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

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Janssen Research & Development *

Statistical Analysis Plan

A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and other Myeloid Malignancies

Protocol CP14B019; Phase 2

JNJ-63935937 (Imetelstat)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Draft: June 30, 2017

ABBREVIATIONS

AE	Adverse Event
CI	Clinical Improvement
CR	Complete Remission
DIPSS	Dynamic International Prognostic Scoring System
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ET MF	Essential Thrombocythemia Myelofibrosis
HI	Hematological Improvement
IV	Intravenous
IWG-MRT	International Working Group for Myeloproliferative Neoplasms Research and Treatment
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPN	Myeloproliferative Neoplasm
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	Overall Survival
PMF	Primary Myelofibrosis
PR	Partial Remission
PV	Polycythemia Vera
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQs	Standardized MedDRA Queries
WBC	White Blood Cell

1. INTRODUCTION

This statistical analysis plan (SAP) is to lay out key analysis elements including definitions of analysis sets, derived variables, and statistical methods for the planned analyses for imetelstat (JNJ-63935937) Study CP14B019.

1.1. Trial Objectives

Primary Objective

To evaluate overall response rate in each of the six study arms (Arm A, B, D, E, F and G). The overall response rate for Arm C will be grouped with either A or B for analysis.

Response for Arms A, B, E, and F will be evaluated according to IWG-MRT criteria. For arm G, response will be according to the International Working Group response assessment as reported by Cheson et al. (2006). Response for Arm D will be defined by reduction in peripheral blood and bone marrow blast count to <5% and lasting for at least 2 months.

Secondary Objectives

- 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 subjects (per IWG-MRT criteria) in each arm.
- To evaluate onset and durability of response as defined in primary and secondary endpoints in each arm.

Exploratory Objectives

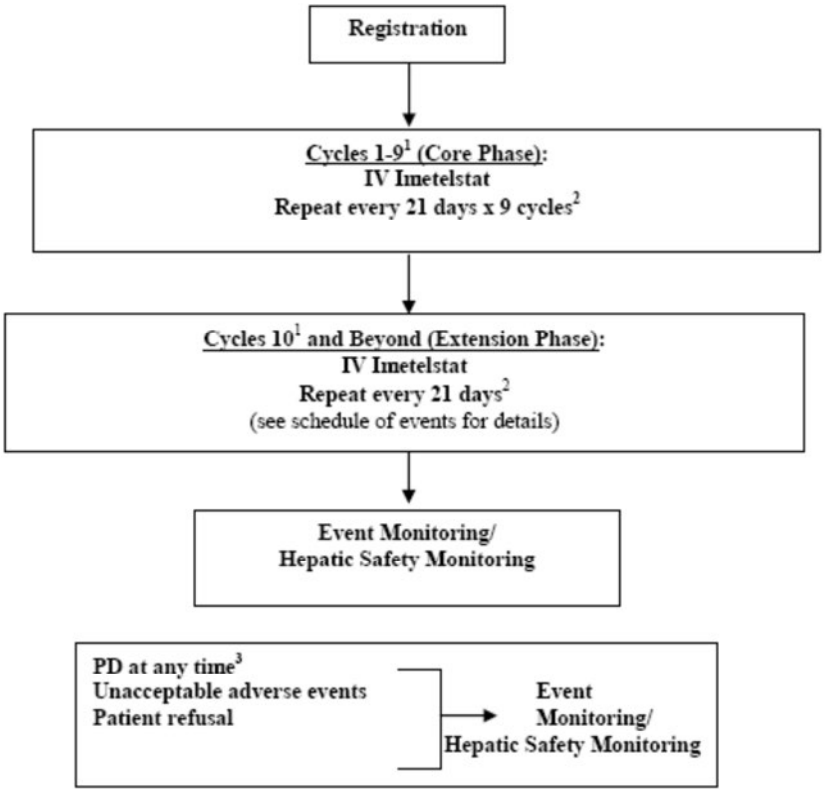
- To evaluate the effect of imetelstat on bone marrow histology, karyotype, and JAK2V617F allele burden in each arm.
- To evaluate the effect of imetelstat on leukocytosis, circulating blast count (blast % x WBC), circulating immature myeloid cell count (sum of blast, promyelocyte, myelocyte, and metamyelocyte % x WBC), and thrombocytosis in each arm.

