increased to every week or every 2 weeks, at the physician's discretion.

[3] For patients whose response has plateaued, without signs of further improvement, for a minimum of 3 months, dosing frequency may be reduced to every 2 to 3 months, or treatment may be interrupted until relapse, at the physician's discretion.

[4] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[5] Except relapse that occurs during dose interruption. These patients may restart treatment at the physician's discretion per Section 7.1.

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Geron Protocol Amendment 11 (prior to transfer to Janssen Research & Development)	31 Jul 2014
Amendment 12	21 Jan 2015
Amendment 13	5 Oct 2015

Amendments are listed beginning with the most recent amendment following transfer to Janssen Research & Development.

Amendment 13 (5 Oct 2015)

The overall reason for the amendment: To limit collection of follow-up study data to that critical for assessment of safety outcomes, and to allow subjects who are benefiting from imetelstat to continue to receive study treatment beyond 3 years.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify and emphasize that additional hepatic laboratory surveillance is explicitly required for subjects in safety follow-up who had ongoing treatment-emergent abnormalities in LFTs or hepatic adverse events when imetelstat was discontinued,	
Figures 1-6	Revised "Event Monitoring" to "Event Monitoring/Hepatic Safety Monitoring" in the schematic diagrams for each treatment arm.
Rationale: To remove the limitation on duration of study treatment for patients who continue to derive clinical benefit beyond 3 years.	
Figures 1-6, footnotes 7.1.1.1 Arm A Treatment Schedule (footnote 1) 7.1.1.2 Arm B Treatment Schedule (footnote 1), 7.1.1.3 Arms C and D Treatment Schedule, (footnote 1) 7.1.1.4 Arms E and G Treatment Schedule, (footnote 1) 7.1.1.5 Arm F Treatment Schedule, (footnote 1) 8.1 Retreatment Criteria	Changed the possible duration of imetelstat study treatment beyond 3 years. Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.
Rationale: The status of other imetelstat studies has changed.	
1.3.3 Clinical Experience with Imetelstat, Table 2	Database lock dates have been added for 4 Phase II imetelstat studies. The title of Study CP14B015 has been corrected to add "or Polycythemia Vera" and the study status has been changed from "Completed treatment (in safety follow up)" to "Completed".

Rationale: To limit study procedures in the Extension Phase and at study completion to those needed for safety follow-up.	
4 Test Schedule, Table 3	Physical examination for hepatomegaly and splenomegaly, and transfusion assessment removed as required assessments during the Extension Phase. Peripheral blood smear and IWG assessment of response removed as required assessments during the Extension Phase and at Study Completion/Early Termination. Urinalysis removed at Study Completion/Early termination.
4 Test Schedule, Table 3, footnote 9	Revised to delete chloride, bicarbonate, glucose, GGT, uric acid, amylase, and lipase from serum chemistry assessment.
4 Test Schedule, Table 3, footnote 10	Revised hematology assessment to replace differential count with absolute neutrophil count and to remove RBC count, MCV, MCH, MCHC, RDW, and MPV.
4 Test Schedule, Table 3, footnote 14	Clarified to allow a ±7-day window for hepatic event follow-up and redefined the end of the Event Monitoring Phase of the study from 5 years after registration for each subject to the time at which the last patient has completed study treatment. Follow-up during the Event Monitoring Phase can be completed via telephone call.
Rationale: To streamline and clarify hepatic monitoring.	
4.1 Test Schedule for Hepatic Safety Monitoring, Table 4, footnote 3	CBC has been limited to WBC count, ANC, hemoglobin, and platelet count.
4.1 Test Schedule for Hepatic Safety Monitoring, Table 4	The footnote "Concomitant medications include alternate treatment for MPN/MDS" has been deleted; remaining footnotes have been renumbered accordingly.
Rationale: To clarify requirements for study drug dose modification.	
8.2 Dose Reduction	Sentence added to the end of the first paragraph clarifying that once an imetelstat dose reduction has occurred, the dose should not be subsequently re-escalated.
Rationale: Update description of drug preparation procedures. Reconstitution time is estimated at 15 minutes based on an updated product description.	
15.1.3 Preparation and Storage	Text describing lyophilized imetelstat as reconstituting easily has been deleted.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or typographical changes were made.

Amendment 12 (21Jan 2015)

The overall reason for the amendment: The overall reason for the amendment is to transfer sponsorship of this study from Geron to Janssen Research & Development and to update safety reporting accordingly.

Applicable Section(s)	Description of Change(s)
Rationale: To update the language in the protocol to indicate the transfer of sponsorship from Geron to Janssen Research & Development and to establish the safety reporting procedures under the new sponsorship.	
10.1. Safety Parameters and Definitions; 10.3.1.9. Pregnancy; 10.6. Post-Study Adverse Events	Language changed to indicate transfer of sponsorship.
10.4.1. Reporting Requirements for Fatal/Life Threatening SAEs Related to Investigational Product	Deleted the former medical monitor contact information and replaced with the following: 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.
10.4.2. Reporting Requirements for All SAEs	Deleted the former procedures for reporting SAEs and replaced with the new procedures.
16.7. Data and Safety Monitoring	Updated the membership of the safety review committee and updated the following text (bold text indicates additions; strikeout indicates deletions): The ~~Medical Monitor~~ **study responsible physician** or ~~Drug Safety Scientist~~ **safety physician** may convene a meeting sooner should any concerns arise from review of data or from the Investigator safety physician. Added text to indicate that an independent hepatic safety panel will review emergent relevant safety data if needed.
Rationale: To align the current protocol with the administrative amendment memorandum that was issued by Geron on 12 Sep 2014.	
4. Test Schedule, Table 3, footnote 6	Removed the check mark in the table for an abdominal ultrasound at study completion or early termination (± 1 week); Revised the footnote to indicate that a Doppler ultrasound of abdomen will be performed post baseline only as clinically indicated at the discretion of the investigator.
4. Test Schedule, Table 3, footnote 9; 4.1. Test Schedule for hepatic safety monitoring and follow up after discontinuing imetelstat, Table 4, footnote 3	Revised the text to state that serum haptoglobin and reticulocyte count should be performed only if clinically indicated.
Rationale: Included information regarding the lift of the clinical hold by the U.S. FDA.	
1.3.4.4. Hepatobiliary Events	Added: Following a complete response submitted by Geron, the clinical hold was lifted by the U.S. FDA on 31 October 2014.
Rationale: To update information regarding Phase II trials with imetelstat.	

1.3.3. Clinical Experience with Imetelstat, Table 2	The study status of protocol number CP14B013 was marked as completed.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

1. BACKGROUND

1.1. Myelofibrosis

The term myelofibrosis (MF) includes both primary myelofibrosis (PMF) and post-polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF) (Tefferi 2011). MF is currently classified as a chronic myeloproliferative neoplasm (MPN) and is characterized by clonal proliferation of pluripotent hematopoietic stem cells and abnormal cytokine expression (Tefferi 2011). Patients with MF typically present with anemia, marked splenomegaly and profound constitutional symptoms (night sweats, pruritus, early satiety, bone pain, cough, fever, etc.). In addition, some patients might display thrombocytopenia, leucopenia, thrombocytosis, leukocytosis, and non-hepatosplenic extramedullary hematopoiesis (EMH) (Tefferi 2011). Current drug therapy for MF, such as erythropoiesis stimulating agents (ESAs), hydroxyurea and JAK inhibitors have not been shown to influence survival and are often used for palliative purposes only (Tefferi 2011). Allogeneic stem cell transplantation (ASCT), which is so far the only curative option, carries a high treatment-related mortality and morbidity (Tefferi 2011).

The International Prognostic Scoring System (IPSS), used for risk stratification in PMF, uses risk factors assessed at time of diagnosis: age >65 years, constitutional symptoms, hemoglobin < 10 gm/dL, leukocyte count >25 x 10^9/L and peripheral blood blasts ≥1% (Tefferi 2011). Subsequently, the IPSS prognostic variables were used to devise a dynamic IPSS (DIPSS) that can be utilized at any point during the disease (Tefferi 2011). Most recently, DIPSS was further revised to DIPSS-plus by the incorporation of 3 additional IPSS/DIPSS-independent risk factors, including red cell transfusion need, platelet count <100 × 10^9/L, and unfavorable karyotype (Tefferi 2011); the latter includes complex karyotype or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement. The 8 DIPSS-plus risk factors are currently used to define low (no risk factors), intermediate- 1 (1 risk factor), intermediate-2 (2 or 3 risk factors), and high (≥4 risk factors) risk groups with respective median survivals of 15.4, 6.5, 2.9, and 1.3 years (Tefferi 2011). Patients with MF can progress into blast phase disease (BP-MF), defined by the same criteria used by WHO for acute myeloid leukemia (AML) (i.e. 20% or more blasts in the peripheral blood or bone marrow). Some patients with MPN share certain morphologic features with those with myelodysplastic syndromes (MDS). The WHO classifies such cases as MDS/MPN overlap and their clinical features are similar to patients with MF (i.e. severe anemia, splenomegaly, leukocytosis and thrombocytosis).

1.2. Telomeres and Telomerase Inhibition

Telomeres consist of tandem repeats of the DNA sequence TTAGGG, forming a T-loop structure to cap the ends of all mammalian chromosomes. Capping prevents chromosomal fusion and prevents their ends from being misinterpreted as DNA double-strand breaks (McEachern 2000). Telomeres shorten approximately 50–120 nucleotides (nt) at each cell division (Harley 2002; Harley 1997). When telomeres get critically short, they can no longer cap the telomere ends, thus destabilizing the T-loop and exposing a 3' overhang which triggers a DNA damage signal, ultimately resulting in senescence, terminal differentiation, or apoptosis. Telomere loss is prevented by the presence of the enzyme telomerase, which consists of two essential

components: the human telomerase RNA template (hTR) and the human telomerase reverse transcriptase (hTERT) catalytic subunit. Telomerase counters telomere loss by the addition of TTAGGG repeats to the chromosome ends (Harley 1997).

Normal somatic cells have relatively long telomeres (~9–12 kilobases) (Rufer 1999) and typically do not express detectable levels of telomerase. In contrast, telomerase activity has been detected in 80–90% of cancers tested to date, and is key to cell immortalization through maintenance of telomere length (TL) (Shay 1997). Most tumors have shorter telomeres, compared to their normal tissue counterparts, in spite of telomerase activation. These two characteristics make telomerase a promising therapeutic target for cancer.

1.3. Imetelstat

Imetelstat (GRN163L) is a covalently-lipidated 13-mer thiophosphoramidate oligonucleotide that acts as a potent specific inhibitor of telomerase. Telomerase inhibition leads to the loss of a cancer cell's ability to maintain TL, resulting in cell-cycle arrest, apoptosis, or senescence. The mechanism of action of imetelstat is not an antisense-based approach. Imetelstat does not cause down regulation of mRNA encoding either the hTR or hTERT subunits of telomerase, nor does it affect RNAse H activity, which typically causes degradation of mRNA when it is targeted by an antisense phosphoramidate oligonucleotide. Imetelstat binds with high affinity to hTR and is a competitive inhibitor of telomerase enzymatic activity (Asai 2003; Herbert 2005). Studies have shown that 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 (Stewart 2010) (Harley 2008).

1.3.1. Nonclinical Pharmacology

1.3.1.1. Efficacy Studies

Data from nonclinical efficacy studies have shown that imetelstat inhibits telomerase in tumor cells and compromises cancer cell viability in vitro. Imetelstat has broad tumor growth inhibition activity in multiple xenograft models, including non-small cell lung, breast, colorectal, pancreatic, glioblastoma multiforme (GBM), myeloma, neuroblastoma, hepatic and ovarian cancers.

1.3.1.2. Effects on Cancer Stem Cells

Numerous studies have identified a relatively rare subpopulation of tumor-initiating cells (TICs), also termed cancer stem cells (CSCs), in multiple cancer types. CSCs are distinct from the bulk tumor cell population, yet share the properties of increased telomerase activity (TA) and short telomeres, making CSCs of multiple tumor types promising targets for telomerase inhibition. In vitro studies have demonstrated that imetelstat inhibits telomerase, and is effective in targeting CSCs from myeloma, melanoma, breast, pancreatic, pediatric glioma, neuroblastoma, prostatic, lung and glioblastoma multiforme tumor types (Joseph et al. 2010b; Marian et al. 2010a). Treatment of CSCs with imetelstat results in increased apoptosis, induction of senescence, and inhibition of proliferation, sphere formation, and clonogenicity. In vivo studies demonstrated that imetelstat is able to significantly inhibit CSC-mediated tumor engraftment and growth in

breast, pancreatic, glioblastoma, neuroblastoma, and myeloma xenograft models (Joseph et al. 2010a; Hochreiter 2006; Shammas 2008; Dikmen 2009; Castelo-Branco 2011; Marian 2010b).

1.3.2. Nonclinical Safety Studies

Imetelstat was evaluated in a broad range of toxicology studies to support its use as a systemically-delivered anticancer agent in humans. The general toxicology of imetelstat was assessed in rodents and non-human primates. Imetelstat nonclinical safety studies were carried out in mice, rats, rabbits, and cynomolgus monkeys. Support for the proposed clinical dose and schedule is based primarily on the repeat-dose studies in mice (dosed twice weekly for 26 weeks) and cynomolgus monkeys (dosed once weekly for 9 months).

Toxicities generally fit into two main categories: (1) those related to plasma concentrations of imetelstat, reflecting interactions with blood components, and (2) those reflecting tissue deposition and associated inflammatory effects, as were evident from histopathology evaluations.

Toxicities observed with imetelstat treatment included cytopenias, complement activation, and coagulation abnormalities. Complement activation and coagulation abnormalities were related to plasma concentrations of imetelstat. The etiology of the cytopenias is not clear; a direct effect on hematopoietic progenitor cells cannot be excluded.

Early intravenous (IV) bolus range-finding studies helped define the high-dose toxicity profile and repeat-dose studies characterized the full range of potential target organs for imetelstat-related adverse effects. At high doses in rodents (i.e., ≥30 mg/kg IV bolus), effects on hematology and coagulation parameters were observed, including elevated activated partial thromboplastin time (aPTT), hemorrhage, and decreased platelet and red blood cell pools. The occurrence of peripheral cytopenias, most notably thrombocytopenia, was sometimes accompanied by decreases in red blood cell (RBC) parameters and mild anemia. In non-human primates, hematological effects (decreases in RBC parameters and platelets at doses ≥15 mg/kg) were present but to a lesser extent than those seen in rodents. In ex vivo colony-forming assays using human bone marrow progenitors, imetelstat did not significantly inhibit erythroid or myeloid colony number (although colony morphology was compromised at 15 μM), but megakaryocyte colony growth was inhibited at ≥3.75 μM (50% inhibitory concentration [IC_{50}] ~5 μM).