1.2. Trial Design

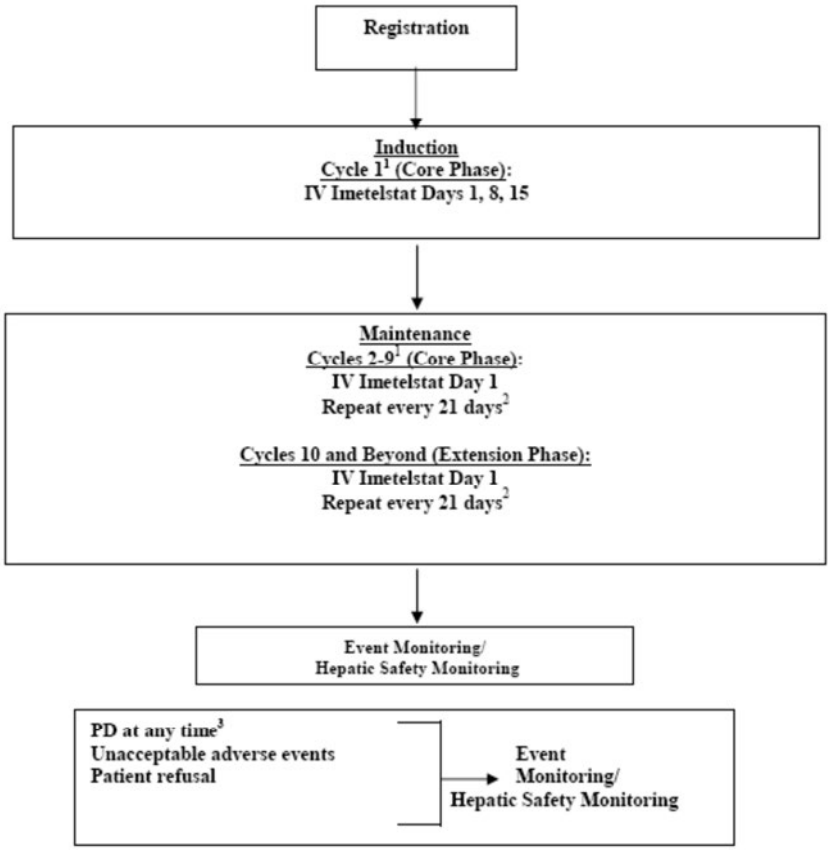
This was a single center, open-label study of imetelstat in subjects with Intermediate-2 or high risk PMF/post-ET/PV MF (Arms A, B, C, E and F) or blast-phase MF (Arm D only) or spliceosome-mutated (or with ring sideroblasts) MDS/MPN (Arm G only).

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

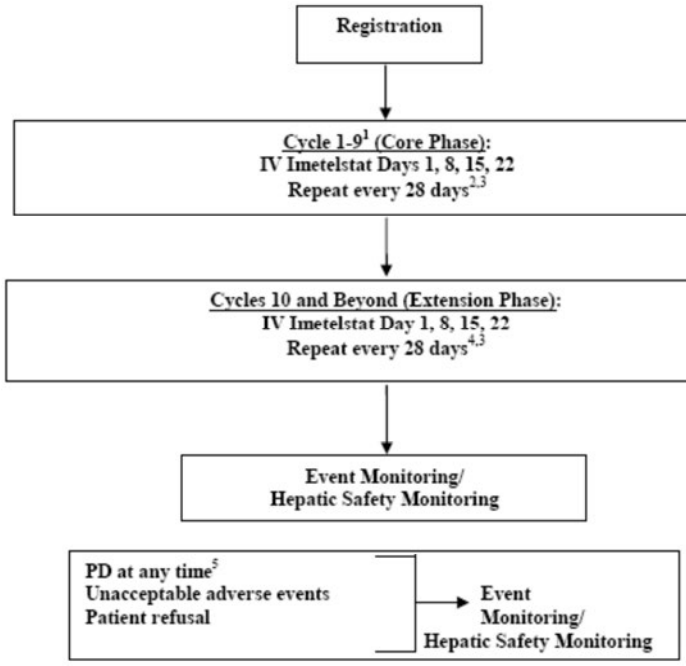
1.2.1. Arm A Treatment Schedule



1.2.2. Arm B Treatment Schedule

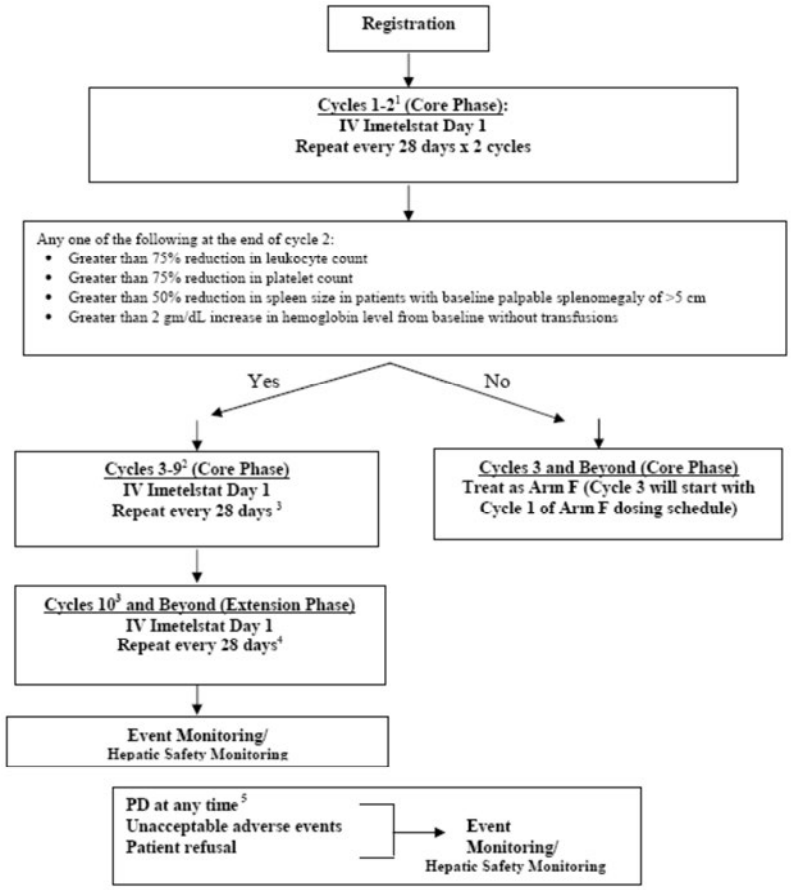