Inhibition of coagulation (aPTT prolongation) and activation of complement pathways (increased plasma levels of Bb and C5a split products and decreased total hemolytic complement [CH_{50}]) were noted. These effects were reversible and similar to acute blood level-related toxicities seen with other polyanionic oligonucleotides. There was no clinical evidence of clotting abnormalities in monkeys at relatively high doses that produced over 3-fold increases in aPTT.

Severe complement-mediated adverse reactions were noted in some of the monkey dose-finding studies; however chronic complement activation at doses ≤ 15 mg/kg did not result in any adverse constitutional outcomes. Similar to other oligonucleotides in this class, imetelstat-mediated activation of the alternative complement pathway is believed to stem from binding to an inhibitory complement protein (Factor H), which, if sufficiently depleted, initiates an activation cascade with the formation of biologically active split products culminating in

hemodynamic changes (mainly hypotension). In monkeys, this may result in significant cardiovascular toxicity. In the case of imetelstat, the threshold blood level for complement activation is approximately 200 μg/mL. Toxicokinetic analyses confirmed that these acute effects are reversible after 24 hours and can be managed by adjusting the dose and duration of infusion of imetelstat.

Administration of imetelstat intravenously to monkeys at doses of up to 15 mg/kg over 2 hours once weekly for 9 months was well tolerated. Data from studies in rats suggested that imetelstat was taken up by many tissues, primarily liver, kidneys and, to a lesser extent, the spleen and bone marrow; these are the target organs for histopathologic alterations. Microscopic examination of tissues revealed mild to moderate changes in the kidney (mesangial thickening, glomerulonephritis/sclerosis, deposition in interstitium, renal tubular hemorrhage, protein casts, and regeneration), liver (telangiectasis and deposition in Kupffer cells), uterus (atrophy of the endometrium), choroid plexus (minimal lymphoid follicle formation and mononuclear cellular infiltration), and general systemic arteritis including at the injection site at doses starting at 5 mg/kg. The observations in the kidney did not show signs of reversibility in the recovery group animals; however, it is not unusual for such inflammatory lesions to persist for several months in monkeys. The endometrial atrophy was only noted after 9 months of chronic dosing at 15 mg/kg and was absent in the recovery animals. The remaining morphological changes in the liver and the inflammatory vasculitis (choroids plexus and systemic arteritis) showed signs of resolution in the recovery group animals.

Most of these histological findings are thought to be due to pro-inflammatory activity common to many oligonucleotides and derived from a programmed physiological reaction of the body to their foreign nucleic acid structure and are heightened when the molecule is chemically modified to inhibit degradation by endogenous nucleases. In general, the changes observed in the groups that received imetelstat at doses up to 15 mg/kg were of limited severity and were not associated with any tissue degeneration or other alterations that would suggest compromised organ function. Most changes showed evidence of recovery after a 14-week drug-free period.

Imetelstat was not teratogenic in mice or rabbits following bolus or 2-hour continuous intravenous (IV) infusion of 30 mg/kg. In rabbits, embryo-lethality was noted as increased post-implantation loss at 30 mg/kg due to an increase in early resorptions, resulting in higher incidence of litter loss at this dose level that correlated to a decrease in litter size and viable fetuses.

Additional findings from nonclinical studies that may predict the safety of the clinical dose include: (1) absence of effects on cardiovascular (human ether-à-go-go related gene [hERG] inhibition, electrocardiogram [ECG]), respiratory, and neurological function, and (2) absence of genetic toxicity in tests for mutagenicity and clastogenicity.

Please refer to the Imetelstat Investigator's Brochure (IB) for further details.

1.3.3. Clinical Experience with Imetelstat

Table 1 and Table 2 summarize all clinical trials with imetelstat initiated by Geron to date.

A total of 491 patients have been enrolled in Geron Phase I and II imetelstat clinical trials of which 374 received imetelstat either as a single agent or as combination therapy.

Six Phase I studies have been initiated since 2005, of which three were single-agent studies and three were combination studies. The study designs and status are summarized below and presented in Table 1. A total of 183 patients were treated with imetelstat in Phase I; enrollment and study treatment has been completed and the databases locked for all six studies.

In Phase II clinical trials, imetelstat was investigated as a single agent in CP14B015 (ET/PV), as single-agent or combination therapy in CP14B013 (multiple myeloma [± lenalidomide]) and CP14B012 (NSCLC [± bevacizumab]), and as combination therapy in CP14B014 (MBC [paclitaxel ± bevacizumab]). As of 21 May 2013, a total of 191 patients were treated with imetelstat in Phase II (Table 2).

Table 1: Phase I Clinical Trials with Imetelstat

Protocol Number	Protocol Title	Patients Enrolled	Patients Treated (Data Cut-off Date)	Dose and Schedule of Imetelstat	Key Study Endpoints	Study Status
Single Agent Trials						
CP14A004	A Phase I Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, and Maximum Tolerated Dose of Weekly Administration of GRN163L in Patients with Refractory or Relapsed Multiple Myeloma	20	20 (Locked 15Nov2010)	3.2, 4.8, 6.0, 7.2 mg/kg over 2 hours weekly; 6.0 mg/kg on Days 1, 8 every 21 days.	Primary: Safety, tolerability, MTD Secondary: PK, anti-tumor activity, pharmacodynamics	Completed
CP04-151	A Phase I/II, Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, and Maximum Tolerated Dose of Weekly Administration of GRN163L in Patients with Refractory or Relapsed Chronic Lymphoproliferative Disease	28	28 (Locked 15Feb2011)	20, 40, 80, 160, and 240 mg/m^2 over 6 hours weekly; 160 and 200 mg/m^2 over 2 hours weekly; 200 mg/m^2 over 2 hours on Days 1 and 8	Primary: Safety, tolerability, MTD Secondary: PK, anti-tumor activity, pharmacodynamics	Completed
CP05-101	A Phase I, Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, Maximum Tolerated Dose, and Optimal Infusion Duration of Weekly Administration of GRN163L in Patients with Refractory or Relapsed Solid Tumor Malignancies	75	75 (Locked 21Mar2011)	0.4, 0.8, 1.6, 3.2, 4.8 mg/kg over 2 hours weekly; 4.8, 6.0, 7.5, 9.4, 11.7 mg/kg on Days 1, 8 every 21 days; 9.4, 11.7 mg/kg once every 28 days	Primary: Safety, tolerability, MTD Secondary: PK, anti-tumor activity, pharmacodynamics	Completed
Combination Trials						
CP14A005	A Phase I Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, and Maximum Tolerated Dose of Weekly Administration of GRN163L in Combination with Paclitaxel and Carboplatin in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer	27	27 (Locked 15Oct2010)	3.2 mg/kg over 2 hours weekly; 3.2 mg/kg over 2 hours once every 21 days; 3.2, 4.8, 6.0 and 7.5 mg/kg on Days 1, 8 every 21 days.	Primary: Safety, tolerability, MTD Secondary: PK, anti-tumor activity	Completed
CP14A011	A Phase I Study of GRN163L in Combination with Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma	9	9 (Locked 15Dec2010)	160, 200 mg/m^2 over 2 hours Days 1, 8 every 21 days	Primary: Safety, tolerability Secondary: PK, anti-tumor activity	Completed
CP14A010	A Phase I/II Study of GRN163L in Combination with Paclitaxel and Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer	24	24 (Locked 28Mar12)	160, 240, 300, 375 mg/m^2 Days 1, 8, 15 every 28 days; 300 and 375 mg/m^2 Days 1, 15 every 28 days; 300 mg/m^2 Day 8 every 28 days.	Primary: Safety, tolerability Secondary: PK, anti-tumor activity	Completed

Table 2: Phase II Trials with Imetelstat

Protocol Number	Protocol Title	Patients Enrolled	Patients Treated	Dose and Schedule of Imetelstat	Key Study Endpoints	Study Status
Randomized Trials						
CP14B012	A Randomized Phase II Study of Imetelstat as Maintenance Therapy after Initial Induction Chemotherapy for Advanced Non-Small Cell Lung Cancer (NSCLC)	116	114 (Locked 19Sep2013	9.4 mg/kg over 2 hours on Days 1,8 every 21 days	Primary: PFS Secondary: Safety, tolerability, ORR	Completed
CP14B014	A Randomized Phase II Study of Imetelstat (GRN163L) in Combination with Paclitaxel (With or Without Bevacizumab) in Patients with Locally Advanced or Metastatic Breast Cancer	166	161 (Locked 10Dec2012)	300 mg/m^2 on Day 1 every 21 days	Primary: PFS Secondary: Safety, ORR, clinical benefit rate	Completed (early termination)
Single-Arm Trials						
CP14B013	A Phase II Trial to Determine the Effect of Imetelstat (GRN163L) on Patients with Previously Treated Multiple Myeloma	13	13 (Locked 20Nov2014)	9.4 mg/kg over 2 hours on Days 1,8 every 28 days	Primary: Improvement in response Secondary: Safety, tolerability, PFS, circulating myeloma CSCs	Completed
CP14B015	A Phase II Trial to Evaluate the Activity of Imetelstat (GRN163L) in Patients with Essential Thrombocythemia or Polycythemia Vera who Require Cytoreduction and Have Failed or Are Intolerant to Previous Therapy, or who Refuse Standard Therapy	20	20 (Locked 06Apr2015)	7.5 -11.7 mg/kg over 2 hours weekly or as needed based on hematologic response	Primary: Hematologic response (ET), Hematocrit (PV) Secondary: Safety, tolerability, duration of hematologic, response, molecular response, histologic response at 2 years, on study, phlebotomy rate (PV)	Completed

1.3.4. Safety Experience

The overall summary of clinical safety for imetelstat is primarily based on the 374 imetelstat treated patients in all 10 Geron sponsored Phase I and II trials to date. Where relevant, additional clinical safety information (e.g., from investigator-sponsored trials) is incorporated. For additional details, refer to the IB. A summary of clinical safety is provided below.

1.3.4.1. Hematologic Events

Cytopenias, in particular thrombocytopenia, were dose-limiting in both single-agent imetelstat trials and when combined with other chemotherapies. The frequency and severity of all cytopenias, particularly thrombocytopenia and neutropenia, were 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.

Grade 2-4 thrombocytopenia typically occurred after 1 to 4 weeks of dosing, with higher dose intensity associated with the earlier onset. The occurrence of the first episode of Grade 3-4 thrombocytopenia was observed as late as Cycle 7 with single-agent imetelstat. Recovery to Grade ≤ 1 usually occurred within 1–2 weeks.

Grades 3 and 4 neutropenia typically occurred after 2 to 3 weeks of dosing, with the first observed episode occurring as late as Cycle 29 in single-agent trials. Resolution to Grade ≤ 1 typically occurred within 1–2 weeks.

The etiology of cytopenias is currently unclear, and may possibly be due to the direct inhibition of telomerase in hematopoietic progenitor cells or the non-specific toxicity related to the molecular class of the compound.

During the course of the current myelofibrosis trial CP14B019 (formerly MC1285) more persistent and profound myelosuppression, particularly thrombocytopenia, was observed. In the cohort (B) treated with an initial intensive weekly regimen for four doses, two patients developed profound prolonged cytopenias following the last dose in the weekly dosing period. One patient recovered after holding the dose and was retreated at a lower dose and schedule 16 weeks after her last imetelstat dose. The second patient experienced associated clinical outcomes of febrile neutropenia and a fatal intracranial hemorrhage (ICH) in the setting of Grade 4 thrombocytopenia. These data suggests that some patients with myelofibrosis may be more susceptible to the myelosuppressive effects of imetelstat.

Bleeding events have been associated with thrombocytopenia in Geron sponsored trials; these may be serious and severe enough to be potentially life threatening. The most frequently observed event was epistaxis. There have been two fatal bleeding events of Intracranial hemorrhage (ICH) in the setting of Grade 4 thrombocytopenia reported. The first was the subject enrolled in CP14B019 (formerly MC1285), as noted above, who experienced a fatal ICH following profound Grade 4 thrombocytopenia for approximately 4 weeks. The second fatal ICH was in a [redacted] IST involving a [redacted] year-old [redacted] with medulloblastoma of the posterior fossa.

This event occurred in the setting of Grade 4 thrombocytopenia approximately 3 weeks after the first cycle of imetelstat.

Febrile neutropenia has been observed at a low incidence, particularly in combination with taxanes. Since Grade 3 and 4 neutropenia with imetelstat treatment is observed quite frequently, patients should be closely monitored for infections and appropriate management instituted per institutional standards to mitigate and manage potentially life threatening infections.

1.3.4.2. Coagulation Changes

In the Phase I imetelstat trials in which serial aPTT was measured following infusion, transient aPTT prolongations were observed in all patients which, at doses ≥ 3.2 mg/kg and 160 mg/m^2, were as high as Grade 3. Resolution to Grade 1 or normal limits was within 24 hours. Nonclinical studies suggest that aPTT prolongation is correlated with plasma concentrations of imetelstat. PT prolongations occurred infrequently and the majority was Grade 1. In the Phase II trials, aPTT and PT were not routinely measured. No bleeding events associated with coagulation abnormalities were reported in these trials.

1.3.4.3. Infections

Infections are frequently reported across all imetelstat trials, with an overall incidence of 43.0%. The most frequently reported events are urinary tract infection and upper respiratory tract infections.

Most patients had normal neutrophil counts proximal to the infection episodes.

Febrile neutropenia is infrequent and significant infections attributed to imetelstat associated with Grade ≥ 3 neutropenia have not been reported.

1.3.4.4. Hepatobiliary Events

Abnormalities in serum aminotransferases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) or alkaline phosphatase (ALP) with, in some cases, accompanying bilirubin elevations were observed in patients in the Phase II ET/PV trial (CP14B015).

Elevations in ALT and AST appear to be early, self-limiting and Grade 1 in severity, although AST elevations were more persistent. Acute Grade 2 and Grade 3 elevations in ALT with accompanying elevations in AST have also been observed (4 patients/20%) at the 9.4 mg/kg weekly dose level, and these resolved to baseline with imetelstat dose holds and dose reductions.

Persistent Grade 1 elevations in ALP and AST were also observed and appear to occur with longer duration of exposure to imetelstat and may be accompanied by Grade 1 hyperbilirubinemia, although some intermittent Grade 2 elevations in bilirubin have also been reported. Bilirubin fractionations were primarily unconjugated among these patients. The clinical significance of these persistent ALP elevations and reversibility upon stoppage of imetelstat is not understood at present and remains under close monitoring.

In this trial (CP14B015) an [redacted] year old [redacted] patient, who had been receiving imetelstat for almost 3 years, developed hepatic encephalopathy and subsequently died of bleeding esophageal varices. [redacted] had experienced persistently elevated Grade 1 AST and ALP on trial. This was a highly complex case, with the subject having multiple comorbidities and concomitant medications making assessment of the role of imetelstat extremely challenging, though it cannot be definitely excluded.

The low grade liver biochemistry patterns observed in CP14B015 trial were also observed in other imetelstat trials, but with lesser frequency, which may be somewhat attributable to shorter treatment and observation time on study in advanced malignancy trials. The abnormal laboratory observations may be dose related and may be more frequent when imetelstat is administered in combination with other cytotoxic agents. The majority of findings attributable to imetelstat are biochemical abnormalities without clinical sequelae and do not appear to be clinically significant in patients with advanced malignancies. Severe hepatobiliary events, including fatal outcomes may, however, occur in these patients. Refer to IB Section 5.3.5.7 for further details.

On 11 March 2014, the United States Food and Drug Administration (U.S. FDA) issued Geron a full clinical hold citing lack of evidence of reversibility of hepatotoxicity, risk for chronic liver injury, and lack of adequate follow up in subjects who experienced hepatotoxicity. All subjects enrolled in Geron-sponsored clinical trials permanently discontinued imetelstat treatment and enrollment of new subjects to clinical trials was not allowed. Continued safety surveillance was implemented as part of an extended hepatic safety follow-up period of all subjects in ongoing Geron-sponsored trials who had liver biochemistry abnormalities and/or hepatic adverse events that first appeared during imetelstat treatment, or worsened from baseline during treatment, and were continuing at the time subjects' discontinued imetelstat treatment. Reversibility of these abnormalities and/or hepatic adverse events back to normal or baseline levels after discontinuing imetelstat were assessed. Data were collected from subjects who discontinued imetelstat treatment as a result of the clinical hold, as well as those who discontinued for any reason and met safety follow-up criteria prior to the clinical hold. Following a complete response submitted by Geron, the clinical hold was lifted by the U.S. FDA on 31 October 2014.

On 12 March 2014, the then sponsor-investigator for Study MC1285 was issued a partial clinical hold by the FDA. The safety issues cited by the FDA for the partial clinical hold included a safety signal of hepatotoxicity identified in clinical trials of imetelstat and whether this hepatotoxicity was reversible. Previously enrolled subjects who were deriving clinical benefit according to the principal investigator were allowed to continue treatment with imetelstat but no new subjects may be registered. Following a complete response submitted by the sponsor-investigator to the FDA, this partial clinical hold was lifted by the FDA on 11 June 2014.

Emergent hepatobiliary data continues to be monitored on an ongoing basis and third party hepatology experts will be consulted as necessary to continue to refine the understanding of this signal as data emerge.

1.3.4.5. Infusion Reactions

Oligonucleotides have been previously reported to cause complement activation and related infusion reactions with the potential to cause non-complement-related hypersensitivity reactions. In the Phase II trials where all patients had routine prophylaxis, 19.4% of imetelstat-treated patients had an infusion reaction. The events are sporadic and a patient may not necessarily experience a subsequent event with successive infusions. Infusion reactions are generally mild to moderate in severity but symptoms and signs may occasionally be Grade 3 or 4 (incidence 3%) in severity. Reactions may be more frequent or severe with imetelstat dose levels exceeding 9.4 mg/kg. Reactions may be ameliorated, but are not always prevented, by required premedication with corticosteroids, diphenhydramine, and/or acetaminophen.

1.3.4.6. Gastrointestinal Events

Gastrointestinal events of all grades are some of the most frequently reported events reported with imetelstat-treatment.

Nausea is the most frequent event. Diarrhea, vomiting, abdominal pain, and constipation were also frequently reported. These events resolve between infusions, usually within 7 days. The majority of these events are Grade 2 or less in severity, but severe episodes of diarrhea, vomiting and abdominal pain necessitating hospitalization for adequate management may occur.

Stomatitis and mucositis, Grade 2 or less in severity, have also been observed with both single-agent imetelstat and in combination regimens. Grade 3 events have been observed in 2 patients receiving imetelstat in combination with taxane chemotherapy, which may be the main contributor to the event. The majority of the episodes reportedly resolve, including all Grade 3 events.

1.3.4.7. Constitutional Symptoms

Constitutional symptoms within a few days of imetelstat infusion, including headache, nausea, vomiting, diarrhea, fatigue, myalgia, arthralgias, fever, flu-like illness, and chills are frequently observed with imetelstat treatment, consistent with what has been reported with other oligonucleotides. These symptoms are also common in oncology patients. The events are usually self-limiting, are mostly Grade 1 to 2 in intensity and resolve within 7 days or less.

The most frequently reported Grade 3 event was fatigue. Other Grade 3 events were diarrhea, musculoskeletal pain, and nausea, all observed in less than 2% of these patients. No Grade 4 events were observed.

Supportive treatment was usually with non-steroidal anti-inflammatory drugs, opiate analgesics, and antiemetics. Corticosteroid use was not frequent, other than as prophylaxis for infusion reactions per protocol, in which case dexamethasone was primarily used.

1.4. Rationale for Conducting this Study

PMF, post-PV/ET MF, BP-MF and MDS/MPN are diseases associated with high morbidity and mortality and in whom currently available medications, including the recently developed JAK inhibitors, carry minimal impact on the natural history of the disease including overall and leukemia-free survival. The currently available drugs have so far failed to favorably affect bone marrow pathology, cytogenetic abnormalities, JAK2V617F allele burden and have had limited effect in alleviating anemia or controlling leukocytosis or thrombocytosis. JAK inhibitors have been shown to provide benefit in reducing spleen size and alleviating symptoms but do not appear to offer any additional value. Furthermore, these medications are often associated with side effects, including anemia and thrombocytopenia.

The key obstacle to the value of JAK inhibitor therapy in MF is the fact that the disease is not necessarily defined by a JAK-STAT-relevant mutation and that its molecular pathogenesis includes many other mutations and aberrant pathways. Imetelstat may be particularly beneficial in this regard since it targets abnormal proliferation regardless of its molecular underpinnings. In addition, the drug has the following properties that are relevant to patients with MF and MDS/MPN:

- Ability to target CSCs and TICs
- Inhibition of colony-forming unit-megakaryocytes (CFU-Mk) in vitro.
- Ability to target diseases with short TL, such as myeloproliferative neoplasms
- Ability to inhibit telomerase, which is highly active in leukocytes of patients with myeloproliferative neoplasms.
- Longer imetelstat PK residence time in the bone marrow and spleen, compared to plasma

While TA is generally undetectable in normal somatic cells, it is expressed in approximately 85% of human cancers as well as in cancer progenitor cells, which are believed to play a critical role in dysregulated cell growth and tumor metastasis (Harley 2008). TA (as measured in granulocytes) is notably high in patients with myeloproliferative neoplasms (Ferraris 2005a). Additionally, TL (measured in granulocytes) in patients with myeloproliferative neoplasms is short, regardless of JAK2 mutational status; therefore, telomerase inhibition could potentially benefit both JAK2 V617F and JAK2 wild-type patients (Terasaki 2002; Ferraris 2005b; Bernard 2009).

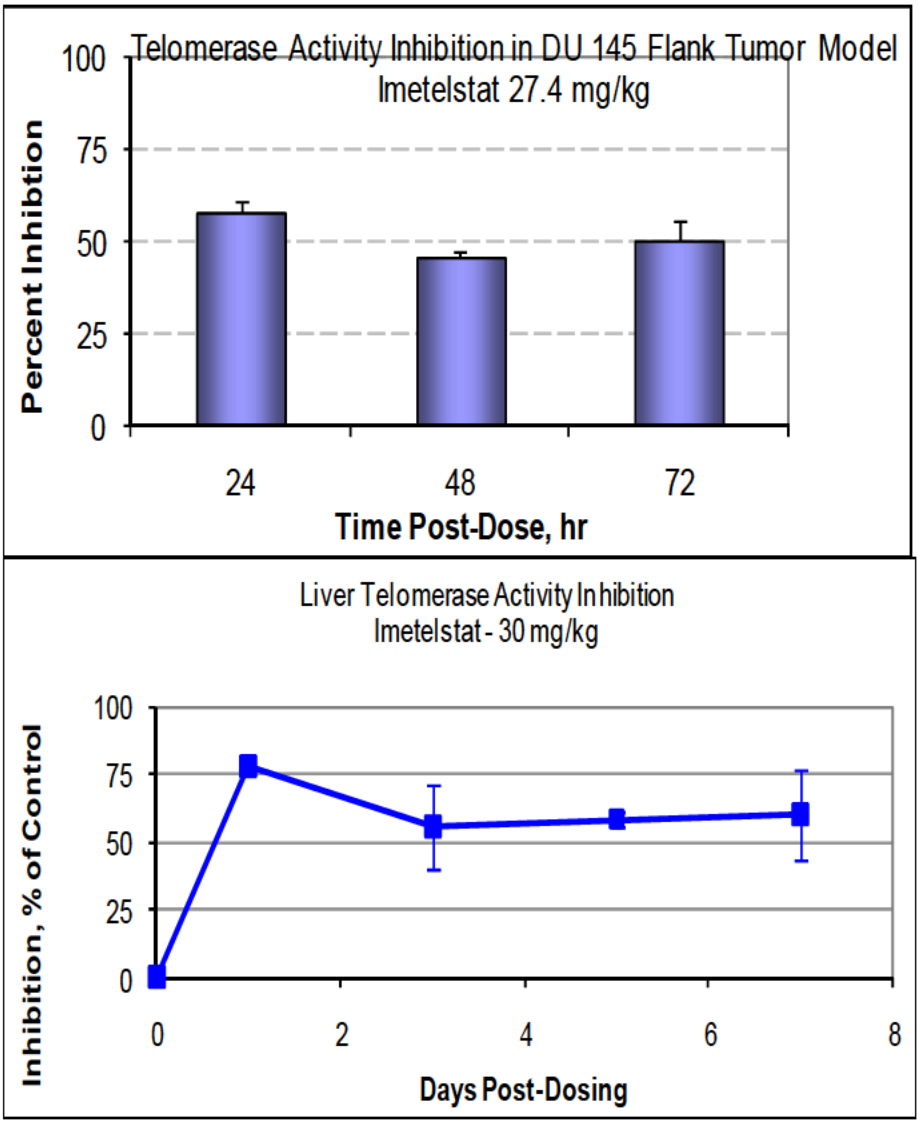
Imetelstat is a potent, specific inhibitor of telomerase. In ex-vivo studies of normal progenitor cells, imetelstat did not inhibit erythroid or myeloid colony number or proliferation (CFU-E, BFU-E, total erythroid, CFU-GM, CFU-GEMM, or total colony forming cells). Imetelstat did selectively reduce megakaryocyte colonies in culture, but only CFU-Mk large colonies, which represent megakaryocyte colonies derived from the most primitive lineage-restricted progenitor cells (data on file; see Figure 4). This suggests a sensitivity of early megakaryocyte progenitors to imetelstat compared to more mature megakaryocytes. This sensitivity appears to coincide with

the period of highest TA during progenitor cell differentiation. As patients with myeloproliferative neoplasms have high TA and shorter TL, imetelstat is expected to have an effect on early megakaryocyte progenitors and the CSC clone, which presumably also have high TA and short TL. Due to the low or transient expression of telomerase in normal tissues, including normal stem cells, and generally longer telomeres in normal cells vs. tumor cells, a degree of tumor specificity may be provided with imetelstat.

1.4.1. Rationale for Dose and Schedule

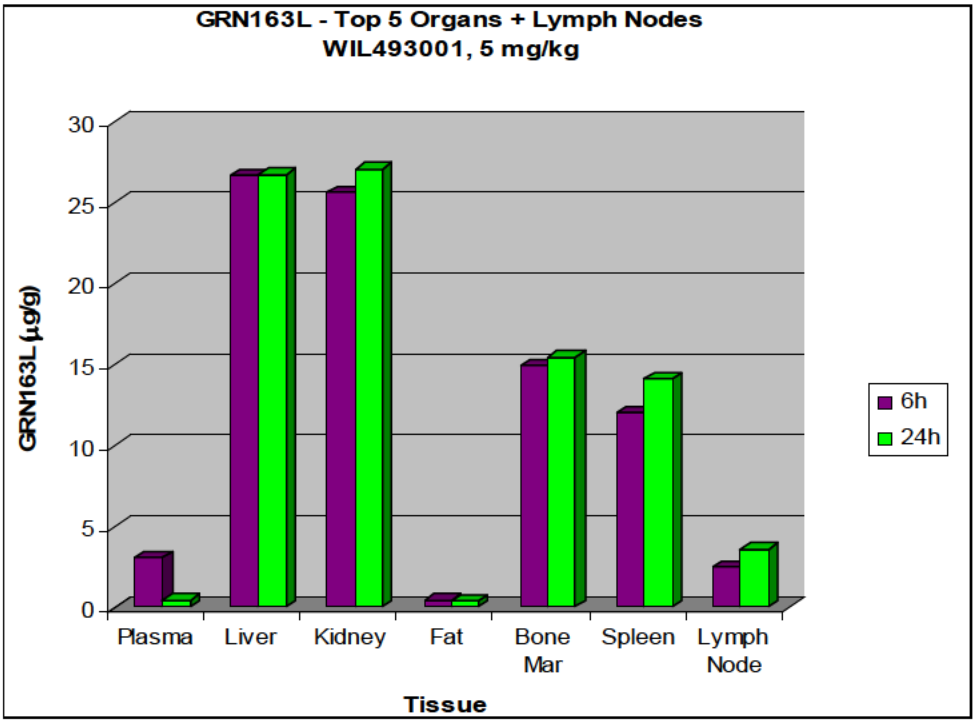
Nonclinical studies indicate that imetelstat inhibits TA for 3–7 days after a single IV administration, as shown in Figure 7 in a DU145 tumor flank model and liver telomerase inhibition model. Accordingly, the rationale to test various starting dose schedules that include weekly dosing to every three weeks dosing is to find the balance between efficacy (need drug present to inhibit telomerase) and toxicity.