1.2.3. Arm C and D Treatment Schedule



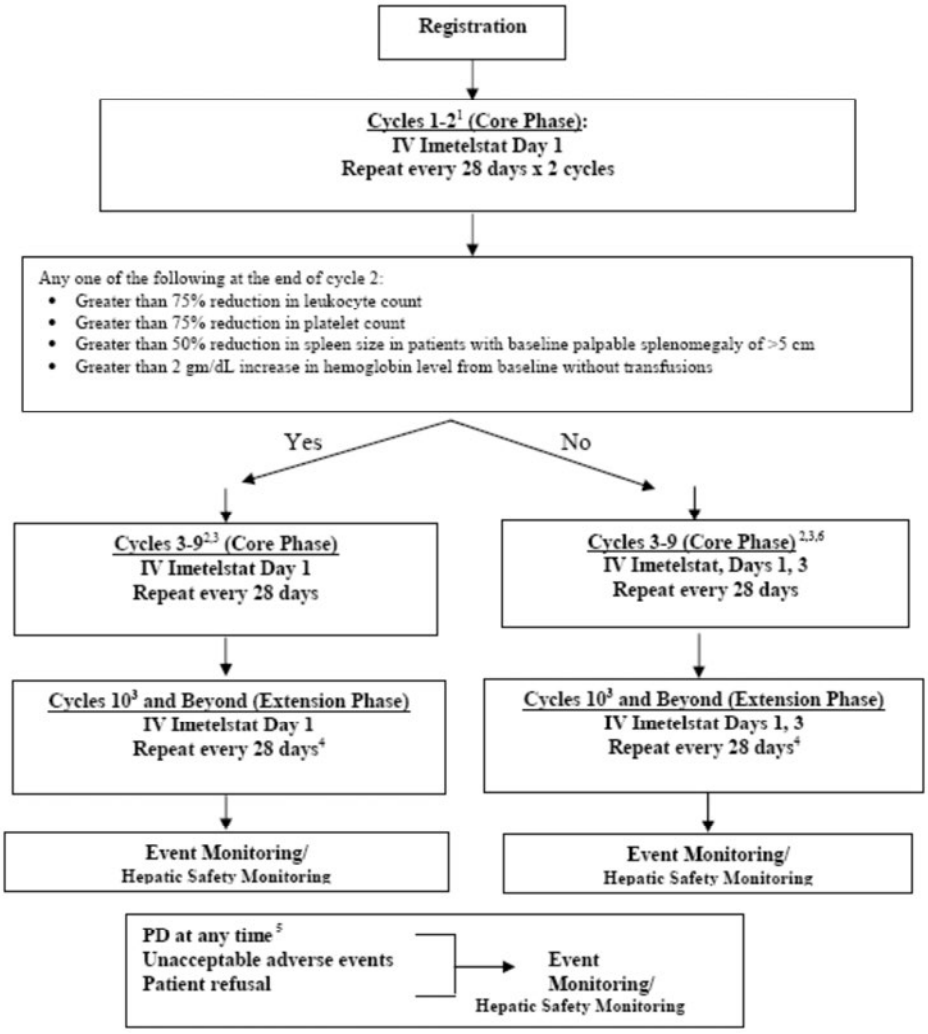
1.2.4. Arm E Treatment Schedule

(myelofibrosis subjects with spliceosome mutations or ring sideroblasts)



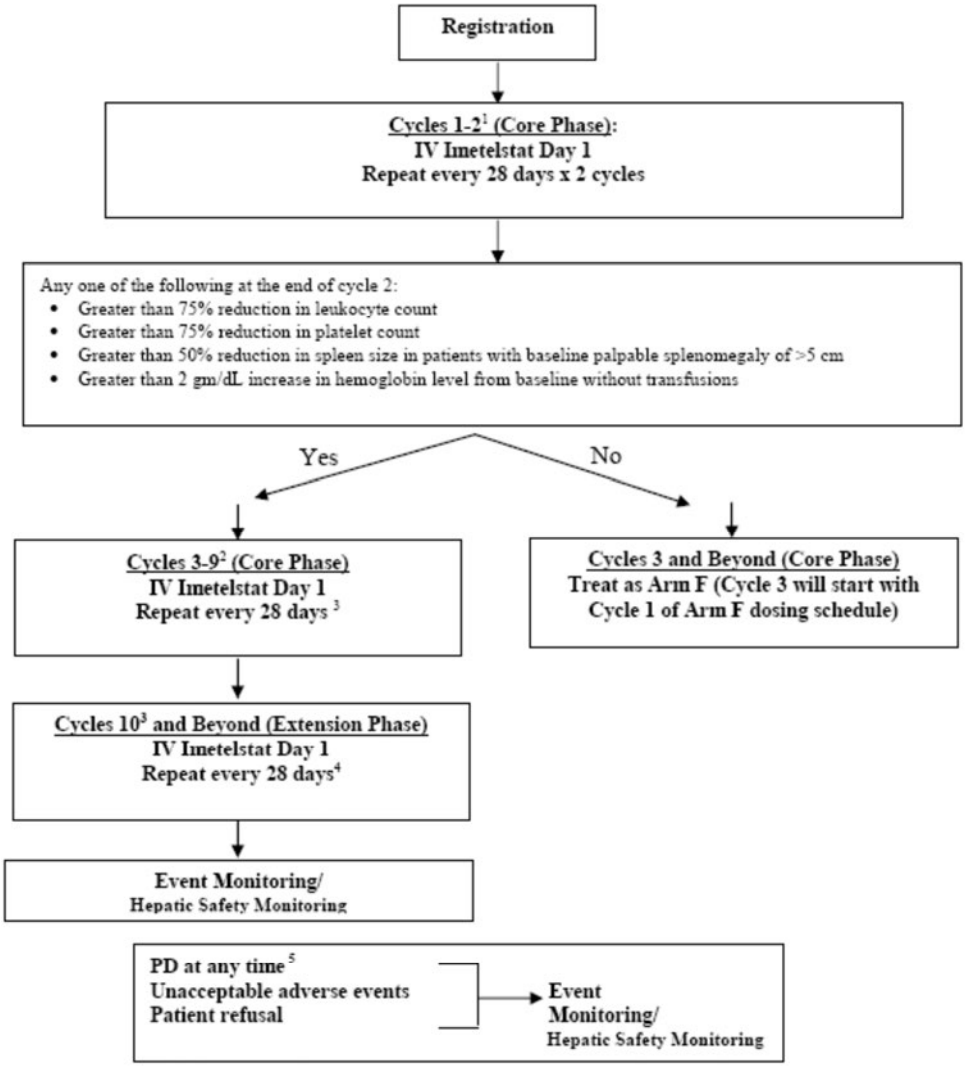
1.2.5. Arm F Treatment Schedule

(myelofibrosis subjects without spliceosome mutations or ring sideroblasts)



1.2.6. Arm G Treatment Schedule

(MDS/MPN or MDS subjects with spliceosome mutations or ring sideroblasts)


Registration
Cycles 1-2[1] (Core Phase):
IV Imetelstat Day 1
Repeat every 28 days x 2 cycles
Any one of the following at the end of cycle 2:
• 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
Yes
No
Cycles 3-9[2] (Core Phase)
IV Imetelstat Day 1
Repeat every 28 days [3]
Cycles 3 and Beyond (Core Phase)
Treat as Arm F (Cycle 3 will start with Cycle 1 of Arm F dosing schedule)
Cycles 10[3] and Beyond (Extension Phase)
IV Imetelstat Day 1
Repeat every 28 days[4]
Event Monitoring/
Hepatic Safety Monitoring
PD at any time [5]
Unacceptable adverse events
Patient refusal
Event
Monitoring/
Hepatic Safety Monitoring

1.3. Sample Size Justification

As a pilot study, the trial was not designed as a fixed sample size study. Instead, the probability of success or futility was estimated under the assumption of various response rates, and the number of subjects was adjusted based on the independent evaluation of each study arm during the trial.

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

As of 22 January 2014, the study was closed to enrollment with a total of 80 subjects enrolled.

2. GENERAL ANALYSIS DEFINITIONS

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median, and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries and for each study arm independently unless otherwise specified.

2.1. Baseline

Unless specified otherwise, the baseline value for each arm is defined as the last non-missing value collected on or before the administration of the first dose of study drug.

2.2. Study Day

Study Day 1 is defined as the day of the first dose of study drug that a subject received.

Study Day = assessment date – Study Day 1 + 1.

2.3. Missing and Partial Dates

In general, imputation of partial missing dates will be made for AE onset date, AE resolution date, date of death, start and end dates of concomitant therapy, and date of initial diagnosis.