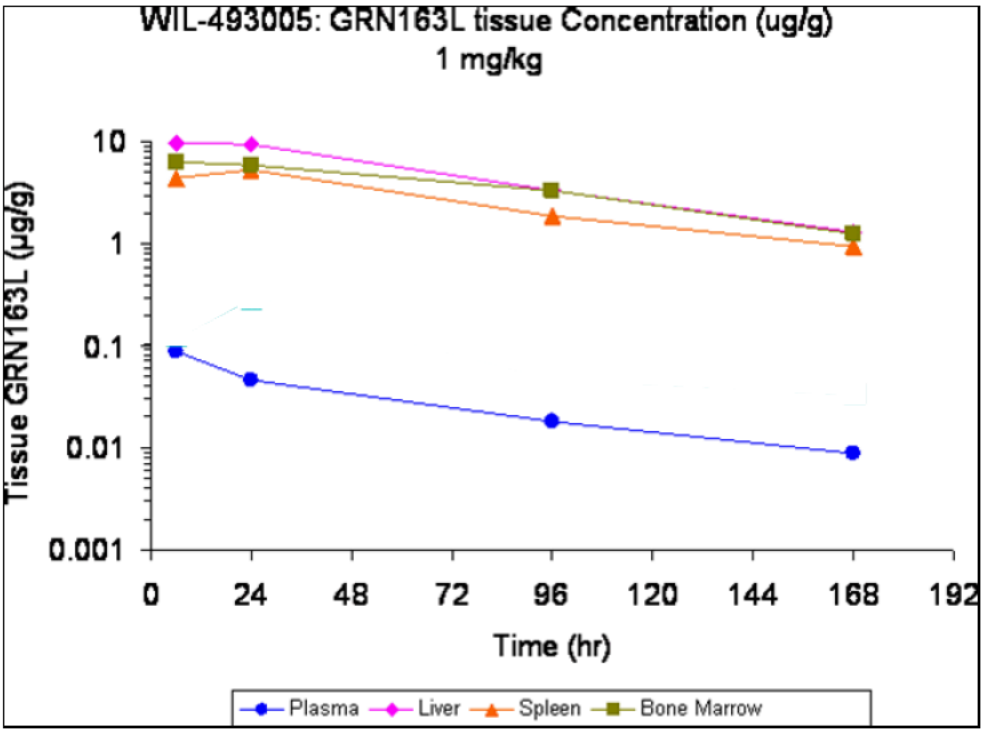
Figure 7: Inhibition of Telomerase Activity by Imetelstat in a DU145 Tumor Flank Model and Liver Telomerase Inhibition Model



Nonclinical data also indicate that imetelstat is highly distributed in the BM, spleen, liver, and kidneys (see Figure 8). Although the data suggest that weekly dosing is required to inhibit TA, it is expected that after prolonged exposure, less frequent dosing may be required for patients due to the long residence time of imetelstat in the BM.

Figure 8: Imetelstat (GRN163L) Tissue Distribution in Rats

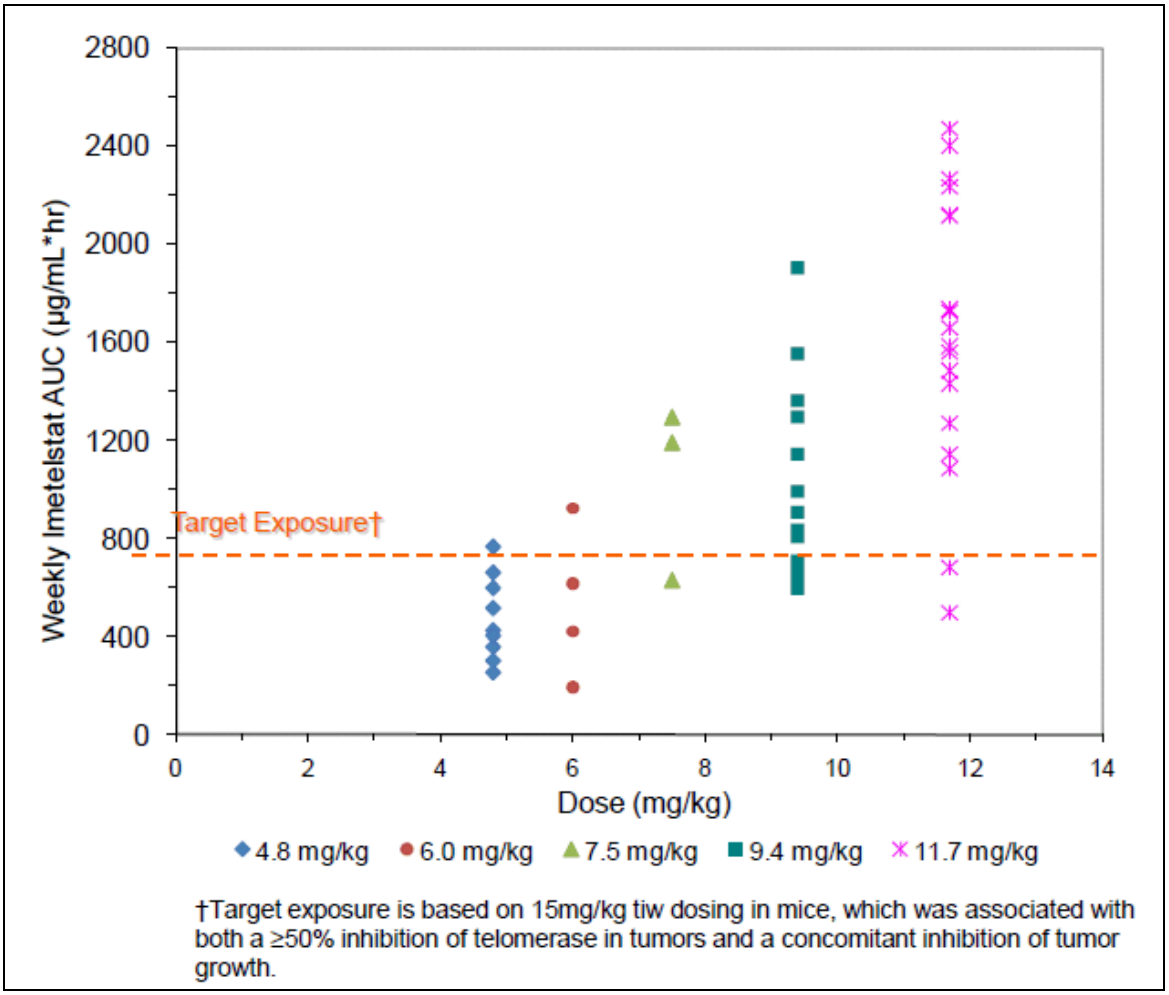




In a Phase I study of 75 patients with solid tumors, imetelstat was administered in sequential dose cohorts of 0.4–4.8 mg/kg weekly, 4.8–11.7 mg/kg on Days 1 and 8 every 21 days, and 9.4 mg/kg

and 11.7 mg/kg Day 1 every 28 days. Doses of 7.5 mg/kg and above led to exposure in patients that was above that associated with tumor growth inhibition in xenograft models (see Figure 9).

Figure 9: Imetelstat Weekly AUC_{inf} in Patients and in Xenograft Mice



In the Phase I study in patients with solid tumors, imetelstat 4.8 mg/kg weekly was the highest weekly dose studied. At this dose, in this heavily pretreated population, there was no dramatic reduction in platelet counts in patients whose baseline platelet counts were > 250 x 10^3/µL. In the higher dose cohorts (7.5, 9.4, and 11.7 mg/kg) in which imetelstat was given on Days 1 and 8 of 21-day cycles, there was a greater reduction in platelet count compared to the 4.8 mg/kg weekly cohort. The greatest impact on platelets was observed in the 9.4 mg/kg and 11.7 mg/kg cohorts. A reduction in platelet counts of approximately 30% from baseline usually occurred after three to six doses in the lower dose cohorts (weekly schedule) and after two to three doses in the higher dose cohorts (Days 1 and 8 every 21 days schedule). Hematologic toxicity was generally mild to moderate in the 7.5 mg/kg dose cohort and occurred less frequently compared with the 9.4 and 11.7 mg/kg dose cohorts of heavily pretreated patients with solid tumors. Grade 4 thrombocytopenia was reported in one patient in each of the 9.4 mg/kg and 11.7 mg/kg dose cohorts and Grade 4 neutropenia was reported in 2 patients in the 9.4 mg/kg dose cohort. However, dosing on Days 1 and 8 were not held until these cytopenias occurred in Cycle 2.

There were no cases of Grade 3 or Grade 4 thrombocytopenia in the 9.4 mg/kg and 11.7 mg/kg every 28 days cohorts and one case of Grade 3 neutropenia in the 11.7 mg/kg dose cohort.

In patients with ET, weekly dosing (7.5 to 11.7 mg/kg) was well tolerated with few Grade 3 or Grade 4 hematologic or non-hematologic toxicity (Baerlocher et al. 2012); Grade 3 or 4 adverse events regardless of attribution included: Grade 4 non-febrile neutropenia 14.3%, Grade 3 neutropenia 28.6%, no Grade 3 or Grade 4 thrombocytopenia, Grade 3 anemia (probably unrelated) 7.1%, Grade 3 increase in transaminases 14.3%, Grade 3 infusion reactions 7.1%, Grade 3 infection (cellulitis) 7.1%, Grade 3 fatigue, Grade 3 bleeding events (post-operative) 7.1% and Grade 3 headaches 7.1%. Based on these data, we want to start with an every 21-day schedule, to first evaluate safety in our MF patient population and subsequently proceed with weekly dosing to maximize efficacy. The particular strategy was chosen because of the fact that patients with MF might be even more vulnerable for the myelosuppressive side effects of the drug. Accordingly, we plan to start with the first cohort of 11 patients receiving 9.4 mg/kg/every 21 days, complemented with appropriate dose reduction in case of toxicity to 7.5 mg/kg and 6 mg/kg every 21 days, if necessary.

After the first 11 patients on Arm A were enrolled and most of them followed for at least 3 cycles, it has become apparent that the every 21 days schedule was safe and no Grade 3 or Grade 4 non-hematologic toxicities were observed. The experience was the same for the second 11-patient cohort in Arm B where patients received weekly treatment x 4 followed by every 3 weeks treatment. Based on this experience in 22 patients, an Arm C cohort was recently added where patients were to receive weekly treatment until toxicity ensued. However, it recently came to our attention that a subset of patients experienced severe Grade 4 myelosuppression and these very same patients were also the ones who ultimately responded to treatment. Close scrutiny allowed us to discover that some of the imetelstat-sensitive patients displayed bone marrow ring sideroblasts, which is a morphological feature that is known to be highly associated with spliceosome mutations. We followed up with this discovery and under a separate IRB-approved laboratory protocol, we discovered that virtually all of our patients that suffered Grade 4 myelosuppression (and treatment response) were spliceosome-mutated. As such we are making the current protocol amendment that includes the following:

- Abandon Arm C and assign the 11 patients slotted to be enrolled in Arm C to either Arm A (if spliceosome-mutated) or Arm B (spliceosome unmutated)

- Consolidate Arms A, B and C (total n = 33) for the purposes of communication of results at meeting and publication of results.

- Add three additional arms (Arms E, F and G) that build on our aforementioned novel observations and allow a more accurate and safer treatment strategy that takes into account spliceosome mutational status.

These amendments are done to hopefully maximize response rate without undermining safety profile (Baerlocher et al. 2012). To that effect, we plan to include patients with BP-MF and spliceosome-mutated MDS/MPN or MDS, considering their poor prognosis and absence of effective therapy for such patients.

2. GOALS

2.1. Primary

- To evaluate overall response rate in each arm. For the purposes of this protocol, response for Arms A, B, C, E, and F will be according to IWG-MRT criteria (see Section 11). For arm G response will be according to the International Working Group response assessment as reported by Cheson et al. (2006; Section 11.2). Response for Arm D is defined by reduction in peripheral blood and bone marrow blast count to <5% and lasting for at least 2 months (see Section 16.2).

2.2. Secondary

- To evaluate the safety and tolerability of imetelstat in each arm (per NCI CTCAE, v4.0).

- To evaluate the efficacy of imetelstat in the reduction of spleen size, as measured by physical examination (palpable distance from the left costal margin) in each arm.

- To evaluate the efficacy of imetelstat in improving anemia or inducing red blood cell transfusion-independence in previously transfusion-dependent patients (per IWG-MRT criteria; see Section 11) in each arm.

- To evaluate onset and durability of response as defined in primary and secondary endpoints in each arm.

2.3. Exploratory

- To evaluate the effect of imetelstat on bone marrow histology, karyotype, and JAK2V617F allele burden in each arm.

- To evaluate the effect of imetelstat on leukocytosis, circulating blast count (blast % x WBC), circulating immature myeloid cell count (sum of blast, promyelocyte, myelocyte and metamyelocyte % x WBC), and thrombocytosis in each arm.

3. PATIENT ELIGIBILITY

3.1. Inclusion Criteria

- Diagnosis of one of the following
  - Arms A, B, E, and F only: PMF per the revised World Health Organization (WHO) criteria (Appendix B),
  - Arms A, B, E, and F only: post-ET/PV MF per the IWG-MRT criteria (Appendix C).
  - Arm D only: Blast-phase MF defined as the presence of 20% or more blasts in the peripheral blood or bone marrow
  - Arm G only: MDS/MPN or MDS patients with spliceosome mutations including SF3B1, SRSF2 and U2AF1 mutations or ring sideroblasts. Diagnosis of MDS/MPN and MDS is per WHO criteria (Tefferi and Vardiman 2008). Direct sequencing will be used to confirm the presence or absence of spliceosome mutations.
- Indication for treatment of one of the following:
  - Arms A, B, E and F only: High-risk or Intermediate-2 risk MF (as defined by the Dynamic International Prognostic Scoring System [DIPSS-plus]; Appendix A).
  - Arm G only: presence of severe anemia defined as hemoglobin of <9 g/dL or other indications for cytoreductive therapy per physician discretion
- Presence of the following:
  - Arms E and G only: spliceosome mutations, including SF3B1, SRSF2 and U2AF1 mutations (by direct sequencing) or ring sideroblasts.
- Absence of the following:
  - Arm F only: spliceosome mutations (by direct sequencing) and ring ring sideroblasts
- ≥ 18 years of age with life expectancy of ≥12 weeks.
- Able to provide informed consent and be willing to sign an informed consent form.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (Appendix D).

- Evidence for acceptable organ function ≤ 14 days of study registration as evidenced by the following:
  - SGOT (AST) ≤2.5 x upper limit of normal (ULN) (or ≤5 x ULN if in the investigator's opinion the elevation is due to extramedullary hematopoiesis)
  - SGPT (ALT) ≤2.5 x upper limit of normal (ULN) (or ≤5 x ULN if in the investigator's opinion the elevation is due to extramedullary hematopoiesis)
  - Total bilirubin ≤3.0 mg/dL (or direct bilirubin <1 mg/dL).
  - Creatinine ≤3.0 mg/dL.
  - Absolute neutrophil count ≥1000/μL (this requirement not needed for Arm D).
  - Platelet count ≥50,000/μL (this requirement not needed for Arm D).
- Females of childbearing potential must have a negative pregnancy test ≤ 7 days prior to registration, unless they are surgically sterile (i.e., hysterectomy), OR postmenopausal (FSH >30 U/mL).
- Females of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through end of study. Permitted methods for preventing pregnancy must be communicated to study subjects and their understanding confirmed.
- Males must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through follow-up. Permitted methods for preventing pregnancy should be communicated to the subjects and their understanding confirmed.