For AE onset and resolution date, imputation rules listed below will be applied.

- Partial AE onset dates will be imputed as follows:
    - If the onset date of an adverse event is missing day only, it will be set to:
        - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose date
        - The day of first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different
        - The day of first dose date or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same

- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is after the first dose date
  - Month and day of the first dose date, if this date is the same year that the AE occurred
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

- Partial AE resolution dates not marked as ongoing will be imputed as follows:

  - If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
  - If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
  - Completely missing resolution dates will not be imputed.

For start and end dates of concomitant therapies, if the start or end date is completely missing, no imputation will be performed. If the start or end date is partially missing, the following imputation rules will be used.

- If only the day is missing, the 15th day of the month will be used.
- If both the day and month are missing, the 30th of June will be used.

If the medication/therapy was taken prior to study start, and the imputed start date is after first dosing date, further adjust the imputed start date as the day prior to first dosing date; if the medication/therapy was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date. Also adjust the imputed medication/therapy end date so that it is on or after first dosing date.

For date of death and date of initial diagnosis, the following rule will be applied.

- If date is completely missing, no imputation will be made.
- If year is missing, no imputation will be made.
- If only year is present but month and day are missing, then June 30th will be used.
- If only day is missing but year and month are available, then the 15th of the month will be used.

However, the above imputations will be modified by the following rules:

- If such imputed date for initial diagnosis is on or after study consent date, then consent date - 1 will be used.
- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date + 1 will be used.

2.4. Analysis Set

All Treated analysis set includes all subjects who received at least 1 dose of study drug and will be used for safety analyses unless otherwise specified.

Eligible analysis set is a subset of the all treated analysis set that excludes ineligible subjects who did not satisfy each and every eligibility criteria for study entry. Eligible analysis set will be used for efficacy analysis unless otherwise specified.

The 11 subjects slotted to enroll in Arm C but treated per the Arm A or Arm B dose schedule will be summarized with Arm A or Arm B subjects based on actual treatment received.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Demographics and disease characteristics data will be summarized for the all treated analysis set and the eligible analysis set, including sex, age (years), race, ethnicity, ECOG performance status, weight (kg), myelofibrosis subtype (primary, post ET, or post PV), DIPSS-Plus risk status, transfusion dependence, baseline laboratory values/categories, spleen and liver assessments.

The corresponding listing will also be provided.

3.2. Disposition Information

Number of subjects treated, discontinued from treatment/study, and reasons for discontinuation will be summarized by study arm for the all treated analysis set.

The corresponding listing will also be provided.

3.3. Extent of Exposure

A listing of subjects' exposure including study day, dose received, dose adjustment, corresponding reason, and other related information will be presented for all subjects in the all treated analysis set.

3.4. Protocol Deviations

A listing of subjects with major protocol deviations including cycle numbers and the type of deviation will be provided.

3.5. Prior and Concomitant Medications

Prior and concomitant medication information collected on eCRF will be listed separately for all subjects in the treated analysis set.

4. EFFICACY

4.1. Analysis Specifications

4.1.1. Level of Significance

All tests and 95% confidence intervals presented will be 2-sided.

4.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed.

4.2. Primary Efficacy Endpoint

4.2.1. Definition

The primary endpoint in each arm is the overall response rate. For Arms A, B, 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%. The primary outcome will be the percentage of responses observed in each arm in the eligible analysis set.

4.2.2. Analysis Methods

The number and percentage of responders in the eligible analysis set will be reported by each treatment arm along with 95% Clopper-Pearson exact binomial confidence intervals. Subjects' response status collected at each cycle will be listed.

4.3. Major Secondary Endpoints

4.3.1. Definition

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.

Transfusion Independence

Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month or a baseline hemoglobin level of less than 85 g/L that was not associated with clinically overt bleeding. For a transfusion dependent subject, transfusion independence is defined as he/she met either of the following conditions:

- Received no more than 1 unit of red blood cell transfusions in a rolling time interval of 30 days or more.
- Had a hemoglobin level increase over baseline more than 2g/dl if his/her baseline hemoglobin level was less than 85 g/L and received no transfusion.