3.2. Exclusion Criteria

- Females who are pregnant or are currently breastfeeding.
- Any chemotherapy (e.g., hydroxyurea), immunomodulatory drug therapy (e.g., thalidomide), immunosuppressive therapy, corticosteroids >30 mg/day prednisone or equivalent, growth factor treatment (e.g., erythropoietin) or JAK inhibitor therapy ≤ 14 days prior to registration.
- Subjects with another active malignancy. Note: Patients with early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin or cervical intraepithelial neoplasia are eligible for enrollment.
- Known positive status for HIV.

- Any unresolved toxicity greater or equal to Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve.
- Incomplete recovery from any prior surgical procedures or had major surgery ≤ 4 weeks prior to registration, excluding the placement of vascular access and other minor surgical procedures.
- Presence of acute active infection requiring antibiotics.
- Uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.

4. TEST SCHEDULE

All routine assessments must be performed within ± 3 days of the day indicated on the Visit Schedule (except for screening).

Table 3: Test Schedule: Core Phase = Cycle 1 – Cycle 9; Extension Phase = Cycle 10 and Beyond

Assessment	**Screening (≤14 days Prior to registration)**	**≤24 hours before each imetelstat infusion Cycles 1-9 or end of cycle during interruption**[1]	**Weekly in first 2 cycles**	**End of Cycle 3**	**End of Cycle 9**	**Every Cycle in extension phase prior to infusion (Cycles 10 and beyond)** [1]	**At study completion or early termination (± 1 week)** [2]	**Event Monitoring Every 3 mo until PD or subsequent treatment for MF Every 6mo after PD or subsequent treatment for MF**[14]
Physical examination including weight (height at screening)[3,4]	X			X	X		X	
Physical examination for hepatomegaly and splenomegaly[3,4]	X	X			X		X	
Transfusion Assessment	X	X						
Record adverse events[4]	X	X			X	X	X	
Record concomitant medication		X				X	X	
ECOG performance status (Appendix D) [4]	X	X			X		X	
12-lead ECG	X							
Chest x-ray	X							
Serum pregnancy test[4,5]	X	X				X		
Abdominal Ultrasound[6]	X							
Urinalysis[7]	X			X	X			

Assessment	Screening (≤14 days Prior to registration)	≤24 hours before each imetelstat infusion Cycles 1-9 or end of cycle during interruption[1]	Weekly in first 2 cycles	End of Cycle 3	End of Cycle 9	Every Cycle in extension phase prior to infusion (Cycles 10 and beyond) [1]	At study completion or early termination (± 1 week) [2]	Event Monitoring Every 3 mo until PD or subsequent treatment for MF Every 6mo after PD or subsequent treatment for MF[14]
Temperature and vital signs [8]	X	X			X	X	X	
Serum chemistry[4,9]	X	X	X		X	X	X	
Serum calcium, phosphorus, magnesium, total protein	X			X	X		X	
CBC[4,10]	X	X	X		X	X	X	
Peripheral blood smear[4]	X	X	X		X			
Serum Epo level	X			X	X			
International Working Group (IWG) Assessment of response[4]		X			X			
INR (or PT) and aPTT7 [4]	X	X						
Bone marrow biopsy and aspirate with cytogenetic and JAK2 V617F studies[11]	X[12]				X[12,13]			
Follow-up for survival and disease status and information of subsequent treatment for MF [14]								X

R Samples may be used by Mayo Clinic or sponsor for research tests that include granulocyte JAK2V617F allele burden measurement, plasma cytokine analysis and other tests that are deemed insightful.

CBC = complete blood count

[1] In case of interruption, a cycle will be 3 months while treatment is held.

[2] For all patients who did not experience a treatment emergent abnormality in liver function tests (LFTs), defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥ 3, or hepatic adverse events are present at imetelstat discontinuation, obtain LFT follow-up until 30 days from the last imetelstat dose. The length of the last cycle will be until 30 days after the last dose. For patients who experienced a treatment emergent abnormality in LFTs, as defined above, or hepatic adverse events

are present at imetelstat discontinuation, obtain follow-up per test schedule (see Section 4 for details) until resolution to at least baseline grade or less than 2x baseline value if baseline was Grade ≥ 3 for at least 2 consecutive determinations. The length of the last cycle will be until the resolution is confirmed.

[3] Screening physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

[4] If screening assessment was performed within 7 days prior to dosing Day 1 Cycle 1 assessment does not need to be repeated, and the screening assessment will serve as baseline.

[5] All women of childbearing potential (including those who have had a tubal ligation). For all other women, documentation must be present in the medical history.

[6] In addition to baseline abdominal ultrasound, a Doppler ultrasound of abdomen will be performed post baseline only as clinically indicated at the discretion of the investigator. The ultrasound will assess status of hepatobiliary architecture, which includes detection of any gross liver abnormalities; results will be compared to the baseline scan.

[7] Urinalysis to include blood, leukocytes, glucose, protein, pH, specific gravity, ketones, and nitrates.

[8] Vital signs will include measurements of temperature, heart rate, and systolic and diastolic blood pressure.

[9] Serum chemistries include sodium, potassium, BUN, creatinine, total and direct bilirubin, albumin, ALT, AST, alkaline phosphatase, LDH, and serum ferritin. In the event of new onset treatment emergent total bilirubin of Grade 2 or higher perform a reading of concurrent fasting bile acids and, to assess for hemolysis, a concurrent peripheral smear. Serum haptoglobin and reticulocyte count should also be performed if clinically indicated.

[10] CBC must be repeated weekly in patients with treatment-emergent ANC $\leq 1.0 \times 10^{9}$/L or platelet count$< 75 \times 10^{9}$/L. CBC includes hemoglobin, platelet count, WBC count, and absolute neutrophil count (ANC).

[11] If bone marrow biopsy and aspirate with cytogenetics and JAK2 V617F studies were performed as standard of care < 30 days prior to the patient signing consent procedure need not be repeated.

[12] Need to be submitted for central review. See Section 17 for details.

[13] Only in patients achieving CI, PR or CR per IWG-MRT criteria (See Section 11) for Arms A, B,C, E, F and G, and for patients achieving <5% peripheral blood blast percentage, for Arm D. The bone marrow examination can be performed earlier if patients were to achieve responses earlier or per investigator discretion. For the extension phase, only perform as clinically indicated.

[14] Follow-up for survival status, disease follow-up status, notice of first relapse or progression in event monitoring phase, notice of first subsequent treatment and notice of new primary malignancy. Patients will be initially followed every 3 months (±7 days) after study completion or early treatment termination until progressive disease or subsequent treatment for MF. Patients will then be followed every 6 months (±7 days). Follow-up during the Event Monitoring Phase can be completed via telephone call. The Event Monitoring Phase of the study will be considered complete once the last patient has completed study treatment.

4.1. Test Schedule For Hepatic Safety Monitoring And Follow Up After Discontinuing Imetelstat

For patients who experienced any treatment emergent abnormality in LFTs, defined as any grade abnormality in patients with normal value at baseline or any higher grade shift from baseline in patients with an abnormal baseline, or value more than 2x baseline if baseline was Grade ≥3, or hepatic adverse events present at imetelstat discontinuation, obtain follow-up as defined in Table 4 below until resolution to at least baseline grade or, less than 2x baseline value if baseline was Grade ≥3 for at least 2 consecutive determinations.

Table 4: Test Schedule for Hepatic Safety Monitoring And Follow Up After Discontinuing Imetelstat

Assessment 1	**Post-Study Completion/ Early Treatment Termination Visit [1] (Monthly ±7 Days)**
Serum chemistry [2]	**X**
CBC; a concurrent reticulocyte count, and peripheral smear (to assess for hemolysis) and a concurrent haptoglobin and fasting bile acids [3]	**X** [3]
Record adverse events [4]	**X**
Record concomitant medications	**X**
Record additional assessments/evaluations [5]	**If performed**
Doppler ultrasound of abdomen (optional) [6]	**Once**

CBC = complete blood count; ET = essential thrombocythemia; PV = polycythemia vera.

[1] Monthly follow up post-study completion/early treatment termination until resolution criteria are met.

[2] Serum chemistries include ALT, AST, ALP, total & direct bilirubin, GGT, BUN, creatinine, and serum ferritin.

[3] Perform only if total bilirubin is elevated. CBC includes white cell count (WBC) count; absolute neutrophil count (ANC); hemoglobin; and platelet count.

[4] Continue to collect adverse events and serious adverse events regardless of attribution until resolution of liver biochemistry or hepatic adverse events.

[5] Record any additional clinical evaluations that are performed based on clinical decisions to evaluate new onset or ongoing liver function abnormalities, or clinical findings. Includes physical examination, laboratory tests, radiographic or other diagnostic studies that are performed to evaluate new onset or ongoing liver function abnormalities, or clinical findings.

[6] Performed once at any time during hepatic safety monitoring/follow-up after imetelstat discontinuation, in patients who had baseline ultrasound performed, unless post baseline assessment previously performed before entering hepatic safety follow-up period. The ultrasound will assess status of hepatobiliary architecture, which includes detection of any gross liver abnormalities; results will be compared to the baseline scan.

5. GROUPING FACTORS

All study arms (A, B, C, D, E, F, and G) are now permanently closed to enrollment.

6. REGISTRATION/RANDOMIZATION PROCEDURES

6.1. Registration Procedures

1. To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

   The instructions for the registration/randomization application are available on the MCCC web page (http://hsrwww.mayo.edu/ccs/training) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

   - Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.

   - Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

2. Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

   In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

   When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

3. Prior to accepting the registration, the registration/randomization application will verify the following:

   - IRB approval at the registering institution
   - Patient eligibility
   - Existence of a signed consent form
   - Existence of a signed authorization for use and disclosure of protected health information (U.S.A. institutions only) [delete parenthetical expression (only) when not applicable, i.e. no non-USA participants]

4. Treatment on this protocol must commence at Mayo Clinic Rochester under the supervision of a hematologist.

5. Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

6. Pretreatment tests/procedures (see Section 4) must be completed within the guidelines specified on the test schedule.

7. All required baseline symptoms (see Section 10.6) must be documented and graded.

8. Study drug is available on site.

7. PROTOCOL TREATMENT

7.1. Treatment Schedule

7.1.1. Imetelstat Treatment

This is a single center, open-label study of imetelstat in patients with Intermediate-2 or high risk PMF/post-ET/PV MF (Arms A, B, C, E and F) or blast-phase MF (Arm D only) or spliceosome-mutated (or with ring sideroblasts) MDS/MPN (Arm G only).

Imetelstat will be administered as a 2-hour IV infusion (± 10 minutes). The current weight will be used to calculate the dose of imetelstat. All patients must be premedicated prior to imetelstat administration.

As of 22 January 2014, all arms are permanently closed to accrual.

7.1.1.1. Arm A Treatment Schedule

(Arm A permanently closed to accrual)

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days[1]
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1[2,3]	Every 21 days

[1] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[2] If the patient has not achieved a CR or PR, by the end of Cycle 6, the dosing frequency may be increased to up to weekly using the **current dose level** at the discretion of the Investigator. The patient must be tolerating the current dose level without significant toxicity. Increase in dosing frequency is only allowed after Cycle 6. The cycle length will be 21-28 days. If the dosing frequency is increased to once weekly, the cycle length will remain 21 days. If the dosing frequency is increased to once every 2 weeks, the cycle length will be 28 days.

[3] For patients whose response has plateaued for a minimum of 3 months, the dosing frequency may be reduced after Cycle 6 and the cycle length will be the length of the dosing interval. For example, if the dosing frequency is decreased to once every 3 months, the cycle length will be 84 days. Dosing can also be interrupted until relapse and restarted, in such patients, per physician discretion. In the case of interruption, a cycle will be 3 months while treatment is held and the patient will restart at the dose level/schedule they were receiving at the time of interruption.

7.1.1.2. Arm B Treatment Schedule

(Arm B permanently closed to accrual)

Induction: Cycle 1				
Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1, 8, 15	Cycle 1 is 21 days
Maintenance: Cycles 2 and beyond[1]				
Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1[2,3]	Every 21 days (Cycles 2 and beyond)

[1] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[2] If the patient has not achieved a CR or PR, by the end of Cycle 6, the dosing frequency may be increased to up to weekly using the **current dose level** at the discretion of the Investigator. The patient must be tolerating the current dose level without significant toxicity. Increase in dosing frequency is only allowed after Cycle 6. The cycle length will be 21-28 days. If the dosing frequency is increased to once weekly, the cycle length will remain 21 days. If the dosing frequency is increased to once every 2 weeks, the cycle length will be 28 days.

[3] For patients whose response has plateaued for a minimum of 3 months, the dosing frequency may be reduced after Cycle 6 and the cycle length will be the length of the dosing interval. For example, if the dosing frequency is decreased to once every 3 months, the cycle length will be 84 days. Dosing can also be interrupted until relapse and restarted, in such patients, per physician discretion. In the case of interruption, a cycle will be 3 months while treatment is held and the patient will restart at the dose level/schedule they were receiving at the time of interruption.

7.1.1.3. Arms C and D Treatment Schedule

(Arms C and D permanently closed to accrual)

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days[1]
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1, 8, 15, 22[2]	Every 28 days

[1] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

[2] For patients without response after the first two cycles, dosing might be increased to either Days 1, 3, 5 or Days 1, 3 every 2 to 4 weeks, per physician discretion. For patients whose response has plateaued for a minimum of 3 months, the dosing frequency may be reduced after Cycle 6 and the cycle length will be the length of the dosing interval. For example, if the dosing frequency is decreased to once every 3 months, the cycle length will be 84 days. Dosing can also be interrupted until relapse and restarted, in such patients, per physician discretion. In the case of interruption, a cycle will be 3 months while treatment is held and the patient will restart at the dose level/schedule they were receiving at the time of interruption.

NOTE: As of Addendum 3, Arms A, B, and C are permanently closed to accrual. The 11 patients slotted to be enrolled in Arm C will now be treated with either the Arm A (if spliceosome-mutated/with ring sideroblasts) or Arm B (if spliceosome unmutated) treatment schedule.

7.1.1.4. Arms E and G Treatment Schedule

(Arms E and G permanently closed to accrual)

Induction Cycle 1 and 2 Dosing				
Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	7.5 mg/kg	IV as 2 hour infusion	1	Cycle is 28 days
Maintenance: Cycles 3 and beyond[1]				

[1] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

If any **one** of the following criteria is met at the end of Cycle 2, then follow the Table 5 dosing schedule below. If no criteria are met, follow the instructions below.

- Greater than 75% reduction in leukocyte count
- Greater than 75% reduction in platelet count
- Greater than 50% reduction in spleen size in patients with baseline palpable splenomegaly of >5 cm
- Greater than 2 gm/dL increase in hemoglobin level from baseline without transfusions

Table 5: Arms E and G Dosing if Criteria met = Yes

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	7.5 mg/kg	IV as 2 hour infusion	1[1,2]	Cycle is 28 days

[1] In patients who do not achieve CR or PR by the end of Cycle 4, the frequency of dosing may be increased to every week or every two weeks, at the physician's discretion

[2] For patients whose response has plateaued, without signs of further improvement, for a minimum of 3 months, dosing frequency may be reduced to every 2 to 3 months, or treatment may be interrupted until relapse and restarted, at the physician's discretion. In the case of interruption, a cycle will be 3 months while treatment is held and the patient will restart at the dose level/schedule they were receiving at the time of interruption.

Criteria met = No

Treat as specified in Arm F (Cycle 3 will start with Cycle 1 of Arm F dosing schedule)

7.1.1.5. Arm F Treatment Schedule

(Arm F permanently closed to accrual)

Induction Cycle 1 and 2 Dosing				
Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1	Cycle is 28 days
Maintenance: Cycles 3 and beyond[1]				

[1] Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

If any **one** of the following criteria is met at the end of Cycle 2, then follow the Table 6 dosing schedule below. If no criteria are met, follow the Table 7 and Table 8 dosing schedule below.

- Greater than 75% reduction in leukocyte count
- Greater than 75% reduction in platelet count
- Greater than 50% reduction in spleen size in patients with baseline palpable splenomegaly of >5 cm
- Greater than 2 gm/dL increase in hemoglobin level from baseline without transfusions

Table 6: Arm F Dosing if Criteria met = Yes

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	9.4 mg/kg	IV as 2 hour infusion	1	Cycle is 28 days

Table 7: Arm F Dosing if Criteria met = No: Cycles 3 and 4

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	7.5 mg/kg	IV as 2 hour infusion	1 and 3[1,2]	Cycle is 28 days

[1] In patients who do not achieve CR or PR by the end of Cycle 4, the frequency of dosing may be increased to every two weeks, at physician's discretion.

[2] For patients whose response has plateaued, without signs of further improvement, for a minimum of 3 months, dosing frequency may be reduced to Day 1 every 28 days or Days 1, 3 every 2 to 3 months, or treatment may be interrupted until relapse and restarted, all at the physician's discretion. In the case of interruption, a cycle will be 3 months while treatment is held and the patient will restart at the dose level/schedule they were receiving at the time of interruption.

Table 8: Criteria met = No: Cycles 5 and beyond

Agent	Dose	Route	Day	Cycle (ReRx) ± 3 days
Imetelstat	7.5 mg/kg	IV as 2 hour infusion	1, 3, and 5[1, 2]	Cycle is 28 days

7.2. Pre-Medication

In Phase I studies, some patients experienced infusion-related reactions to imetelstat, including but not restricted to allergy/hypersensitivity reaction (e.g., rash, fever, urticaria, dyspnea, bronchospasm, chills/rigors, myalgias, headache, fatigue, nausea and/or vomiting) during or within 24 hours of an infusion. Reactions were sporadic in nature and did not occur at a higher frequency with the first administration of imetelstat. These reactions were usually mild to moderate and generally resolved with slowing or interruption of the infusion and with supportive care (diphenhydramine, corticosteroids, and/or IV saline). The mechanism is not entirely clear but may involve complement activation. (See Section 8 for the Infusion reaction guidelines and Appendix E.)

All patients will require premedication with diphenhydramine (25–50 mg, PO or IV) and hydrocortisone (100 mg PO or IV) or equivalent before receiving imetelstat.

8. DOSAGE MODIFICATION BASED ON ADVERSE EVENTS

8.1. Retreatment Criteria

Subjects may receive treatment for a maximum of 9 cycles during the "Core Phase" of the study. Subjects may be allowed to continue therapy beyond 9 cycles in an "Extension Phase" of the study if they do not meet any of the withdrawal criteria, do not have disease progression and are receiving some clinical benefit, at the discretion of the principle investigator. Patients may continue to receive imetelstat study treatment for as long as they derive clinical benefit or until study end. The study will end when all subjects have discontinued study drug, the last patient enrolled has been treated for 5 years, or imetelstat is commercially available in the United States, whichever occurs first.

Patients will be evaluated for safety and efficacy at the end of each cycle during both the core and extension phases of the study.

8.2. Dose Reduction

Once the need for dose reduction has been established (as per Table 11), treatment with imetelstat may be restarted, after reversal of drug-related toxicity (as per Table 11), with one level dose reduction, for patients receiving treatment every 21 days (see Table 10), or an increase in dosing interval (using the same drug dose) in patients receiving the drug every week; in the latter instance, dosing frequency is first increased to every two weeks and then to every 3 weeks, in case of recurrent toxicity that requires dose reduction (see Table 9). Once a dose reduction has been instituted, the dose should not be re-escalated.

Table 9: Dose Reductions

Dose Frequency	Action
Once weekly	Reduce to once every 2 or once every 4 weeks at same dose level (dose level might also be decreased per physician discretion per Table 10)
Once every 2 weeks	Reduce to once every 4 weeks at same dose level (dose level might also be decreased per physician discretion per Table 10)
Once every 3 weeks	Reduce one dose level per Table 10
Once every 4 weeks	Reduce one dose level per Table 10

Table 10: Dose Levels (Based on Adverse Events in Table 9)

Dose Level	All arms
0[1]	9.4 mg/kg D1
-1	7.5 mg/kg D1
-2	6 mg/kg D1

[1] Dose level 0 refers to the starting dose (except Arms E and G).

Table 11: ALERT: Serious Adverse Event (SAE) reporting may be required for some adverse events (See Section 10)

ADVERSE EVENT/ laboratory test abnormality (must be at least possibly related to drug to qualify as a dose-modifying event)	AGENT	ACTION[1]
AT TIME OF RETREATMENT (i.e. imetelstat infusion beyond Day 1, Cycle 1)		
Absolute neutrophil count (ANC) <1.0 x 10^9/L	Imetelstat	Hold imetelstat.[2]Restart at the next lower dose level (see Section 8.2), once ANC recovers to ≥1.0 x 10^9/L
Platelet count <50 x 10^9/L	Imetelstat	Hold imetelstat.[2] Restart at the next lower dose level (see Section 8.2), once platelet count recovers to ≥ 50 x 10^9/L.
Absolute neutrophil count (ANC) <1.5 x 10^9/L and also associated with >75% drop from ANC recorded at Day 1 of the previous cycle	Imetelstat	Hold imetelstat.[2] Restart at the next lower dose level (see Section 8.2), once ANC recovers to ≥ 1.5 x 10^9/L
Platelet count <100 x10^9/L and also associated with >75% drop from platelet count recorded at Day 1 of the previous cycle	Imetelstat	Hold imetelstat. [2]Restart at the next lower dose level (see Section 8.2), once platelet count recovers to ≥ 100 x 10^9/L.
SGOT (AST) and SGPT (ALT) ≥ Grade 3	Imetelstat	Hold imetelstat. Restart at the next lower dose level see Section 8.2), if recovered to Grade 1 or less (or to pre-study baseline).
Total Bilirubin >3.0 mg/dL (or direct bilirubin 1≥ mg/dL)	Imetelstat	Hold imetelstat. Restart at the next lower dose level (see Section 8.2), if recovered to Grade 1 or less (or to pre-study baseline).
Creatinine >3.0 mg/dL	Imetelstat	Hold imetelstat. Restart at the next lower dose level (see Section 8.2), if recovered to Grade 1 or less (or to pre-study baseline).

ADVERSE EVENT/ laboratory test abnormality (must be at least possibly related to drug to qualify as a dose-modifying event)	AGENT	ACTION[1]
Allergic Reaction Grade 2	Imetelstat	Hold imetelstat. Restart at the next lower dose level if adverse event reduced to ≤ Grade 1. Discontinue imetelstat if event reoccurs at lower dose.
Allergic Reaction Grade 3	Imetelstat	Discontinue imetelstat and go to event monitoring per Section 4
Any Grade 3[3]	Imetelstat	Hold imetelstat. Restart at the next lower dose level (see Section 8.2), if adverse event reduces to ≤ Grade 2.
Any Grade 4[4]		Hold imetelstat. Restart at the next lower dose level (see Section 8.2), if adverse event reduces to ≤ Grade 2.

[1] Use the following to describe actions in the Action column:
- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs. Hold for maximum of 28 days, and then contact principal investigator and medical monitor.
- Discontinue = The specified drug(s) are totally stopped.

[2] Not required for cohort D.

[3] Except fatigue, nausea, vomiting, diarrhea and hyperuricemia that persist despite treatment with optimal anti-diarrheals or anti-emetics. Such toxicity will be taken into account, for dose holding only when it persists despite appropriate treatment.

[4] Except Grade 4 uric acid toxicity. Such toxicity will be taken into account for dose holding only when refractory to appropriate treatment.

In addition to any of the above toxicities, in the event of a drug-related Grade 2 or higher toxicity that the patient cannot tolerate or at the discretion of the Investigator, dosing may be reduced.

8.2.1. Hepatoxicity

- Diagnosis of a treatment emergent hepatic adverse event such as hepatitis, jaundice or other hepatic AEs or hepatic biochemistry abnormalities of clinical significance should lead to additional monitoring and an evaluation of ongoing benefit-risk with imetelstat; dose modification and/or study treatment termination should be considered in such cases and discussed with the medical monitor. Consider a hepatic consultation if indicated. External experts may also be consulted by the sponsor to review each case individually.

- See Table 11 above for dose modifications. All imetelstat dose reductions due to liver enzyme elevations are permanent.

- Discontinue imetelstat permanently and enter follow-up if a significant hepatic event, including hepatic biochemistry abnormalities, indicating the potential for severe hepatic injury is observed without a more likely cause than study treatment. Baseline liver laboratory abnormalities and clinical presentation should be taken into consideration. Bilirubin should be fractionated and be primarily conjugated.

For patients who enter hepatic safety monitoring and follow up after imetelstat discontinuation refer to Table 4 for details of clinical parameters and duration of follow-up.

8.3. Infusion Reaction

The guidelines described in Table 12 should be followed for managing imetelstat infusion reactions (See Appendix E).

Table 12: Guidelines for Managing Infusion Reactions

Infusion Reaction	**Management Guideline**
Grade 1 Mild and transient (e.g., mild flushing, rash, pruritis, fever)	• Evaluate and manage symptomatically as needed. • May complete infusion if reaction remains mild, with stable vital signs and does not worsen to Grade 2 or more.
Grade 2 Moderate (e.g., moderate flushing, rash, dyspnea, chest discomfort, hypotension)	• Stop infusion • Manage symptomatically: – Administer diphenhydramine 25 mg and dexamethasone 10 mg IV, if required (particularly if not received within last 4 hours) – Consider IV fluids, acetaminophen, oxygen, bronchodilators etc. • After recovery, resume infusion at half the previous rate for 15 minutes – If no further symptoms occur, complete the infusion at the full dose rate – If symptoms recur, discontinue imetelstat
Grade 3 Severe (not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• Stop infusion • Administer supportive care as indicated – Consider epinephrine, corticosteroids, diphenhydramine, IV fluids, acetaminophen, oxygen, bronchodilators, vasopressors, etc. • Discontinue imetelstat

Grade 4 Life-threatening (e.g., anaphylaxis, angioedema severe hypotension requiring vasopressors, respiratory distress requiring ventilator support)	• Stop infusion • Administer supportive care as indicated • Discontinue imetelstat

9. ANCILLARY TREATMENT/SUPPORTIVE CARE

- Antiemetics may be used at the discretion of the attending physician.
- Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).
- In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.
- If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10. ADVERSE EVENT (AE) REPORTING AND MONITORING

10.1. Safety Parameters and Definitions

Safety assessments will consist of recording all adverse events (AEs) and serious adverse events (SAEs); protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of imetelstat.

Janssen Research & Development or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Janssen Research & Development or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Janssen Research & Development or its designee will report other relevant SAEs associated with the use of the study medication to the regulatory agencies and competent authorities by a written safety report within 15 calendar days of notification or other agreed upon timelines.

10.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution.

During the extended hepatic safety follow-up, once patients have discontinued imetelstat treatment, an AE is defined as an unfavorable and unintended sign, symptom, or disease occurring during the follow-up period or temporally associated with a protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MF that were not present prior to the AE reporting period (see Section 10.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in)
- Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

10.1.2. Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)

- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the Investigator (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

10.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 10.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

10.2.1. Adverse Event Reporting Period

After initiation of imetelstat, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or at study completion/early treatment termination. After this period, Investigators should report only SAEs that are felt to be related to study treatment, unless the patient is continuing on study for additional hepatic safety monitoring as defined in Section 10.3.1.10.

For patients who have discontinued imetelstat and are undergoing extended hepatic safety follow-up due to ongoing liver biochemistry abnormalities or hepatic AEs, monitoring and data collection, including all AEs and SAEs regardless of attribution, should continue as defined in Table 4.

See Section 10.6 for post-study AE reporting.

10.2.2. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

10.2.3. Assessment of Severity and Causality of Adverse Events

The Investigator will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the Investigator will make an assessment of seriousness (see Section 10.1.2 for seriousness criteria), severity, and cause. Table 14 provides guidance for assessing the causal relationship to the investigational product.

The AE grading (severity) scale found in the NCI CTCAE v4.0 will be used for AE reporting (see Table 13). Regardless of severity, some events may also meet regulatory serious criteria (see Section 10.1.2).

Table 13: Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description[1]
1	Mild (apply event-specific NCI CTCAE[2] grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

[1]Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.
[2]NCI CTCAE v4.0

To ensure consistency of causality assessments, the Investigator should apply the following general guidelines:

Table 14: Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

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

10.3. Procedures for Recording Adverse Events

10.3.1. Recording Adverse Events on the eCRF

The Investigator should use correct medical terminology/concepts when recording AEs on the eCRF. Avoid colloquialisms and abbreviations.

A separate Adverse Event eCRF should be used for each medical concept that needs to be recorded.

10.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on a separate eCRF. If a diagnosis is subsequently established, it should be reported to Janssen Research & Development per the CRF Completion Guidelines.

10.3.1.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

10.3.1.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

10.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

10.3.1.5. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2), regardless of attribution, will be recorded on an eCRF and expeditiously reported to the Sponsor. This includes death attributed to progression of MF.

If the death is attributed to progression of MF, record “Mylefibrosis progression” as the SAE term on the SAE Report Form.

When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death.”

10.3.1.6. Preexisting Medical Conditions

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse

Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.3.1.7. Worsening of MF

Worsening of and/or progression of MF should not routinely be recorded as an AE or SAE if not resulting in death. These data will be captured as efficacy assessment data. However worsening and/or progression of MF should be recorded an SAE if fatal (see Section 10.1.2 or if the investigator assesses the disease progression to be related to imetelstat.

10.3.1.8. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

10.3.1.9. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of investigational product, a Pregnancy Notification Form should be completed, printed, and faxed to the Sponsor or its designee within 24 hours of learning of the pregnancy, using the fax numbers provided by the Sponsor.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on a Serious Adverse Event Form (SAE Form) and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

10.3.1.10. Hepatic Adverse Events and Abnormal Liver Biochemistries

Abnormal liver biochemistries and hepatic AEs should be reported per routine protocol reporting procedures on the relevant eCRF (e.g., Adverse Event eCRF, chemistry CRF).