Time to Response (TTR)

Time to response is defined as the duration from Study Day 1 to the earliest date that a response is first documented. For non-responders, it will be censored at the date of progressive disease/relapse or the date of the last adequate assessment, whichever comes first.

Duration of Response (DoR)

Duration of response is defined for responders as the interval from date of the initial documentation of a response to the date of first documented evidence of disease progression (or relapse for subjects who experience CR). For those subjects who are still without progression/relapse, DoR will be censored at the last adequate assessment.

Overall Survival (OS)

OS is defined as the interval from Study Day 1 to the date of death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up.

4.3.2. Analysis Methods

Subjects' status of spleen response and transfusion-independence will be listed for all eligible subjects.

Duration of 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 for OS.

4.3.3. Other Measurements Collected

Time to response, transfusion, bone marrow, physical exam, spleen/liver assessment, and ultrasound result will be listed separately.

5. SAFETY

Safety will be analyzed using the incidence and severity of adverse events and laboratory tests based on the all treated analysis set.

5.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of adverse events is assessed in National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) Version 4.0.

Treatment-emergent AEs will be defined as those events that 1) occur on or after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier; 2) any event that is considered study drug-related regardless of the start date of the event; or 3) any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator.

An overview summary table of treatment-emergent AEs will be provided, including drug related AEs, CTCAE grade $\geq$ 3 AEs, serious AEs, and deaths.

Treatment-emergent AEs will be summarized by system organ class and preferred terms. For each treatment-emergent adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by frequency in incidence (the highest to lowest incidence) in the total column. The same summary will be provided for the treatment-emergent AEs with CTCAE grade $\geq$3, treatment-emergent AEs considered related to study treatment, and serious treatment-emergent AEs.

A summary of the number of subjects who discontinued study treatment because of 1 or more AEs by system organ class and preferred term will be provided. This table includes AEs leading to discontinuation of study treatment for those subjects indicated as having discontinued study treatment due to an adverse event on the end of treatment eCRF page.

Treatment-emergent bleeding events will be identified using standardized MedDRA queries (SMQs) by matching the event terms in SMQ "HAEMORRHAGES" and the first SMQ subcategory "HAEMORRHAGE TERM (EXCL LABORATORY TERMS)." The number of subjects with treatment-emergent bleeding events will be summarized for each treatment arm.

A listing of all adverse events will be provided.

5.2. Death

A summary of all deaths and cause of death will be tabulated by treatment arm. Specifically, the number of subjects who died during the study will be summarized for the all treated population. The primary cause of death collected on eCRF page will be reported.

A listing of death information will be provided.

5.3. Clinical Laboratory Tests

The evaluation of clinical laboratory tests will focus on the following selected laboratory analytes or events:

- Maximum post baseline CTCAE grade of hematological toxicity (anemia, leukemia, neutropenia, thrombocytopenia)
- Maximum post baseline CTCAE grade related to liver function test (ALT, AST, alkaline phosphatase, total bilirubin)
- Incidence of persistent (≥4 weeks) and severe (grade ≥3) cytopenia (thrombocytopenia/neutropenia)

The above analyses will be tabulated by treatment arm.

In addition, descriptive statistics (mean, SD, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each treatment arm.

Shift tables for each cycle will be produced as number of subjects with each baseline CTCAE grade and changes to the maximum CTCAE grade by analyte. Shift tables from baseline to worst value on treatment will also be provided.

All the lab data collected (hematology, chemistry, coagulation, urinalysis, and other lab tests) will be listed.

5.4. Other Safety Tests

ECOG performance status, physical exam and infusion reaction will be listed separately by cycle.

REFERENCES

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore SD, Schiffer CA, Kantarjian H. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108(2):419-25.