In the event a patient has discontinued imetelstat, but qualifies for the extended hepatic safety follow-up due to ongoing liver biochemistry abnormalities or hepatic AEs at the study

completion/early treatment termination visit, monitoring and data entry into the relevant eCRF (i.e., adverse event, laboratory data, and concomitant medications) should continue per the guidelines in Table 4. These assessments should occur regardless of the initiation of alternate MF treatments.

10.4. Expedited Reporting Requirements for Serious Adverse Events

10.4.1. Reporting Requirements for Fatal/Life Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the Investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an SAE Form within 24 hours as described in Section 10.3.

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.

10.4.2. Reporting Requirements for All SAEs

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 may be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information may 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)

10.5. Type and Duration of Follow-Up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, are determined to be irreversible by the Investigator, the patient initiates alternate MF treatment (unless undergoing extended hepatic safety follow-up), the patient is lost to follow-up, or it has been determined that the study treatment is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10.6. Post-Study Adverse Events

For patients who discontinue the study and are not in the extended hepatic safety follow-up, the Investigator should report any death or other SAE occurring beyond 30 days following the last administration of study drug that the Investigator deems related to study drug.

For patients undergoing extended hepatic safety follow-up, SAEs will continue to be collected regardless of attribution, beyond 30 days following the last administration of study drug, per the guidelines in Section 10.3.1.10.

The Investigator should also, upon becoming aware of, report the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events on an SAE Form to the Sponsor as described in Section 10.3 above.

11. TREATMENT EVALUATION

11.1. Myelofibrosis

Table 15: Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) response criteria for myelofibrosis.

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks in order to qualify as a response)
Complete Remission (CR)	*Bone marrow:* [1] Age-adjusted normocellularity; <5% blasts; ≤Grade 1 myelofibrosis[2], AND *Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells[3], AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH
Partial Remission (PR)	*Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥ 100 x 10^9/L and <UNL; <2% immature myeloid cells[3], AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH, OR *Bone marrow:* [1] Age-adjusted normocellularity; <5% blasts; ≤Grade 1 myelofibrosis[2], AND *Peripheral blood:* Hemoglobin ≥85 but <100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥50 but <100 x 10^9/L and <UNL; <2% immature myeloid cells[3], AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH
Clinical Improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia or neutropenia[4]
Anemia response	*Transfusion-independent patients:* a ≥20 g/L increase in hemoglobin level[5] *Transfusion-dependent patients:* becoming transfusion-independent[6]
Spleen response[7]	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable[8], OR A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%[8] *A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response* *Confirmation by MRI or CT showing ≥35% spleen volume reduction is recommended (but not required)*

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks in order to qualify as a response)
Progressive disease[9]	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 to 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 one month, OR Loss of spleen response persisting for at least one month

Key: CT = computed tomography; EMH = extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven non-hepatosplenic EMH); LCM = left costal margin; MRI = magnetic resonance imaging; UNL = upper normal limit

[1] Baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

[2] Grading of myelofibrosis is according to the European classification (*Thiele et al. Haematologica 2005;90:1128*) . It is underscored that the consensus definition of "a complete remission bone marrow" is to be used only in those patients where all other criteria, including resolution of leukoerythroblastosis, are met. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histological remission.

[3] Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

[4] See table 15 for definitions of anemia response, spleen response and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pre-treatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pre-treatment baseline, in platelet count or absolute neutrophil count, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to clinical improvement (CI) requires a minimum platelet count of ≥25,000 x 10^9/L and absolute neutrophil count of ≥0.5 x 10^9/L.

[5] Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion-dependency at the time of study enrollment (see below), but have received transfusions within the previous month, the pre-transfusion hemoglobin level should be used as the baseline

[6] 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 <85 g/L, 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 ≥85 g/L.

[7] In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy

[8] Confirmation of spleen or liver responses by imaging studies is recommended (but not required), where a ≥35% reduction in spleen or liver volume, assessed by magnetic resonance imaging (MRI) or computed tomography (CT), is required for confirmation. Furthermore, a≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.
Symptoms are evaluated by the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS). The MPN-SAF TSS is assessed by the patients themselves and includes fatigue, concentration,

early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. 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 MPN-SAF TSS is the summation of all the individual scores (0-to-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

[9] Confirmation by MRI or CT is recommended (but not required) to confirm progressive disease assignment for splenomegaly, where a ≥25% increase in spleen volume from baseline is required for confirmation. Baseline values for both physical examination and imaging studies refer to pre-treatment baseline and not to post-treatment measurements.

11.2. MDS

The International Working Group response assessment as reported by Cheson et al. (2006) will be utilized.

Table 16: Definition of Disease Response in MDS:

Category	Response Criteria
Complete Remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[1] Persistent dysplasia will be noted[1,2] Peripheral blood[3] Hgb ≥ 11 g/dL Platelets ≥ 100 x 10^9/L Neutrophils ≥ 1.0 x 10^9/L[2] Blasts 0%
Partial Remission (PR)	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure (FAIL)	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence

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

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

Table 17: Proposed Modified International Working Group Response Criteria for Hematologic Improvement

Hematologic improvement[1]	Response criteria[2]
Erythroid response (pretreatment,< 11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation[2]
Platelet response (pretreatment, < 100 X 10^9/L)	Absolute increase of ≥30 X 10^9/L for patients starting with > 20 x 10^9/L platelets Increase from < 20 _X 10^9/L to > 20 X 10^9/L and by at least 100%[2]
Neutrophil response (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 X_10^9/L[2]
Progression or relapse after HI[3]	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Note: To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
[1] Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
[2] Modification to IWG response criteria.
[3] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

12. DESCRIPTIVE FACTORS

- Category of MF (see Appendix B): Primary Myelofibrosis vs. Post ET Myelofibrosis vs. Post PV Myelofibrosis vs. blast-phase MF vs MDS/MPN or MDS
- DIPSS-plus risk (see Appendix A): High-risk MF vs. Intermediate-2 risk MF

13. TREATMENT/FOLLOW–UP DECISION AT EVALUATION OF PATIENT

Patients who are CR, PR, CI, or SD will continue treatment per protocol.

Patients will be discontinued from treatment and go to event-monitoring phase per Section 4 for any of the following reasons:

- Disease progression (Except relapse that occurs during dose interruption).
- Leukemic transformation (as per WHO criteria)
- Any clinical adverse event, laboratory abnormality, intercurrent illness or other medical condition or situation which occurs such that continued participation in the study would not be in the best interest of the participant
- Hepatotoxicity criteria for treatment discontinuation (see Section 8.2.1)
- Pregnancy
- Diagnosis of positive status for HIV or hepatitis B or C
- Continued failure to comply with study procedures or use of the drug as specified in the study protocol such that continued participation in the study would not be in the best interest of the participant
- Withdrawal of consent
- Initiation of non-protocol therapies
- Administrative decision by investigator or sponsor

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 4 of the protocol.

- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4 of the protocol.

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14. BODY FLUID BIOSPECIMENS

Peripheral blood will be obtained according to IRB-approved collect and store protocol #11-005599 and #12-003574 (PI, [redacted]).

15. DRUG INFORMATION

15.1. Imetelstat (GRN163L)

15.1.1. Background

Imetelstat is a potent specific inhibitor of telomerase and is currently in development as a potential therapeutic agent for the treatment of solid tumor and hematological malignancies. Imetelstat has also shown additive and synergistic effects in multiple in vitro and in vivo tumor models when combined with approved anticancer agents, supporting clinical investigation of imetelstat in combination with approved anticancer therapies to potentially improve clinical responses. Additionally, imetelstat is a potent and effective inhibitor of cancer stem cells in vitro and in vivo, suggesting that imetelstat may improve the durability of clinical responses in cancers that have a stem cell component contributing to their maintenance and progression.

[redacted]

[redacted]

15.1.4. Administration

Administer imetelstat at a constant rate over 2 hours using a programmable volumetric infusion pump. In-line filters may be used but are not required.

Imetelstat will be administered as a 2-hour IV infusion (± 10 minutes). 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. All patients must be pre-medicated prior to imetelstat administration (see Section 7 for details). Patients require regular monitoring for hematologic toxicity.

15.1.5. Pharmacokinetic information:

a. Absorption – There was a measurable level of imetelstat in a post-treatment bone marrow sample collected 1 day after dosing at 6 mg/kg, resulting in a concentration at

24 hrs post-treatment of 5.54 μg/mL. This confirmed the presence of imetelstat in the target tissue, bone marrow, after IV administration to MM patients.

b. Distribution – V_{dss} ranged from 41/3 to 71.2 mL/kg at doses of 4.8 to 11.7 mg/kg.
c. Excretion – $T_{1/2}$ following a single-dose ranged from 4 to 5 hours. Similar to other oligonucleotides, imetelstat excretion is probably mainly via the urinary tract following metabolism of the oligonucleotide sequence into smaller fragments. Based on a preliminary population pharmacokinetic analysis of 59 patients who received 2- or 6-hour weekly IV infusions of imetelstat 0.4 to 11.7 mg/kg (30−1155 mg) or 20−240 mg/m^2 (37.4−516 mg), the estimated CL of imetelstat varied by body size (body weight or BSA) and dose. After correcting for body size, the CL at a BSA of 1.86 m^2 was 0.206 L/hr and total CL was 0.84 L/hr at a dose of 9.4 mg/kg (≈ 380 mg/m^2).

15.1.6. Potential Drug Interactions

To date, no known drug interactions have been identified with imetelstat treatment.

15.1.7. Safety Experience

Refer to Section 1.3.4 for safety experience.

For further details, see the Imetelstat Investigator's Brochure.

15.1.8. Drug Procurement

Imetelstat will be provided free of charge to study participants by Janssen Research & Development.

15.1.9. Nursing Guidelines

As drug is early in development, not all side effects can be known at this time. Monitor patients carefully and instruct patient to report any side effects to the treating physician and/or study team immediately.

In Phase I studies cytopenias (thrombocytopenia and neutropenia) were the primary dose-limiting side effects especially when administered with other cytotoxic agents. Monitor CBC w/differential closely. Instruct patients in signs and symptoms of infection and to report any unusual bruising or bleeding to the study team immediately.

Infusion reactions have been seen and are usually mild-moderate in nature. These usually occur shortly after infusion initiation and can occur with subsequent cycles, despite tolerability of previous cycles. Have emergency medications on hand and administer at the physician's discretion (See Section 8.3 and Appendix E).

Patients may experience prolonged aPTT times. Instruct patients to report any unusually bleeding to study team immediately.

Gastrointestinal side effects (diarrhea, nausea, vomiting, etc.) have been seen (See Section 9). Treat symptomatically and monitor for effectiveness.

Fatigue is common. Instruct patient in energy conserving lifestyle.

16. STATISTICAL CONSIDERATIONS AND METHODOLOGY

Overview: This protocol will assess the efficacy of different schedules of imetelstat in six cohorts of patients with myelofibrosis (including blast-phase disease in Arm D) and one cohort of patients with MDS/MPN or MDS with spliceosome mutations or ring sideroblasts using a phase II study design in each arm independently.

Descriptive statistics will be used to summarize baseline patient characteristics, treatment administration, efficacy, and safety outcomes. Descriptive summaries of discrete data will present the number of patients and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size.

For regulatory reporting purposes, there are two time points for the analyses: (1) the primary analysis 48 weeks after the last patient has been enrolled, and (2) the final analysis after all patients have completed the study. A separate and detailed statistical analysis plan (SAP) developed prior to primary analysis will supersede analyses specified in the protocol. Deviations from the SAP will be noted in the final study report.

Primary Endpoint: The primary endpoint in each arm of this trial is overall response rate. Overall response will be defined as a CI, PR, or CR (for Arms A, B, C, E, and F) according to the IWG-MRT consensus criteria for MF, or as a HI, PR or CR (for Arm G) according to the IWG consensus criteria for MDS, or the achievement of <5% peripheral blood and bone marrow blast % that lasts for at least two months (for Arm D).

16.1. Statistical Design (To Be Evaluated Independently in Each Arm)

In a phase II study conducted at Mayo Clinic including 27 myelofibrosis patients treated with single agent Lenalidomide, 37% of patients responded in terms of anemia or splenomegaly. In a similar study conducted at M.D. Anderson Cancer Center, a response rate of 24% in terms of anemia or splenomegaly was seen in 41 myelofibrosis patients also treated with single agent lenalidomide (Tefferi et al. 2006). A response rate similar to or better than Lenalidomide would be of interest for myelofibrosis patients treated with single agent Imetelstat. Although this study also includes response in terms of platelets or ANC, we would expect the majority of these patients to also have a response in terms of anemia or splenomegaly. In addition, we would expect patients with MDS/MPN or MDS with spliceosome mutations or ring sideroblasts to show similar outcomes to myelofibrosis. Therefore, an overall response rate of 30% would be considered early evidence of promising activity, for Arms A, B, C, E, F, and G. For Arm D, 20% response rate would be considered promising based on our single institutional experience of 91

patients with blast phase MF (Mesa et al. 2005); in the particular study, induction chemotherapy resulted in 0% CR and short-lived reversal to chronic phase disease in 41%.

Arms A, B, C, D, and G: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following two-stage Simon optimum design (Simon 1989) uses 11 or 26 patients to test the null hypothesis that the true success proportion in a given patient population is at most 10%.

16.2111Stage 1: Enter 11 patients into each arm of the study (i.e. 11 patients each in Arms A, B, C, D, and G). If 0 or 1 successes are observed in the first 11 evaluable patients for each arm of the study, we will consider the regimen ineffective and terminate the particular arm of the study. Otherwise, if the number of successes is at least 2, we will proceed to Stage 2.

Stage 2: Enter an additional 15 patients into each arm of the study. If 4 or fewer successes are observed in the first 26 evaluable patients, considering each arm of the study separately, we will consider this regimen ineffective as it applies to the particular arm of the study. If 5 or more successes are observed in the first 26 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

Power and Significance Level: Assuming that the number of successes is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions and the probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen is promising and warrants further study is…	0.09	0.28	0.52	0.72	0.85
And the probability of stopping after the first stage is…	0.70	0.49	0.32	0.20	0.11

As of Addendum 3, accrual to Arm C will be permanently discontinued due to preliminary evidence showing difference in outcome based on presence vs. absence of spliceosome mutations. The 11 patients slotted to enroll on Arm C will now be treated per the Arm A or Arm B dose schedule and then Arms A and B will permanently close. A total of 34 patients will be accrued between Arms A, B, and C. Due to incomplete accrual in these arms, the 33 evaluable patients that have been accrued to these arms will be combined and reported together as a pilot study. Since this group will not have a formal statistical design, the reporting of results in this group will be primarily descriptive in nature.

Arms E and F: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The

following one-stage binomial design uses 25 patients to test the null hypothesis that the true success proportion in a given patient population is at most 10%.

Final Decision Rule: If 4 or fewer successes are observed in the first 25 evaluable patients, we will consider this regimen ineffective in this patient population. If 5 or more successes are observed in the first 25 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

Power and Significance Level: Assuming that the number of successes is binomially distributed, with a significance level of 10%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen is promising and warrants further study is…	0.10	0.32	0.58	0.79	0.91

Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.6.

Sample Size: As of Addendum 3, accrual to Arm C will be permanently discontinued. The 11 patients slotted to enroll on Arm C will now be treated per the Arm A or Arm B dose schedule. A total of 34 patients will be accrued between Arms A, B, and C. Accrual will continue per protocol in Arm D and three additional arms (Arms E, F, and G) will be added. A total of 26 evaluable patients (Arms D and G) or 25 evaluable patients (Arms E and F) will be accrued in each of the remaining arms. An additional 3 patients will be accrued in each arm to account for patients who need to be replaced. Therefore, the maximum overall sample size across all arms of the study is now 148 patients.

As of 22Jan2014 study is closed to enrollment with a total of 80 patients enrolled.

Accrual Rate and Study Duration: As of 22Jan2014, all arms have permanently discontinued accrual. The 11 patients slotted to enroll on Arm C will now be treated per the Arm A or Arm B dose schedule.

Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.2. Analysis Plan

For regulatory reporting purposes, the primary analysis will commerce 48 weeks after the last patient has been enrolled, and the final analysis after all patients have completed the study. Analysis of patients with blast-phase MF (Arm D) and those with MDS/MPN or MDS (Arm G) will be performed and presented separately.

16.3. Primary Outcome Analyses(to be evaluated in each arm independently)

Definition: The primary endpoint in each arm of this trial is the overall response rate. For Arms A, B, C, E, and F overall response is defined to be a CI, PR, or CR noted as the objective status according to the IWG-MRT consensus criteria for MF. Response in Arm G is defined as HI, PR or CR according to the IWG criteria for MDS (Cheson et al. 2006). Response in Arm D is defined by a durable (2 months or more) decrease in peripheral blood and bone marrow blast percentage to less than 5%. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response.

Estimation: The proportion of successes will be estimated in each arm by the number of successes divided by the total number of evaluable patients. Ninety-five percent Clopper-Pearson exact binomial confidence intervals for the true success proportion will be calculated.

16.4. Secondary Outcome Analyses (to Be Evaluated in Each Arm Independently)

16.4.1. Adverse Events

All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.4.2. Spleen Response

Spleen response is defined as either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at less than 10 cm but more than 5 cm at baseline becomes not palpable. Spleen size will be measured by physical examination (palpable distance from the left costal margin) at baseline and as part of each response assessment. The proportion of patients achieving spleen response per the IMG-MRT criteria (Section 11) will be calculated by the number of patients who achieve spleen response divided by the total number of evaluable patients with spleen involvement at baseline (estimated to be approximately 80% of patients). Same method will be applied to splenectomized patients for assessment of hepatomegaly response. Ninety-five percent Clopper-Pearson exact binomial confidence intervals for the true proportion of patients with spleen response will be calculated.

16.4.3. Transfusion-Independence

Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin level of less than 85 g/L that was not associated with clinically overt bleeding (see IWG-MRT criteria; Section 11). The proportion of patients achieving transfusion independence during the first 9 cycles of treatment will be estimated by the number of patients who achieve transfusion independence divided by the total number of evaluable patients who were transfusion dependent at baseline. Ninety-five percent Clopper-Pearson exact

binomial confidence intervals for the true proportion of patients who become transfusion independent will be calculated. The same statistical method will be applied to anemia response for Arms A, B, E and F per IWG-MRT for myelofibrosis (Tefferi et al. 2013) and erythroid response for Arm G per IWG response criteria for MDS (Cheson et al. 2006).

16.4.4. Durability of Response

Durability overall response will be estimated using the Kaplan-Meier method. Approximate 95% confidence intervals for median duration of response will be computed using the formula proposed by Brookmeyer and Crowley. The same method will be applied to hepatosplenic response and anemia response for Arms A, B, E, F, and D and erythroid response for Arm G.

16.5. Exploratory Outcomes (to Be Evaluated in Each Arm Independently)

Due to the small overall sample size, the results of the following analyses will be considered exploratory and hypothesis-generating in nature.

16.5.1. Bone Marrow Histology and JAK2V617F Allele Burden

Bone marrow fibrosis and granulocyte JAK2V617F allele burden will be assessed for all patients at baseline and at the time of the response bone marrow examination for patients who achieve a CR, PR, or CI for Arms A, B, C, E, and F, CR, PR, and HI for Arm G and for patients achieving durable (2 months or more) decrease in peripheral blood and bone marrow blast to less than 5% for Arm D. Bone marrow fibrosis grade will be evaluated by a central review pathologist and the fibrosis grade will be confirmed by the PI. The proportion of patients achieving reversal of bone marrow fibrosis to a lower grade will be assessed and reported descriptively. JAK2V617F allele burden will be summarized descriptively at each time point and changes over time will be evaluated.

16.5.2. Leukocytosis, Thrombocytosis, Peripheral Blood Blast and Immature Cell Count

The proportion of patients with baseline leukocytosis, thrombocytosis or increased peripheral blood blast or immature cell count, who achieve normalization or at least a 50% reduction in their counts will be calculated and reported descriptively

16.6. Over Accrual

If more than the target number of patients are accrued, the additional patients will be included in final endpoint estimates and confidence intervals.

16.7. Data and Safety Monitoring

A safety committee internal to Janssen Research & Development will review the safety data after approximately every 3 months until all patients have terminated from the study. The safety review committee will consist of a study responsible physician, safety physician and a

biostatistician. The findings of the safety committee will be shared with the study Investigator. The study responsible physician or safety physician may convene a meeting sooner should any concerns arise from review of data or from the Investigator.

In addition to the safety committee, an independent hepatic safety panel will review emergent relevant safety data, if needed. If there is evidence that imetelstat is responsible for the occurrence of a life-threatening, irreversible, or fatal hepatotoxicity a full investigation will be conducted on the data available for imetelstat treatment of patients with myelofibrosis. The investigation may include, but is not limited to, a benefit-risk analysis with external adjudication by the hepatic safety panel and other specialties as necessary. Trial modifications, including trial closure, will be considered based on the results of this investigation.

16.8. Adverse Event Stopping Rules (to Be Evaluated in Each Arm Independently)

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

- If 3 or more out of the first 10 treated patients experience Grade 4 non-hematological toxicities
- If after the first 10 patients have been treated, 30% of patients experience Grade 4 non-hematologic toxicities

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

16.9. Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to

exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3% of patients will be classified as minorities by race and about 50% of patients will be women. Expected sizes of racial by gender subsets are shown in Table 18 below.

Table 18: Expected Sizes of Racial by Gender Subsets

	Sex/Gender			
Ethnic Category	**Females**	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	73	73	0	146
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	74	74	0	**148**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	72	72	0	144
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	74	74	0	**148**

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17. PATHOLOGY CONSIDERATIONS/TISSUE BIOSPECIMENS

Central review of the bone marrow will be performed by Dr. [redacted] at the Mayo Clinic in Rochester, MN. Fibrosis grading and other histology changes will be documented.

17.1. Tissue and Biospecimen Submission

Table 19: Summary Table of Tissue Biospecimens for this Protocol

Type of Tissue Biospecimen to Submit	Mandatory or Optional	When to Submit	Reason for Submission
Initial Bone Marrow Biopsies	Mandatory	Patients who achieve a CR, PR, or CI in the core phase (Cycles 1-9)[1]: Submit with the response bone marrow biopsy Patients who do not achieve a CR, PR, or CI in the core phase (Cycles 1-9): Submit at the end of Cycle 9 or at the time of early discontinuation if patient receives < 9 cycles	Central review to evaluate extent of marrow involvement by myelofibrosis, bone marrow cellularity and percentage of blasts and ring sideroblasts
Response Bone Marrow Biopsies in patients who achieve a CR, PR, or CI during the core phase	Mandatory	≤30 days after response bone marrow biopsy	Central review to evaluate extent of marrow involvement by myelofibrosis, bone marrow cellularity and percentage of blasts and ring sideroblasts

[1] During the core phase 9 cycles, PR, or CI by the end of Cycle 9: Submit at the end of Cycle 9 or at the time of early discontinuation.

17.2. Initial and Response Evaluation Materials

Submit the following materials to Dr. [redacted]:

- 8-10 unstained and charged slides (or tissue block) from each bone marrow biopsy
- Bone Marrow Form for each bone marrow being submitted
- Baseline and Response Bone Marrow Biopsy Report

Slides should be placed in appropriate slide container(s) and labeled with the protocol number, study patient number, and patient initials.

The pathologist will forward the completed Bone Marrow Form and accompanying reports to the study QAS for scanning and data entry purposes to the following:

QAS for CP14B019 (formerly MC1285)
200 First Street SW
NW Clinic 3-24
Rochester, MN 55905
Phone: [redacted]

Refer to Test Schedule (Section 4). Data will be collected using an electronic data capture system (EDC) based upon pre-specified electronic case report forms (eCRFs) and completion guidelines (CCGs).

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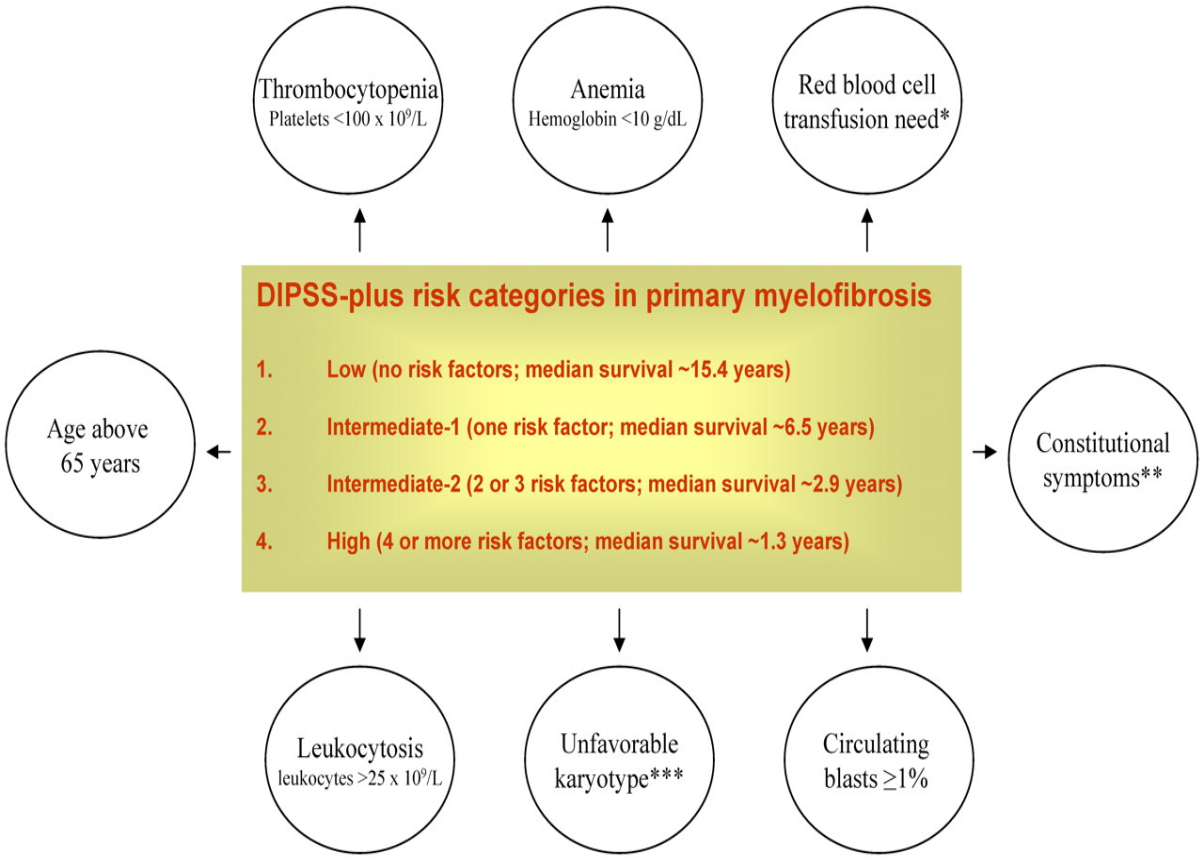
APPENDIX A. DIPSS-PLUS RISK CATEGORIES IN MYELOFIBROSIS.



The Dynamic International Prognostic Scoring System (DIPSS)-plus prognostic model for primary myelofibrosis (PMF). The DIPSS-plus prognostic model for PMF uses 8 risk factors to predict survival: age >65 years, hemoglobin level <10 g/dL, leukocyte count >25 × 109/L, circulating blasts ≥ 1%, presence of constitutional symptoms, presence of unfavorable karyotype, platelet count <100 × 109/L, and the presence of red cell transfusion need.

* Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin level of less than 85 g/L that was not associated with clinically overt bleeding. Please note that a transfusion-dependent patient automatically has 2 risk factors because of transfusion need (1 risk point) and hemoglobin level <10 g/dL (1 risk point).

** Constitutional symptoms constitute weight loss >10% of baseline value in the year preceding diagnosis, unexplained fever, or excessive sweats persisting for >1 month.

*** Unfavorable karyotype constitutes complex karyotype or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q− 12p−, or 11q23 rearrangement.

APPENDIX B. WORLD HEALTH ORGANIZATION (WHO) DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA, ESSENTIAL THROMBOCYTHEMIA AND PRIMARY MYELOFIBROSIS[3]

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 109/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 two 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 (i.e. pre-fibrotic PMF).

APPENDIX C. 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 (two 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 (two 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:[5] 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:[6] 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.

APPENDIX D. PERFORMANCE STATUS SCALE

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX E. ANAPHYLAXIS PRECAUTIONS

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use, as indicated per standard institutional practice
- Antihistamines
- Corticosteroids
- Bronchodilators, vasopressors, etc.
- Endotracheal tube and other resuscitation equipment
- IV infusion solutions, tubing, catheters, etc.

PROCEDURES

In the event of a suspected anaphylactic reaction during infusion, the following procedures should be performed:

1. Stop the infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway and monitor vital signs.
4. Administer antihistamines, epinephrine, or other medications such as bronchodilators, vasopressors, corticosteroids, etc. to manage patient symptomatically, as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations and manage symptomatically.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted] MD, PhD

Institution: Janssen Research & Development

Signature: [redacted] Date: 6 October 2015
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE