Cell Therapeutics, Inc.

PERSIST-2 Protocol

PAC326

Pacritinib

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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Sponsor:
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Investigator Responsibilities, Required Documentation, and Signature

Cell Therapeutics, Inc. will select the investigator(s) on the basis of their expertise in the field of clinical studies in hematologic oncology and in the care and treatment of patients with chronic myeloproliferative diseases. Investigators will also be selected on the appropriateness of their facility to conduct a research study of this nature, and the characteristics of the patient population treated at the institution. The investigator will:

- Obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol and amendments to the protocol and Informed Consent Form before initiation of the protocol or any amendments for the study, and obtain annual IRB or IEC renewal, as required.
- Ensure that current FDA and/or ICH-E6 regulations are followed.
- Select all patients in accordance with the selection criteria outlined in the study protocol.
- Treat and follow patients as described in this research protocol. Complete all electronic case report forms (eCRFs) in a timely manner and review eCRFs for accuracy and completeness. Provide the original clinical source documents to verify all data entered on eCRFs or SAE reports and all data that document the course of the patient throughout their participation on the study. Provide a clinical summary to the sponsor's clinical research monitor.
- Report all adverse events to Cell Therapeutics, Inc., or designee, as required by the protocol.
- Ensure that the investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing information is recorded and all drug can be accounted for at all times.
- Before initiation of the study, each participating investigator will submit to CTI:
  - FDA Form 1572 and, if applicable, other ministry of health required forms
  - Copies of the medical licenses of principal investigators and subinvestigators
  - Addresses and descriptions of all clinical laboratory facilities to be used
  - Laboratory certification and expiration dates
  - Normal ranges and effective dates for all required laboratory tests
  - IRB/IEC approval letter referencing the protocol (and amendments, if applicable).
  - IRB/IEC Membership List: A list of the IRB/EC members, their respective titles or occupations, and their institutional affiliations.
  - A sample copy of the IRB/IEC-approved Informed Consent Form
  - Curricula vitae: Curricula vitae for the principal investigator and all subinvestigators
  - Financial disclosure for the principal investigator and all subinvestigators
  - Protocol signature page, signed by the principal investigator

Investigator Statement and Signature:

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

_____

Principal Investigator Signature Date

_____

Principal Investigator Name, Printed Date

Protocol Synopsis

Study Title	A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis
Protocol Number	PAC326
Version	Original
Sponsor	Cell Therapeutics, Inc.
Clinical Phase	Phase 3

Objectives

Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arms(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan and the proportion of patients achieving a ≥ 50% reduction in total symptom score (TSS) from baseline to Week 24 as measured by the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

Secondary Objectives

The secondary objectives are:

1 To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2 To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1 Overall survival (OS)
2 Progression-free survival (PFS)
3 Leukemia-free survival (LFS)
4 Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥ 35% reduction in spleen volume from baseline
6 Best response in spleen volume by MRI or CT scan
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)

9 Achievement of reduced RBC transfusion dependence (Appendix 1a)
10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4).

Pharmacokinetic and Pharmacodynamic Objectives
The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on the safety and efficacy of pacritinib.

Study Design

This study is a multicenter, randomized, controlled, phase 3 study. It will compare the efficacy and safety of two dose schedules of pacritinib in pooled and individual group analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter. The analysis of the primary outcome of spleen response will be performed when all randomized patients have completed the Week 24 MRI or CT evaluation, met progressive disease criteria, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

Number of Centers

Approximately 100 centers is planned to enroll patients over an estimated period of 11 months.

Number of Patients

The study will randomize approximately 300 patients, with approximately one-third of patients randomized to pacritinib dosed QD, one-third to pacritinib dosed BID, and one-third to BAT.

Randomization

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT. Randomization will be stratified by geographic region (US versus Canada versus Europe versus rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. The most recent platelet count obtained prior to randomization on Days -3 to 1 will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pretransfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification.

Diagnosis and Inclusion Criteria

1. Intermediate-1, intermediate -2, or high-risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤ 100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the lower costal margin (LCM) in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 × ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)

15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study
17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcome instrument
19. Able to understand and willing to sign the Informed Consent Form

Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
4. More than 6 months of cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplant (ASCT), or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion, with the approval of the medical monitor, if the arrhythmias are stable, asymptomatic, and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450ms, or other factors that increase the risk for QT interval prolongation (eg, heart failure, hypokalemia [defined as serum potassium <3.0mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

Study Drug, Dose, and Mode of Administration

Patients taking pacritinib will be supplied with 100-mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally once a day at the same time of day, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib orally twice each day at the same times of day, with or without food.

Duration of Study Treatment, Continuation of Treatment, and Crossover to Pacritinib

Each patient is to receive pacritinib or BAT until progression of disease (defined in the Study Treatment and Follow-up synopsis section), the occurrence of unacceptable toxicity, or the patient no longer derives benefit from treatment.

Patients on BAT may cross over to pacritinib at the time of splenic progression (defined in the Study Treatment and Follow-up synopsis section), at any time after splenic progression (if leukemic transformation, splenectomy, and splenic irradiation have not occurred), or after completing 24 weeks of treatment, with or without progression. When it is decided that a patient will crossover from BAT to pacritinib treatment, the investigator will also specify the patient's pacritinib dose schedule (QD or BID); this dose schedule will not be changed again for the duration of study treatment. Patients may continue on active (drug) study treatment after progression of disease (see Study Treatment and Follow-up synopsis section).

Patients who crossover from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT. Spleen size at the time of crossover will be the new baseline for subsequent determination of progression.

Patients on BAT who have splenic progression, but do not wish to crossover to pacritinib, will be followed for safety, survival, and leukemic transformation; they will not be followed for splenic progression, as long as they continue the BAT treatment they were taking at the time of progression. Patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will not be followed for safety, but will be followed for leukemic transformation and survival.

Patients on pacritinib may continue pacritinib treatment with an unchanged dose schedule after splenic progression, if they are still deriving benefit from treatment and not experiencing excessive drug toxicity. Patients on pacritinib who have splenic progression, but wish to continue taking pacritinib will be followed for spleen volume, safety, survival, and leukemic transformation (but not for splenic progression) until they discontinue taking pacritinib.

Study Treatment and Follow-up

Progression of Disease
A patient may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced and both should be reported.

***Progression of disease* is defined as one or more of the following:**

- Splenic progression, defined as an increase in splenic volume of ≥ 25% from baseline, based on

centrally read MRI or CT scan

- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥ 20%, sustained for ≥ 8 weeks
  - Bone marrow blast count ≥ 20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Criteria for Treatment Continuation After Progression of Disease
To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥ 25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF

Criteria for Crossover from BAT to Pacritinib Treatment
To crossover from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

A patient who crosses over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment.

If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT scan must be completed within 30 days prior to the start of pacritinib treatment. This scan serves as a new baseline spleen volume; the patient will be followed for a second, post-crossover event of splenic progression relative to the new baseline measurement.

Study Assessments
All patients will be followed for response, splenic and leukemic progression, survival, and other endpoints according to **Table--1** the Study Assessments Calendar.

Special Cases - Modifications to Study Assessments Calendar
Patients crossing over from BAT to pacritinib based on the criteria for crossover (described in this

section) will follow the Study Assessments Calendar, starting at *Start of Week 1 (BL)*, except that no PK or PD assessments will be performed.

Patients who continue an active BAT despite splenic progression will be followed per the Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT scan. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in the Study Assessments Calendar if they opt to not crossover to pacritinib.

Patients who continue pacritinib despite splenic progression will continue to be followed per the Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in the Study Assessments Calendar.

Patients who discontinue pacritinib, but have not progressed, will continue to be followed per the Study Assessments Calendar until progression occurs. After progression, these patients will be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

Patients who undergo splenic irradiation or splenectomy or initiate any non-protocol-directed anti-MF treatment will subsequently be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

All patients will be followed per the Study Assessments Calendar for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

Evaluation

Efficacy

Spleen Volume Assessment by MRI or CT - Spleen volume measurement by MRI or CT will be performed at screening and every 12 weeks thereafter, until progression of disease or withdrawal from study. MRI is the preferred modality; CT will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Imaging for spleen volume assessment may be performed at other time points, if progressive disease is suspected by palpation or as indicated by the treating physician. All scans should be submitted for central reading. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement.

Spleen Size Assessment by Physical Examination - Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

Disease-Related Signs and Symptoms - The MPN-SAF TSS 2.0 will be completed daily for 7 to 10 consecutive days prior to starting treatment and then daily through Week 48 of the study, as long as the patient is receiving study treatment. The pain medication log will be completed daily as long as the MPN-SAF TSS 2.0 is being completed. The patient global impression assessment will be completed every 8 weeks through Week 24, and then every 12 weeks, until the MPN-SAF TSS 2.0 is discontinued.

Survival - Patients will be followed for survival and for transformation to acute myeloid leukemia (as assessed by the investigator, investigator-obtained records, or, if these are not available, by patient-provided history) until 3 years after the first of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

Quality-of-Life Assessments - The EQ-5D-5L and EORTC-QLQ-C30 will be completed at baseline, every 8 weeks for the first 24 weeks, and then every 12 weeks during study treatment.

Patients will also be followed for frequencies of RBC and platelet transfusions, and other exploratory endpoints.

Safety

Adverse Events - AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. SAEs that the investigator or Sponsor considers related to study drug or study procedure shall be followed until the event resolves, stabilizes or the patient is lost to follow-up, whichever occurs first. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

Hematology - Hematology parameters (complete blood count [CBC] with differential and platelet count) will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final hematology testing will be performed at treatment termination. In addition, unscheduled CBC with differential and platelet counts may be performed locally and/or centrally, when clinically indicated.

Blood Chemistry - Blood chemistry parameters to be evaluated include alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.

These parameters will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final chemistry testing will be performed at treatment termination. In addition, unscheduled chemistries may be performed locally and/or centrally, when clinically indicated.

ECG Assessment - For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening; within 1 hour prior to dosing; at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3; and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening; at baseline; on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing); and as clinically indicated. Local ECG readings will be used throughout the study.

Gastrointestinal Toxicity Management - Patients will be evaluated at baseline to assess usual bowel habits and will be instructed on the need for early intervention for possible GI side effects of treatment. At the baseline visit, all patients will be provided with a prescription for an antidiarrheal drug and instructed to start taking it as soon as diarrhea is noted. The investigator or a surrogate will contact each patient by telephone during Week 1 (Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to

pacritinib) and at the beginning of Week 3 of initial treatment or after crossover to pacritinib to evaluate GI toxicity and assess the need for modifying the treatment for GI side effects. Standard supportive care measures should be provided to control symptoms of GI toxicity, such as diarrhea, constipation, nausea and vomiting.

Ruxolitinib Dose Management - Patients on BAT who are being treated with ruxolitinib or other approved JAK2 inhibitors must be dosed according to current local labeling recommendations.

Pharmacokinetic-Pharmacodynamic Assessments

Pharmacokinetics and Pharmacodynamics – PK samples without PD sampling will be collected from approximately 130 patients taking pacritinib at the Week 12 and Week 24 visit days (predose [Hour 0]).

In addition to assessment of pacritinib plasma concentrations, STAT3 phosphorylation (an established pharmacodynamic marker for JAK-STAT signaling pathway inhibition) will be assessed. PK/PD samples for assessment of exposure-response will be collected from the remaining approximately 70 patients taking pacritinib at a prespecified subset of clinical sites at Day 1 of Week 1 (predose [Hour 0] and 4 hours postdose; only a PD sample will be collected at the predose time point), Day 1 of Week 3 (predose [Hour 0] and at 4 hours postdose), and at Week 12 and Week 24 visit days (predose [Hour 0]). The resulting data will be used to assess exposure, and exposure-safety and exposure-efficacy relationships.

JAK2 Mutation Status - *JAK2V617F* mutation burden will be assessed by a central laboratory in all patients at screening, then at Week 12, and every 12 weeks thereafter in patients who have the mutation.

Statistical Methods

The study has two primary endpoints: the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by MRI or CT scan, and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

The primary hypotheses of the study are to compare the pacritinib arms QD and BID (pooled) versus BAT arm for the two primary endpoints. The study will be claimed to be successful when both endpoints reach statistical significance ($p \leq 0.05$) individually.

The secondary hypotheses are to compare QD vs BAT and BID vs BAT, separately at a significance level of 0.025, on spleen reduction and TSS reduction, the two primary endpoints.

The Fisher Exact test will be used to evaluate both endpoints. Patients who meet the criteria for disease progression or drop out of the study before Week 24 will be considered non-responders.

A total of 300 patients is planned to be randomized (1:1:1) in the study. This sample size provides at least 95% power on the primary hypotheses (QD+BID vs BAT) for both endpoints individually (at an α-level of 0.05, 2-sided), and at least 93% power for each secondary hypothesis (QD vs. BAT; BID vs. BAT) independently (at an α-level of 0.025, 2-sided).

No interim analysis is planned.

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
Patients who continue an active BAT despite splenic progression will follow this calendar, except for discontinuation of Spleen Volume by MRI or CT. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in this calendar.
Patients who continue pacritinib despite splenic progression will continue to follow this Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in this calendar.
Patients who discontinue pacritinib, but have not progressed will continue to follow this Study Assessments Calendar until progression occurs, and then will follow the *Survival-Only Follow-up* column in this calendar. Note: patients who have stopped taking pacritinib must complete a termination visit within 7 days of stopping the drug.
Patients who undergo splenic irradiation, splenectomy, or who initiate any non-protocol-directed anti-myelofibrosis treatment will subsequently be followed per the *Survival-Only Follow-up* follow-up column in this calendar.

Week	**Con-sent and Platelet Eligibil-ity**	**Screen**[2]	**Symptom Assessment & Screening MRI Visit**	**Random-ization** (patient need not be present)	**Start of Wk 1 (BL)**[3]	**Wk 1**[4]	**Start of Wk 2**[5]	**Start of Wk 3**	**End of Wk 4**	**End of Wk 8**	**End of Wk 12**[6]	**End of Wk 16**	**End of Wk 20**	**End of Wk 24**	**End of Wk 36 & q12w**	**Term**[7]	**30 d Post-Term**	**Survival-only** (Off Treatment) Follow-up
Day	-35 to -7	-14 to -5	-10 to -4	-3 to 1	1	4	8	15	28	56	84	112	140	168	252			q 6 mo
Window (+/- d):						1	3	3	3	3	7	7	7	7	7	7	3	30
Informed consent[25]	x	x																
Platelet count[1]	x			x														
Medical history		x																
Vital signs[8]		x			x		x	x	x	x	x	x	x	x	x	x		
Physical exam, including spleen measurement[9]		x			x		x	x	x	x	x	x	x	x	x	x		
GI assessment[4]		x			x	x		x										
12-lead ECG[10]		x			x		x	x										
ECOG performance status		x			x		x	x	x	x	x	x	x	x	x	x		
Hematology[11]		x		x	x			x	x	x	x	x	x	x	x	x		
Chemistry[12]		x			x			x	x	x	x	x	x	x	x	x		
Serum pregnancy test[24]		x									x			x	x			
Spleen volume by MRI or CT[13]			x								x			x	x	x		
Daily patient-reported symptoms: MPN-SAF TSS 2.0 Begin recording after receiving eDiary[14]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Daily pain medication log[15]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
Patients who continue an active BAT despite splenic progression will follow this calendar, except for discontinuation of Spleen Volume by MRI or CT. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in this calendar.
Patients who continue pacritinib despite splenic progression will continue to follow this Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in this calendar.
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Patient global impression assessment[16]										x		x		x	x	x		
Quality of life assessments; EORTC-QLQ-C30 EQ-5D-5L					x					x		x		x	x	x		
Pharmacokinetic (PK) assessment[17]					x			x			x			x				
Pharmacodynamic(PD) assessment[18]					x			x			x			x				
JAK2 mutation burden[19]		x									x			x	x			
Bone marrow biopsy[22]		x												x				
Distribute pacritinib					x				x	x	x	x	x	x	x			
Begin pacritinib dosing					x													
Perform pacritinib accountability[23]					x				x	x	x	x	x	x	x	x		
Toxicity assessments/AEs[20]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Record BAT treatments					x	x	x	x	x	x	x	x	x	x	x	x		
Transfusion history (RBC and platelet)		x			x	x	x	x	x	x	x	x	x	x	x	x		
Leukemic Transformation		x			x			x	x	x	x	x	x	x	x	x		x
Survival Only Follow-up (phone)[21]																		x

Table--1
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Abbreviations:																		
AEs = adverse events			BAT = best available therapy			BL=baseline								BUN = blood urea nitrogen				
CBC = complete blood count			CRF = case report form			CT = computed tomography								d = day(s); ECG = electrocardiogram				
ECOG = Eastern Cooperative Oncology Group			eCRF = electronic case report form			GI = gastrointestinal								LDH = lactate dehydrogenase				
MRI = magnetic resonance imaging			PD = pharmacodynamic(s)			PET-MF = post-essential thrombocythemia myelofibrosis								PK = pharmacokinetic(s)				
PMF = primary myelofibrosis			PPV-MF = post-polycythemia vera myelofibrosis			RBC = red blood cell(s)								Term=study treatment termination visit				
Wk = Week																		

1 Eligibility platelet count may be obtained at any time between Days -35 and -7 prior to randomization. Platelet count obtained during the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value should be used for platelet rebound stratification determination. If more than one such nadir count is obtained prior to randomization, the count obtained closest to randomization will be used for stratification. If patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion performed before randomization.

2 Screening procedures must be completed between Days -14 and -5, before treatment initiation. Clinical laboratory tests collected at screening must be performed at least 7 days after any prior therapy for PMF, PPV-MF, or PET-MF.

3 Day 1 assessments are required to be performed prior to initiation of study treatment. The baseline visit should also be conducted for patients on BAT who have documented disease progression and are planning to cross over to pacritinib if they meet the criteria for continuation or crossover. For these patients, the termination and baseline visits may be combined (all termination procedures plus locally obtained 12-lead ECG and pharmacodynamic assessment). Patients who cross over to pacritinib after Week 24 must complete an MRI within 30 days of starting pacritinib. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any change in frequency or consistency of bowel movements after starting study treatment.

4 The site will contact all patients by telephone on Day 4 ± 1 day to assess the need for modifying supportive treatment of any GI side effects. Patients will also be assessed at the beginning of Week 3 and throughout the study for GI safety.

5 The study visits at Weeks 2, 3, 4, and 8 have a scheduling window of ± 3 d; however, all procedures other than MRI or CT should be performed on the same day's visit.

6 The study visits at Weeks 12 and beyond have a scheduling window of ± 7 d; however, all procedures other than MRI or CT should be performed on the same day's visit.

7 The treatment termination visit is scheduled within 7 d after completing or terminating each study treatment arm. A final visit to assess events is scheduled 30 ± 3 d after the last study treatment day. If termination takes place at a regularly scheduled visit, these procedures may be performed at that time. Patients on BAT who have documented progression of disease and are planning to cross over to pacritinib must complete all baseline procedures except PK and PD procedures (all termination procedures plus local 12-lead ECG and central pharmacodynamic assessment) and record this information on the crossover Week 1 visit CRF. The spleen size at the end of BAT will serve as the new baseline for the patient. For patients on BAT who cross over to pacritinib after Week 24, spleen imaging must be performed within 30 days prior to starting pacritinib, and the spleen size at that time will serve as the new baseline.

8 Vital signs include blood pressure, pulse, respiratory rate, temperature, and body weight.

9 Height should be measured only on Day 1. Measurement of spleen by physical examination will be performed during screening, at baseline, and at each visit until study termination.

10 For patients assigned to pacritinib or those who have crossed over to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours post dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2 and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study. QTc interval prolongation identified on automated ECG calculations that is ≥grade 1 should be manually recalculated using the same method for any given patient. The manual recalculation should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.

11 Hematology: CBC, differential count, and platelet count. The most recent hematology evaluation obtained prior to randomization must be used to stratify the patient by baseline DIPSS risk category. Screening hematology assessments used to identify strata for randomization may be performed by local laboratories, but screening samples will also be sent for central laboratory evaluation.

12 Eligibility may be based on local laboratory values. Central blood chemistry values will include: ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect) creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.

13 Spleen volume by MRI or CT will be reviewed centrally by an independent radiology facility. The screening MRI or CT must be performed prior to randomization between Days -10 to -4. Imaging should be performed without

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contrast agents. MRI or CT will be performed at the end of Week 12 ± 7 d and every 12 weeks thereafter, and at the termination of treatment. For each patient, the same imaging modality should be used throughout the study. Unscheduled imaging studies may be performed at the physician's discretion, if he/she considers disease-related symptoms to be worsening. Splenic progression will be followed for patients who discontinue treatment, but have not progressed. Patients with progressive disease documented prior to Week 24 who opt to continue on study treatment will not undergo Week 24 imaging if the date of progression is at or later than Week 20. For patients who cross over after Week 24, an MRI must be performed within 30 days prior to the start of pacritinib treatment.

14 Daily patient-reported disease-related symptoms assessed after receiving an eDiary and throughout treatment. Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment and daily through Week 48 of the study, as long as the patient is receiving study treatment.

15 Patients will complete the pain medication log daily while reporting symptoms on the MPN-SAF TSS 2.0.

16 Patient global impression assessment will be done every 8 weeks through Week 24, and then every 12 weeks thereafter until the daily MPN-SAF TSS 2.0 is discontinued.

17 Five PK samples from patients in the pacritinib arm(s) will be collected from approximately 70 patients at a prespecified subset of clinical sites. Blood samples will be collected postdose (Hour 4) on Day 1, Week 1, predose (Hour 0) and postdose (Hour 4) on Day 1, Week 3 and predose (Hour 0) on the visit day of Weeks 12 and 24. Two PK samples will be collected from approximately 130 patients taking pacritinib at the remaining sites predose (Hour 0) on the visit day of Week 12 and Week 24.

18 PD assessment for patients in the pacritinib arm will be collected from patients at a prespecified subset of of clinical sites. Blood samples will be collected predose (Hour 0) and postdose (Hour 4) on Day 1 of Weeks 1 and 3 and predose (Hour 0) on the visit day of Weeks 12 and 24.

19 Samples for central analysis of *JAK2* mutation burden will be collected at screening, Week 12, and every 12 weeks thereafter in patients who have the mutation.

20 Toxicity assessments/AEs: Patients will be evaluated from the time of signing the Informed Consent Form through 30 d after the last study treatment. However, each SAE assessed as related to study treatment or study procedures will be collected through the patient's last day of study participation the event will be followed until it is resolved, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever occurs first.

21 Survival-only follow-up for each patient will continue for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

22 Bone marrow biopsy must be obtained within 24 weeks prior to randomization and may be obtained any time before Day -3. Bone marrow biopsy will also be performed at Week 24. Patients who discontinue study treatment prior to Week 24 do not need another bone marrow biopsy.

23 At time of dispensing, the lot number for capsules dispensed and the number of capsules in bottle(s) should be recorded. Instruct patient to bring bottle to every visit. When a patient returns one or more bottles, count the remaining capsules in all bottle(s).

24 All women of child-bearing potential must have a pregnancy test at screening. Additional pregnancy tests every 12 weeks while on study treatment may be mandated as a country-specific requirement.

25 Informed consent must be obtained before any study-specific washout. This may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and standard MF treatments), or 7 days (potent CYP 3A4 inhibitors). Patients not requiring washout may sign the Informed Consent Form at any time prior to screening procedures.

Abbreviations	
Abbreviation	**Full Term**
AE	adverse event
ALT	alanine aminotransferase (syn: see SGPT)
AML	acute myeloblastic leukemia (or acute myeloid leukemia)
ANC	absolute neutrophil count
ASCT	allogeneic stem cell transplantation
AST	aspartate aminotransferase (syn: see SGOT)
BAT	best available treatment
bid	twice daily
BL	baseline
BUN	blood urea nitrogen
CBC	complete blood count
CI	clinical improvement
CMH	Cochran-Mantel-Haenszel
CR	complete remission or complete response
CRF(s)	case report form(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
d	day, days
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESA	erythropoiesis-stimulating agent
ET	essential thrombocythemia
FDA	Food and Drug Administration
FLT3	fms-like receptor tyrosine kinase 3
GCP	Good Clinical Practice
GI	gastrointestinal
h	hour, hours
HIV	human immunodeficiency virus
IC_{50}	50% inhibitory concentration

Abbreviations	
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Us
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
IRF	independent radiology facility
ITT	intent-to-treat
IWG	International Working Group
JAK2	Janus kinase 2
L	liter(s)
LCM	lower costal margin
LDH	lactate dehydrogenase
LFS	leukemia-free survival
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent(s)
mo	month(s)
MPD	myeloproliferative disease
MPN-SAF TSS 2.0	Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0
MRI	magnetic resonance imaging
ms	millisecond(s)
MTD	maximum tolerated dose
NCI	National Cancer Institute
nM	nanomolar
NYHA	New York Heart Association
OS	overall survival
^{32}P	phosphorus-32
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PFS	progression-free survival
PK	pharmacokinetic(s)
po	per os, oral(ly)
PMF	primary myelofibrosis

Abbreviations	
PPV-MF	post-polycythemia vera myelofibrosis
PV	polycythemia vera
qd	daily
QTc	corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
ROC	receiver operating characteristic curve
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic-oxaloacetic transaminase (syn: see AST)
SGPT	serum glutamic pyruvic transaminase (syn: see ALT)
STAT	signal transducers and activators of transcription
T_{max}	time of maximum concentration
ULN	upper limit of normal
uMPD	unclassifiable myeloproliferative disease
wk	week, weeks

1 Background Information

1.1 JAK2 in Hematologic Malignancies

The Janus kinases (JAK) are a family of cytoplasmic tyrosine kinases consisting of JAK1, JAK2, JAK3, and TYK2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones, and growth factors. Their intracellular substrates include the signal transducer and activator of transcription (STAT) family of proteins. The JAK/STAT pathways, through the proper actions of the ligands, regulate important physiological processes, such as the immune response to viruses, hematopoiesis, lactation, and lipid homeostasis. However, dysfunctional signaling caused by a myriad of factors results in pathological conditions, such as allergies, asthma, rheumatoid arthritis, severe combined immune deficiency, and hematological malignancies. In particular, mutations in the *JAK2* gene have been associated with myeloproliferative disorders (MPDs), including polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF).

The incidence of the *JAK2V617F* mutation, as determined by allele-specific polymerase chain reaction in granulocytes from patients with MPDs, occurs in 35% to 50% of patients with primary MF (PMF), 32% to 57% of patients with ET, and 74% to 97% of patients with PV. This mutation, however, can also be found on rare occasions in patients with other chronic myeloid diseases, including myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative diseases (MDS/MPD), and unclassifiable MPD (uMPD). There is strong evidence that the *JAK2* mutation (and corresponding continuously active JAK2 tyrosine kinases) significantly contributes to the existence and progression of the disease. Its inhibition thus presents a suitable target for drug development. Even in patients without *JAK2* mutation, the JAK/STAT pathway may be deregulated, and these patients may also benefit from JAK2 inhibitor therapy.

1.2 Myelofibrosis

1.2.1 Clinical Presentation and Disease-related Symptoms

Myelofibrosis may present as either a primary myeloproliferative disorder or follow a diagnosis of PV or ET. Regardless of the original diagnosis, PMF, PPV-MF, and PET-MF have a common pathophysiological profile, characterized by elevated numbers of CD34-positive cells in the marrow in the early phase of the disease, followed in the later phases by marrow fibrosis, with decreasing numbers of CD34 cells in the marrow and a corresponding increase in splenic and liver engorgement by CD34 cells.

PMF, PPV-MF and PET-MF usually present with a white blood cell (WBC) count < 30,000/mm^3, prominent teardrops on peripheral smear, normocellular or hypocellular marrow with moderate to marked fibrosis, an absence of the Philadelphia chromosome or the BCR-ABL translocation, and frequent positivity for the *JAK2* mutation (Campbell et al 2006). In addition to the clonal proliferation of a multipotent hematopoietic progenitor cell, an event common to all chronic MPDs, these disorders are characterized by colonization of extramedullary sites, such as the spleen or liver (Barosi 1999, Tefferi 2000).

About 70% of patients with MF are symptomatic at presentation. The main physical findings are splenomegaly and hepatomegaly. Other symptoms include those secondary to a hypercatabolic state (fever, weight loss, and night sweats) and peripheral blood abnormalities (fatigue and dyspnea resulting from anemia and bleeding, and petechiae resulting from thrombocytopenia and/or abnormal platelet function). Gout and renal stones secondary to hyperuricemia are also common [4] (Ahmed et al, 2006). Other clinical manifestations of the disease include thromboembolic episodes, hemorrhage, splenic pain, early satiety, anemia, and bone pain.

PMF, PPV-MF, and PET-MF have similar types and distributions of bone marrow cytogenetic abnormalities (Tefferi, Mesa et al 2001), and they are known to harbor a common mutant allele, *JAK2V617F* (James et al 2005).

Transformation from PV to PPV-MF significantly worsens survival. *JAK2* mutations are almost always present in patients with PV and PPV-MF. Common clinical and laboratory findings in PPV-MF include a hyperproliferative bone marrow, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) Grade 2 to 3 marrow fibrosis, anemia, splenomegaly, and constitutional symptoms (Passamonti et al 2008).

Diagnostic tools for PMF, PPV-MF, and PET-MF include complete blood count (CBC), bone marrow aspiration and biopsy, cytogenetic analysis, peripheral blood smear analysis for teardrop-shaped RBCs, the number and kinds of WBCs, platelet count, and the presence of blast cells.

1.2.2 Current Strategies for Treating PMF, PPV-MF, and PET-MF

Currently, as no therapeutic strategy has been efficacious at reducing overall mortality, medical therapy for PMF, PPV-MF, and PET-MF is administered with supportive intent. Treatment is aimed at improving quality of life through palliation of symptoms and control of peripheral blood counts (Arana-Yi et al 2006). Therapeutic interventions usually are used only in symptomatic patients with MF, since asymptomatic patients demonstrate prolonged survival (Barosi 1999, Dupriez et al 1996).

At present, allogeneic stem cell transplantation (ASCT) is the only available method for altering the natural history of PMF, PPV-MF, or PET-MF (Passamonti et al 2008, Rondelli et al 2005). ASCT can completely reverse the fibrosis in bone marrow (Ni et al 2005) and restore normal hematopoiesis. However, while ASCT is potentially curative for patients with PMF, PPV-MF, and PET-MF, this form of treatment is largely limited to young patients with negligible comorbidities (Arana-Yi et al 2006). The International Working Group – Myelofibrosis Research and Treatment considers it "…reasonable to recommend ASCT for high- or intermediate-risk 2 patients" (Cervantes et al 2009). Thus far, no therapy has proven effective in prolonging overall survival (OS) in PMF, PPV-MF, or PET-MF (Arana-Yi et al 2006).

Current treatment approaches are aimed at mitigating specific disease symptoms, such as anemia. Transfusion therapy is the core strategy for treatment of disease-related anemia, and it is also used to manage thrombocytopenia. Long-term RBC transfusion therapy should be accompanied by oral iron chelation therapy to avoid long-term consequences of iron overload. Disease-associated anemia occasionally responds to erythropoietin, hydroxyurea, cladribine, thalidomide, lenalidomide, or interferon treatment (Ahmed et al 2006). These and other agents have been used to correct cytopenias, halt the progression of splenomegaly, or reduce the size of a site of extramedullary hematopoiesis in patients with PMF, PPV-MF, and PET-MF.

Danazol, a synthetic attenuated anabolic steroid with androgenic activity, has been used to treat anemia in PMF, PPV-MF, and PET-MF. Erythropoietin has been administered to patients with these diseases for palliation of constitutional symptoms and anemia (Arana-Yi et al 2006). The use of interferon-α can result in hematologic responses, including reduction in spleen size, but many patients do not tolerate this medication (Sacchi 1995, Gilbert 1998). Antiangiogenic and immunomodulatory drugs, such as thalidomide and lenalidomide, have shown activity in patients with MF (Gilbert 1998, Barosi et al 2002, Marchetti et al 2004, Tefferi, Cortes et al 2006, Mesa et al 2004, Strupp et al 2004), but they are not routinely used for the indications proposed in this study of pacritinib.

Other antiangiogenic agents, such as vatalanib and sorafenib, have been studied in PMF, PPV-MF, and PET-MF, but the data are not promising. Etanercept has been evaluated, but it was not superior to the combination of thalidomide and prednisone (Arana-Yi et al 2006).

The use of signal transduction inhibitors, such as imatinib, have resulted in an increase in the number of clonogenic megakaryocytic progenitors in bone marrow, suggesting they may be an effective treatment for thrombocytopenia in patients with MF (le Bousse-Kerdiles et al 2005).

For patients with PMF, PPV-MF, or PET-MF who have painful splenomegaly and no other treatment options, splenectomy may be performed. The decision to perform splenectomy involves weighing the benefits (long-term improvement in symptomatic splenomegaly, anemia, portal hypertension, and severe thrombocytopenia in 30% to 70% of patients) versus the risks (10% postoperative mortality, and 30% postoperative morbidity caused by infection, bleeding, or thrombosis; additionally, some investigators have reported accelerated progression to blast crisis).

1.2.3 Targeted Therapy for Myeloproliferative Disease

In 2011, JAK 1/2 inhibitor ruxolitinib received approval in the United States for the treatment of patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF based on the COMFORT I and II randomized controlled trials showing that treatment with ruxolitinib decreased spleen size and symptom score (Verstovsek et al 2012; Harrison et al 2012). Entry criteria for both studies was limited to patients with platelet counts >100,000/μL. The median platelet counts at entry for the two studies were 262,000/μL and 244,000/μL, respectively.

Ruxolitinib causes significant dose-related thrombocytopenia, and the dose must be adjusted in patients with platelet counts < 200,000/μL. In patients taking ruxolitinib who develop a platelet count < 50,000/μL, withholding all dosing is recommended until the platelet count recovers to 50,000/μL. In clinical trials, patients taking ruxolitinib who had pretreatment platelet counts between 100,000/μL and 200,000/μL had a higher frequency of grade 3 or 4 thrombocytopenia (16.7%) than patients with higher initial platelet counts (7.2%).

The incidence of thrombocytopenia (all grades) during randomized treatment in COMFORT I was 69.7% in the ruxolitinib arm compared with 30.5% in the placebo arm. The dose of ruxolitinib was adjusted downward for patients with platelet counts <100,000/μL and withheld for those with platelet counts <50,000/μL. In COMFORT II, protocol-specified dose modifications for thrombocytopenia were more frequent in the ruxolitinib arm than the best available therapy arm (41% vs. 1%).

Median time to recovery of platelet counts to above 50,000/μL was 14 days in patients requiring interruption of treatment due to thrombocytopenia (Jakafi label).

1.3 Pacritinib

Pacritinib is a novel JAK2/FLT3 inhibitor that has demonstrated promising antitumor activity in two mouse models of human malignancies. Preclinical toxicology studies have identified a safe starting dose for clinical trials. The potential indications that may be targeted include: (i) PV, ET, and MF, all of which are MPDs with a high frequency of a *JAK2V617F* mutation; (ii) certain leukemias and lymphomas where other forms of JAK aberrations have been reported; and (iii) acute myeloid leukemia (AML), in which FLT3 inhibitors have shown preliminary clinical promise.

1.3.1 Pharmacology

Pacritinib is a potent, selective inhibitor of JAK2 and FLT3 kinase activities (IC_{50} = 23 nM and 22 nM, respectively), as well as JAK2V617F mutant kinase activity (IC_{50} = 19 nM). Pacritinib is also a potent inhibitor of cellular proliferation in human leukemia and lymphoma cell lines selected for their dependence on the target kinases (cellular IC_{50} ranges from 0.03 to 0.24 μM). Consistent with these activities, exposure to pacritinib resulted in the reduction of phospho-JAK2, phospho-STAT3, or phospho-STAT5 in the relevant cell lines.

The therapeutic effects of pacritinib were assessed in an orthotopic model of MPD induced with Ba/F3-JAK2V617F cells. Pacritinib treatment at 150 mg/kg po bid significantly ameliorated symptoms, with 60% normalization of spleen weight and 92% normalization of liver weight. It was also very well tolerated.

1.3.2 Pharmacokinetics in Animals

PK following single intravenous or oral administration of pacritinib was evaluated in mice, rats, and dogs. Following oral administration, pacritinib showed rapid absorption in mice (T_{max} from 0.5 to 1.3 hours) and moderately fast absorption in rats and dogs (T_{max} ~ 4 hours). The oral terminal half-lives were 2.2, 5.7 and 4.4 h in mice, rats, and dogs respectively. As measured by liver blood flow, the systemic clearance of pacritinib from plasma was high in mice (8 L/h/kg) and dogs (1.6 L/h/kg) and moderate in rats (1.6 L/h/kg). The i.v. terminal half-lives were 5.6, 6, and 4.6 hours in mice, rats, and dogs, respectively. The oral bioavailability of pacritinib was 39% in mice, 10% in rats, and 24% in dogs.

1.3.3 Preclinical Toxicology

The adverse effects of pacritinib were evaluated in 30-day repeated oral dose toxicity studies with 14-day recovery in both mice and dogs, and in 26- and 39-week chronic toxicity studies in mice and dogs, respectively. Key findings included dose-dependent leukopenia accompanied by neutropenia (dog) and neutrophilia (mice) that partially reversed during recovery. Mice also showed dose-dependent but reversible thrombocytosis and anemia. In the chronic toxicity studies, low-magnitude decreases in neutrophils and red blood cell parameters were observed. No treatment-related hepatic changes were observed with the exception of increased AST (to +109%, male dogs) and increased triglycerides (to +57%, male and female dogs).

In the 30-day study in dogs, animals receiving mid and high doses of pacritinib experienced vomiting and diarrhea that increased in severity despite treatment with antiemetic and antidiarrheal medication. Similarly, in the 39-week study in dogs, an increased incidence of nausea and vomiting was observed at doses of 20 mg/kg/day and higher. Periods of low food consumption in individual animals receiving 40 and 50 mg/kg/day were accompanied by rapid weight loss (which was controlled and reversed with subcutaneous fluid and supplemental food) and were considered treatment related and adverse.

Based on these studies, the no observed adverse effect level was determined to be 100 mg/kg bid in mice and 10 mg/kg bid in dogs.

1.3.4 Summary of Clinical Pharmacology and Phase I Studies with Healthy Volunteers with Pacritinib

To date, CTI has completed two PK studies for pacritinib in healthy volunteers, including a food-effect study (SB1518-2010-006) characterizing the effects of a high calorie, high fat meal on the bioavailability and PK of pacritinib and a study assessing inter- and intra-individual variability of oral pacritinib in

healthy volunteers under fasted conditions at 100 mg, 200 mg and 400 mg doses (SB1518-2010-004). In addition, the single and multiple dose population PK of pacritinib has been characterized following multiple dose administration of pacritinib in two trials (SB1518-2007-001 and SB1518-2008-003) in patients with advanced myeloid malignancies.

After administration of single doses of pacritinib in a randomized, three-treatment, three-period crossover study in healthy volunteers under fasting conditions in study SB1518-2010-004, peak plasma concentrations were reached at a median T_{max} ranging from 4.5 h to 5.5 hours across the 100-400 mg dose range. While between-subject variability was relatively high (28-45%), the within-subject variability was low (13-15%), highlighting the consistent systemic exposure for pacritinib in individual subjects. The mean elimination half-life was approximately 34 hours and was not dependent on dose. The systemic exposure of pacritinib is healthy volunteers was comparable to that in patients. After oral administration of single 200-mg doses (2×100 mg capsules) of pacritinib under fed and fasted conditions in study SB1518-2010-006, the 90% confidence intervals for the geometric mean ratios (fed to fasted) for C_{max}, AUC_{0-t}, and AUC_{inf} were between 80% and 125%, demonstrating lack of an effect of food on absorption. Given this data, pacritinib can be orally administered without regard to timing of meals.

Pooled analyses of PK assessments from the two completed clinical trials in patients at pacritinib dose levels up to 600 mg QD showed slow absorption (T_{max} 4-6 hrs) and dose-related increases in systemic exposure up to 400 mg QD. Beyond the 400 mg QD dose level, there was minimal increase in exposure with doses up to 600 mg QD suggesting involvement of a saturable process in oral absorption of pacritinib. In addition, the results demonstrated a prolonged elimination half-life (mean Day 1 $t_{1/2}$ = 47 hrs), supporting a QD regimen of pacritinib in clinical development. Comparison of systemic exposure of pacritinib on Days 1 and 15 showed a 1.5- to 2-fold increase in systemic exposure at steady-state.

Pacritinib is not a PgP substrate at clinical exposure levels. While in vitro metabolism studies suggest that pacritinib is a potential substrate for CYP3A4 isozyme, the results of a mouse mass balance ADME study demonstrate that pacritinib is overwhelmingly eliminated by biliary excretion with minimal involvement of metabolism or renal excretion in the systemic clearance of pacritinib. Overall, the preclinical in vitro and in vivo data suggest limited liability of pacritinib in metabolic and PgP-related drug interactions.

At a pacritinib 100 mg QD regimen, mean steady-state plasma levels of pacritinib exceeded the in vitro IC_{50} values for inhibition of targeted kinases (JAK2/FLT3) and inhibition of whole cell proliferation (BaF3-JAK2 and MV4-11 cells). Pacritinib potently inhibited the proliferation of only a few tumor cell lines at submicromolar concentrations, consistent with its target selectivity. The most sensitive cell lines were either JAK2-dependent or mutant FLT3-dependent, including murine 32D (IC_{50} = 160 nM), human Karpas 1106P (IC_{50} = 240 nM), and mutant FLT3-dependent MV4-11 cells (IC_{50} = 32 nM). In a study using ex vivo expanded erythroid progenitors (EPs) treated with pacritinib, phos-STAT5 levels were inhibited in a dose-dependent manner (IC_{50} < 200 nM) and reduced the viability of expanded EPs from both normal volunteers with JAK2wt (IC_{50} = 260 nM) and PV patients with JAK2V617F (IC_{50} = 230 nM), with no significant differences observed between arms. Moreover, pacritinib treatment had no effect on the JAK2V617F allele frequency in EPs from PV patients, indicating similar drug sensitivity for EPs from the same patient, regardless of the presence of JAK2 mutation. A study to assess the effects of pacritinib on intracellular JAK2 signaling showed that phos-STAT3 was reduced in a dose-dependent manner in both Karpas 1106P and 32D cells.

1.3.5 Overview of Clinical Studies of Pacritinib in Patients with Myelofibrosis

Patients with MF have been studied in two clinical trials of pacritinib. Both phase 1/2 trials included dose-finding PK portions and safety and efficacy portions. SB1518-2007-001 enrolled patients with advanced myeloid malignancies, and SB1518-2008-003 enrolled patients with chronic idiopathic MF.

1.3.6 SB1518-2007-001: Phase 1/2 Study in Patients with Advanced Myeloid Malignancies

1.3.6.1 Phase 1

During the phase 1 portion of SB1518-2007-001, cohorts of 3 to 6 patients with advanced myeloid malignancies were enrolled into one of a series of escalating doses of pacritinib, ranging from 100 to 600 mg/day. Treatment was administered orally once a day for 28 d (defined as one cycle). Preliminary data were presented in 2009 (Verstovsek et al 2009).

Dose-limiting toxicities (DLTs) included grade 3 QTc prolongation in 1 patient with AML taking 150 mg and grade 3 diarrhea in 1 patient at 300 mg. At the 600-mg dose level, 1 patient reported grade 3 GI toxicity and 1 patient reported grade 2 blurred vision, dizziness, and unsteady gait. No DLTs were reported at 400 mg or 500 mg. Thus, the 500 mg dose level was determined to be the maximum tolerated dose (MTD).

Diarrhea and general GI toxicities, the most common toxicities that affected dosing, often resulted in dose interruption and dose reduction. On the basis of the safety and efficacy observations during long-term dosing, 400 mg/day was chosen as the recommended dose for the phase 2 study. The most commonly reported treatment-emergent events (> 20%) were diarrhea, nausea, vomiting, constipation, dyspnea, fatigue, and peripheral edema. Most events were mild to moderate in severity. Grade 3 or greater anemia and thrombocytopenia were each reported in 16% of patients and were the only events of grade 3 or higher severity that occurred in more than 10% of patients. Sixteen of the 43 patients (37%) had grade 3 (25,000 – 50,000/μL) or grade 4 (< 25,000/μL) thrombocytopenia at baseline.

Of the 36 patients with MF enrolled in the phase 1 portion, 25 had baseline splenomegaly ≥ 5 cm below the left costal margin. Eighteen of these 25 patients had at least 25% reduction in spleen size; these 18 patients included 6 patients whose spleens became nonpalpable.

PK analysis showed that pacritinib was rapidly absorbed, with T_{max} ranging from 3 to 5 hours. The estimated terminal half-life was 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations, measured by inhibition of STAT3 and STAT5 phosphorylation, were achieved at the starting dose of 100 mg/day.

1.3.6.2 Phase 2

The primary objective of this portion of the study was to assess spleen response rate as measured by the change in spleen volume between baseline, Day 1 of Cycle 4, and Day 1 of Cycle 7. Response was defined as a decrease of at least 35% in MRI-determined spleen volume any time between baseline and Week 24. Secondary objectives included spleen response by physical examination, duration of spleen response, safety, and tolerability.

Thirty-one patients were enrolled and received at least one dose of study drug (Table--2). Of these 31 patients, 13 had a history of either PV (11 patients) or ET (2 patients). Twenty-seven patients had received prior treatment for MF, and all had baseline splenomegaly that measured at least 5 cm below the LCM.

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
Age (yr)	
N	31
Mean (SD)	65.4 (8.62)
Median	67
25 - 75 percentile	60 - 72
Range	47 - 83
Gender	
N	31
Female	9 (29%)
Male	22 (71%)
Race	
N	31
American Indian or Alaska Native	0
Asian	0
Black or African American	1 (3%)
Native Hawaiian or Other Pacific Islander	0
White	30 (97%)
Other	0
Time Since Last Cancer Treatment (mo)	
N	31
Mean (SD)	121.1 (241.40)
Median	2
25 - 75 percentile	1 - 30
Range	1 - 606
ECOG Performance Status	
N	31
0	6 (19%)
1	17 (55%)
2	8 (26%)
>2	0
JAK 2 Mutation	

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
N	31
No	6 (19%)
Yes	25 (81%)
Type of JAK 2 Mutation	
N	25
V617F	25 (100%)
Other	0
FLT 3 Mutation	
N	23
No	23 (100%)
Yes	0
Baseline Hemoglobin (g/dL)	
N	31
Mean (SD)	9.845 (2.6000)
Median	9.000
25 - 75 percentile	8.10 - 11.80
Range	3.70 - 14.40
Baseline Platelet Count ($10^3/\mu L$)	
N	31
Mean (SD)	172.61 (130.924)
Median	126.00
25 - 75 percentile	62.0 - 260.0
Range	28.0 - 494.0
Baseline Platelet Count Category N(%)	
N	31
<50,000/μL	4 (12.9)
50,000 – 100,000/μL	9 (29.0)
≥100,000/μL	18 (58.1)
Baseline WBC ($10^3/\mu L$)	
N	31
Mean (SD)	12.180 (9.2365)
Median	8.910

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
25 - 75 percentile	4.40 - 18.00
Range	1.50 - 38.20
Baseline Absolute Neutrophil Count ($10^3/\mu L$)	
N	31
Mean (SD)	8.86 (6.989)
Median	6.98
25 - 75 percentile	3.0 - 13.3
Range	0.9 - 29.4

Source: Table 2 (t02_demog 2012-02-29), Table 14 (t14_hema 2012-02-29), Table 1 (t_base_platelet_ph2_myel).
Abbreviations:
µL = microliter(s) ECOG = Eastern Cooperative Oncology Group FLT3 = fms-like receptor tyrosine kinase 3
g/dL = gram(s) per deciliter JAK2 = Janus kinase 2 N = number
SD = standard deviation WBC = white blood cell(s) yr = year(s).

Reasons for study drug discontinuation were lack of response (8 patients), disease progression (4 patients), withdrawal of consent (3 patients), adverse event (2 patients), and death (2 patients).

The most common treatment emergent adverse events (AEs) were diarrhea (90%), fatigue (58%), nausea (52%), and vomiting (35%). Most of these AEs were mild to moderate in severity (Table--3). Grade 3 AEs reported by more than one patient were anaemia (10%), thrombocytopenia (6%), cardiac failure congestive (10%), diarrhea (16%), abdominal pain (10%), fatigue (13%), pneumonia (6%), hypokalaemia (6%), and bone pain (13%). Grade 4 AEs were anemia (6%), thrombocytopenia (3%), pancytopenia (3%) fatigue (3%), hyperuricemia (6%), failure to thrive (3%), hyperglycaemia (3%), pain in extremity (3%), and muscular weakness (3%). Two serious adverse events (SAEs) were thought to be possibly related to treatment: grade 3 diarrhea in 1 patient and grade 3 dehydration in another. Both resolved without sequelae. No treatment-related deaths occurred and no SAE was reported in more than one patient.

Table--3 Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001						
SOC/Preferred Term	**Phase II (N = 31)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Subjects with any Event	2 (6%)	7 (23%)	12 (39%)	6 (19%)	4 (13%)	31 (100%)
Blood and Lymphatic System Disorders	0	0	6 (19%)	3 (10%)	0	9 (29%)
Anaemia	0	1 (3%)	3 (10%)	2 (6%)	0	6 (19%)
Thrombocytopenia	0	0	2 (6%)	1 (3%)	0	3 (10%)
Cardiac Disorders						
Cardiac failure congestive	0	0	3 (10%)	0	0	3 (10%)
Gastrointestinal Disorders	9 (29%)	9 (29%)	13 (42%)	0	0	31 (100%)
Diarrhoea	14 (45%)	9 (29%)	5 (16%)	0	0	28 (90%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nausea	9 (29%)	6 (19%)	1 (3%)	0	0	16 (52%)
Vomiting	7 (23%)	3 (10%)	1 (3%)	0	0	11 (35%)
Abdominal pain	3 (10%)	3 (10%)	3 (10%)	0	0	9 (29%)
Constipation	5 (16%)	0	0	0	0	5 (16%)
Abdominal pain upper	2 (6%)	0	1 (3%)	0	0	3 (10%)
Ascites	0	2 (6%)	1 (3%)	0	0	3 (10%)
General Disorders and Administration Site Conditions	6 (19%)	13 (42%)	5 (16%)	1 (3%)	0	25 (81%)
Fatigue	2 (6%)	11 (35%)	4 (13%)	1 (3%)	0	18 (58%)
Oedema peripheral	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Asthenia	4 (13%)	1 (3%)	0	0	0	5 (16%)
Pyrexia	4 (13%)	0	0	0	0	4 (13%)
Chills	2 (6%)	1 (3%)	0	0	0	3 (10%)
Infections and Infestations	1 (3%)	4 (13%)	7 (23%)	0	1 (3%)	13 (42%)
Upper respiratory tract infection	2 (6%)	1 (3%)	0	0	0	3 (10%)
Urinary tract infection	0	2 (6%)	1 (3%)	0	0	3 (10%)
Investigations	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Cardiac murmur	0	4 (13%)	0	0	0	4 (13%)
Weight decreased	4 (13%)	0	0	0	0	4 (13%)
Metabolism and Nutrition Disorders	5 (16%)	2 (6%)	3 (10%)	2 (6%)	1 (3%)	13 (42%)
Hyperuricaemia	2 (6%)	0	0	2 (6%)	0	4 (13%)
Hyperkalaemia	2 (6%)	1 (3%)	0	0	0	3 (10%)
Hypoalbuminaemia	1 (3%)	2 (6%)	0	0	0	3 (10%)
Hypokalaemia	1 (3%)	0	2 (6%)	0	0	3 (10%)
Musculoskeletal and Connective Tissue Disorders	7 (23%)	5 (16%)	4 (13%)	2 (6%)	0	18 (58%)
Bone pain	1 (3%)	1 (3%)	4 (13%)	0	0	6 (19%)
Pain in extremity	3 (10%)	2 (6%)	0	1 (3%)	0	6 (19%)
Back pain	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Muscle spasms	3 (10%)	0	0	0	0	3 (10%)
Nervous System Disorders	5 (16%)	2 (6%)	1 (3%)	0	0	8 (26%)
Neuropathy peripheral	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Psychiatric Disorders	6 (19%)	5 (16%)	1 (3%)	0	0	12 (39%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Insomnia	7 (23%)	2 (6%)	0	0	0	9 (29%)
Respiratory, Thoracic and Mediastinal Disorders	9 (29%)	1 (3%)	5 (16%)	0	0	15 (48%)
Dyspnoea	4 (13%)	0	1 (3%)	0	0	5 (16%)
Cough	3 (10%)	0	0	0	0	3 (10%)
Dyspnoea exertional	3 (10%)	0	0	0	0	3 (10%)
Skin and Subcutaneous Disorders	10 (32%)	10 (32%)	2 (6%)	0	0	22 (71%)
Pruritus	4 (13%)	4 (13%)	1 (3%)	0	0	9 (29%)
Night sweats	4 (13%)	3 (10%)	0	0	0	7 (23%)
Rash	2 (6%)	1 (3%)	1 (3%)	0	0	4 (13%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations: N = number; SOC = system organ class.

Grade 4 thrombocytopenia was reported in 1 patient (923), a 59-year-old male with a prior diagnosis of PV. His baseline platelet count was 30,000/μL (grade 3) and his on-study nadir was 22,000/μL (grade 4). Associated splenic volume change was -20%.

Grade 3 thrombocytopenia was reported in 2 patients (907 and 916). Patient 907, a 76-year-old male with a prior diagnosis of PV, had a baseline platelet count of 59,000/ μL (grade 2) and an on-study nadir of 41,000/μL (grade 3). Associated splenic volume change was -26%. Patient 916, a 71-year-old male, had a baseline platelet count of 58,000/ μL (grade 2) and an on-study nadir of 54,000/μL (grade 2). Associated splenic volume change was -35%.

Among the 3 patients reporting grade 3 anemia, 2 had grade 2 anemia and one had grade 4 anemia at baseline. Both of the 2 patients reporting grade 4 anemia had grade 3 anemia at baseline.

Myelosuppression has been uncommon, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with normal platelet counts and those with baseline thrombocytopenia have tolerated pacritinib and responded equally well.

By MRI assessments, 17 patients (55%) experienced a spleen volume decrease of ≥ 25% from baseline through Week 24, and 5 patients (16%) experienced a spleen volume decrease of ≥ 35% from baseline through Week 24. According to organ measurement by physical examination, 12 patients (39%) experienced a spleen size decrease of ≥ 50% from baseline through Week 24 (data derived from T5.2-A_spleen_ALL.2012-02-29 using ITT denominator of 31). Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

A patient-reported outcome related to MF symptoms was assessed in this study using the myelofibrosis symptom assessment form (MFSAF) form (Mesa RA et al 2009). The study did not include a control arm, so it is not possible to evaluate the actual effect of pacritinib treatment on disease symptoms. However, on Day 1 of Cycle 7, patients who had a baseline score of ≥ 4 showed improvement in all symptoms most relevant to MF; a mean score change of ≥ 2 was experienced in abdominal pain, bone pain, early satiety, inactivity, night sweats, pruritus, and fatigue.

1.3.7 SB1518-2008-003: Phase 1/2 Study in Patients with Chronic Idiopathic Myelofibrosis

1.3.7.1 Phase 1

During the phase 1 portion of SB1518-2008-003, cohorts of 3 to 6 patients with MF were enrolled into one of a series of escalating doses of pacritinib ranging from 100 to 600 mg/day. DLTs were observed in 2 of 4 patients at the 600 mg dose level: 1 experienced grade 3 diarrhea and 1 experienced grade 3 nausea, fatigue, and dehydration. The safety findings in this study were similar to those in SB1518-2007-001. The MTD based on first cycle data was determined to be 500 mg/day, and the recommended dose for phase 2 study, based on multicycle safety and efficacy data, was 400 mg/day.

The most commonly reported treatment-emergent AEs (> 20%) were diarrhea, nausea, vomiting, fatigue, constipation, abdominal pain, dizziness, ALT increased, anorexia, cough, pain in extremity, abdominal distension, peripheral edema, bone pain, headache, and rash. Most AEs were mild to moderate in severity. The only AEs of grade 3 or greater severity that occurred in more than 10% of patients were anemia, diarrhea, thrombocytopenia, and fatigue, each of which occurred in 15% of patients.

PK analysis showed a T_{max} of 3 to 7 hours and a terminal half-life of 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations were achieved at the starting dose of 100 mg on Day 1. No drug accumulation occurred upon repeated dosing over several cycles.

1.3.7.2 Phase 2

The objectives of the phase 2 portion of this study included spleen response rate, duration of spleen response, safety, and tolerability. Spleen response rate was defined as the proportion of patients achieving an MRI-determined reduction in spleen volume of 35% or more between baseline and Week 24.

Data are available for 34 patients in this trial (Table--4). Twenty-nine patients were previously treated for MF, and all enrolled patients had baseline splenomegaly that measured at least 5 cm below the LCM. Seven patients discontinued the study for the following reasons: AE (1 patient each for hyperbilirubinemia, allergic reaction, thrombocytopenia, and subdural hematoma), disease progression (1 patient), lack of response (1 patient), and withdrawal of consent (1 patient).

Table--4
Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003

Demographic/Baseline Characteristics	MRI Phase II (N=34)
Age (yr)	
N	34
Mean (SD)	66.6 (10.44)
Median	69
25 - 75 percentile	60 - 72
Range	44 - 84
Gender	
N	34
Female	9 (26%)

Table--4 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003	
Demographic/Baseline Characteristics	**MRI Phase II (N=34)**
Male	25 (74%)
Ethnicity	
N	34
Hispanic or Latino	2 (6%)
Not Hispanic or Latino	32 (94%)
Race	
N	34
American Indian or Alaska Native	0
Asian	1 (3%)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	33 (97%)
Other	0
ECOG Performance Status	
N	32
0	9 (28%)
1	21 (66%)
2	2 (6%)
>2	0
Number of Prior Systemic Therapies	
N	34
Mean (SD)	1.9 (1.60)
Median	1
25 - 75 percentile	1 - 2
Range	0 - 6
Initial Stage of Disease	
N	34
MF0	1 (3%)
MF1	1 (3%)
MF2	7 (21%)
MF3	9 (26%)
Unknown or N/A	16 (47%)
Baseline Hemoglobin (g/dL)	
N	33
Mean (SD)	10.142 (1.8755)

Table--4
Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003

Demographic/Baseline Characteristics	MRI Phase II (N=34)
Median	10.200
25 - 75 percentile	8.90 - 11.40
Range	5.50 - 14.10
Baseline Platelet Count (10^3/µL)	
N	33
Mean (SD)	167.39 (168.857)
Median	119.00
25 - 75 percentile	53.0 - 214.0
Range	15.0 - 859.0
Baseline Platelet Count Category	
<50,000/µL	7 (21.2)
50,000 – 100,000/µL	8 (24.2)
≥100,000/µL	18 (54.9)
Baseline WBC (10^3/µL)	
N	33
Mean (SD)	18.204 (19.5116)
Median	10.800
25 - 75 percentile	6.10 - 22.45
Range	1.14 - 89.60
Baseline Absolute Neutrophil Count (10^3/µL)	
N	34
Mean (SD)	12.21 (11.963)
Median	7.92
25 - 75 percentile	4.0 - 20.1
Range	0.3 - 56.4

Source: Table 2 (t02_demog 27FEB2012), Table 3 (t03_disease 27FEB2012), Table 14 (t14_hema 27FEB2012), Table 1 (t_base_platelet_ph2_myel).
Abbreviations:
µL = microliter(s) ECOG = Eastern Cooperative Oncology Group g/dL = gram(s) per deciliter
MRI = magnetic resonance imaging N = number SD = standard deviation
WBC = white blood cells yr = year(s).

Most AEs were mild to moderate in severity (Table--5). The most frequently occurring treatment emergent AEs were diarrhea (79%), nausea (41%), anemia (38%), fatigue (35%), abdominal pain (26%), pruritus (24%), and thrombocytopenia (24%). Grade 3 AEs reported by more than one patient were anemia (18%), thrombocytopenia (15%), fatigue (15%), diarrhea (9%), abdominal pain (6%), GI hemorrhage (6%), pneumonia (6%), AST increased (6%), QT prolongation (6%), dehydration (6%), and iron overload (6%). Grade 4 AEs were anemia (9%), thrombocytopenia (6%), hyponatremia (6%), atrial fibrillation (6%), neutropenia (3%), leukopenia (3%), fatigue (3%), cellulitis (3%), septic shock (3%),

blood uric acid increased (3%), hyperuricemia (3%), and renal cell cancer (3%). Grade 5 AEs were septic shock (3%), sepsis (3%), and subdural hematoma (3%). The only death considered related to treatment was the subdural hematoma. The only SAE reported in more than one patient was septic shock (2 patients, 6%). Ten SAEs reported in 6 patients were thought to be related to treatment; each SAE was reported in a single patient: grade 3 febrile neutropenia, grade 3 hyperbilirubinemia, grade 3 dehydration, grade 4 thrombocytopenia, grade 4 myocardial infarction, grade 4 septic shock, grade 4 hyperuricemia, grade 4 hyponatremia, and grade 5 subdural hematoma.

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Subjects with any Event	3 (9%)	3 (9%)	15 (44%)	9 (26%)	3 (9%)	33 (97%)
Blood and Lymphatic System Disorders	2 (6%)	5 (15%)	9 (26%)	5 (15%)	0	21 (62%)
Anaemia	0	4 (12%)	6 (18%)	3 (9%)	0	13 (38%)
Thrombocytopenia	1 (3%)	0	5 (15%)	2 (6%)	0	8 (24%)
Gastrointestinal Disorders	17 (50%)	9 (26%)	5 (15%)	0	0	31 (91%)
Diarrhoea	15 (44%)	9 (26%)	3 (9%)	0	0	27 (79%)
Nausea	13 (38%)	1 (3%)	0	0	0	14 (41%)
Vomiting	8 (24%)	3 (9%)	0	0	0	11 (32%)
Abdominal pain	5 (15%)	2 (6%)	2 (6%)	0	0	9 (26%)
Flatulence	6 (18%)	0	0	0	0	6 (18%)
Constipation	3 (9%)	1 (3%)	0	0	0	4 (12%)
General Disorders and Administration Site Conditions	10 (29%)	5 (15%)	5 (15%)	1 (3%)	0	21 (62%)
Fatigue	3 (9%)	3 (9%)	5 (15%)	1 (3%)	0	12 (35%)
Asthenia	2 (6%)	1 (3%)	1 (3%)	0	0	4 (12%)
Pyrexia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Investigations	9 (26%)	2 (6%)	4 (12%)	1 (3%)	0	16 (47%)
Aspartate aminotransferase increased	3 (9%)	0	2 (6%)	0	0	5 (15%)
Metabolism and Nutrition Disorders	6 (18%)	5 (15%)	7 (21%)	2 (6%)	0	20 (59%)
Dehydration	1 (3%)	3 (9%)	2 (6%)	0	0	6 (18%)
Anorexia	2 (6%)	3 (9%)	0	0	0	5 (15%)
Hyperuricaemia	3 (9%)	0	1 (3%)	1 (3%)	0	5 (15%)
Hypomagnesaemia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Musculoskeletal and Connective Tissue Disorders	12 (35%)	3 (9%)	0	0	0	15 (44%)
Musculoskeletal pain	2 (6%)	2 (6%)	0	0	0	4 (12%)
Nervous System Disorders	10 (29%)	1 (3%)	1 (3%)	0	0	12 (35%)
Dizziness	5 (15%)	1 (3%)	0	0	0	6 (18%)

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dysgeusia	4 (12%)	0	0	0	0	4 (12%)
Headache	3 (9%)	0	1 (3%)	0	0	4 (12%)
Psychiatric Disorders	4 (12%)	2 (6%)	0	0	0	6 (18%)
Insomnia	4 (12%)	0	0	0	0	4 (12%)
Respiratory, Thoracic and Mediastinal Disorders	5 (15%)	8 (24%)	4 (12%)	0	0	17 (50%)
Dyspnoea	1 (3%)	3 (9%)	0	0	0	4 (12%)
Skin and Subcutaneous Disorders	15 (44%)	4 (12%)	1 (3%)	0	0	20 (59%)
Pruritus	6 (18%)	1 (3%)	1 (3%)	0	0	8 (24%)
Alopecia	4 (12%)	0	0	0	0	4 (12%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations: N = number; SOC = system organ class.

Among the patients reporting grade 3 anemia, all had grade 2 or grade 3 anemia at baseline. Among the 3 patients reporting grade 4 anemia, 1 had grade 3 anemia, 1 had grade 1 anemia, and 1 had no lab value at baseline.

Myelosuppression has been relatively infrequent, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with severe baseline hematologic abnormalities, including those with platelet counts <150,000/μL, appear to tolerate pacritinib as well as patients with normal and lesser degrees of abnormal hematopoiesis.

By MRI assessments, 12 patients (35%) experienced a decrease in spleen volume of at least 25% from baseline through Week 24, and 8 patients (24%) experienced a decrease in spleen volume of at least 35% from baseline through Week 24 (data derived from Table 5.2-A [t05.2-A_spleen_ALL.27FEB2012 using ITT denominator of 34]). According to organ measurement by physical examination, 14 patients (41%) experienced a decrease in spleen size of at least 50% from baseline through Week 24. Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

Patients completed the MFSAF (Mesa RA et al 2009) at baseline and throughout the trial. Intra- and inter-patient symptom severity varied widely at baseline. On Day 1 of Cycle 4, patients who had a baseline score of ≥4 showed improvement in some symptoms, with mean decreases of ≥2 in early satiety, abdominal pain, night sweats, and pruritus.

1.3.8 Phase 1 and 2 Experience with Pacritinib in Myelofibrosis: Summary and Conclusions

- Fifty-six patients with MF have been treated with escalating doses of pacritinib in the phase 1 portions of studies SB1518-2007-001 and SB1518-2008-003. An additional 65 patients have been treated in the phase 2 portions of these studies in Australia and the US.
- A total of 36 patients with starting platelet counts ≤150,000/μL have been treated, with an apparent response rate similar to those with higher platelet counts and no consistent treatment-related platelet suppression.

- Pacritinib did not appear to increase anemia or RBC transfusion requirements.
- Pacritinib has a favorable safety profile and is generally well tolerated in patients with MF, including those with PMF, PPV-MF, and PET-MF. Side effects are predominantly GI and are readily managed with symptomatic treatment and/or study drug interruption or dose reduction. AEs associated with myelosuppression are uncommon, and pacritinib is well tolerated and active in patients with cytopenias-particularly thrombocytopenia.
- Median baseline platelet counts in patients treated with pacritinib in phase 2 studies were 126,000/μL and 119,000/μL, approximately half of those in the ruxolitinib studies (262,000/μL and 244,000/μL).
- The overall incidence of all grades of thrombocytopenia reported as adverse events in efficacy and safety trials with pacritinib was 17%. Twelve percent of patients experienced a 2-grade or greater shift in platelet counts from baseline to worst platelet count, and 5% experienced a 2-grade or greater shift in platelet counts from baseline to end of study (Table--6).
- In comparison, the incidence of all grades of thrombocytopenia was 69% in the COMFORT I trial, and the incidence of thrombocytopenia requiring dose adjustment was 41% in the COMFORT II trial.

Table--6
Shift from Baseline Platelet Count by CTC Grade in Phase 2 of SB1518-2007-001 and SB1518-2008-003

	Baseline Platelet Count CTC Grade (N = 65)				
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nadir Platelet Count CTC Grade (N = 64)					
0	16 (25.0%)	0	0	0	0
1	11 (17.2%)	3 (4.7%)	0	0	0
2	0	4 (6.3%)	5 (7.8%)	0	0
3	1 (1.6%)	5 (7.8%)	6 (9.4%)	4 (6.3%)	0
4	1 (1.6%)	0	1 (1.6%)	5 (7.8%)	2 (3.1%)
End of Study Platelet Count CTC Grade (N = 64)					
0	20 (31.3%)	4 (6.3%)	0	0	0
1	7 (10.9%)	2 (3.1%)	2 (3.1%)	0	0
2	0	5 (7.8%)	6 (9.4%)	1 (1.6%)	0
3	1 (1.6%)	1 (1.6%)	4 (6.3%)	6 (9.4%)	1 (1.6%)
4	1 (1.6%)	0	0	2 (3.1%)	1 (1.6%)

Source: (t_platelet_shift_from_base_ph2_myel).
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number

- A notable proportion of the 65 patients with MF who were treated with pacritinib experienced a reduction of splenomegaly on both MRI and physical examination assessments. Among 49 patients with post-baseline follow-up evaluations, 29 (59%) had a 25% or greater reduction in MRI-assessed spleen volume and 13 (27%) had a 35% or greater reduction in MRI-assessed spleen volume. Twenty-six (41%) of 63 evaluable patients had at least a 50% reduction in physical examination-assessed spleen size as a best response. Patients with thrombocytopenia showed similar treatment effects.
- Clinical experience through phase 2 has demonstrated the safety and activity of pacritinib in patients with MF and warrants phase 3 trials to confirm the efficacy and safety of this drug in this patient population.

1.3.9 PERSIST-1: Phase 3 Study of Pacritinib versus Best Available Therapy in Patients with PMF, PPV-MF, or PET-MF

This ongoing phase 3 study will compare the efficacy of pacritinib with that of BAT in patients with PMF, PPV-MF, or PET-MF. The primary objective is to assess the proportion of patients in each arm achieving a ≥35% reduction in spleen volume from baseline to Week 24. The secondary objective is to assess the proportion of patients in each arm with ≥50% reduction from baseline to Week 24 on the MPN-SAF TSS 2.0.

A total of 252 patients at approximately 100 centers in the US, Europe, Russia, and Oceania will be randomized in a 2:1 allocation to pacritinib or BAT. BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, with the exclusion of JAK2 inhibitors. BAT also includes watchful waiting (no treatment). Spleen volume will be measured at baseline and every 12 weeks thereafter. Patients previously treated with JAK2 inhibitors are excluded. There are no exclusion criteria based on platelet count.

2 Rationale for Study

Two phase 2 studies of pacritinib have been conducted in patients with MF. Data from these trials show that pacritinib can be safely administered to patients with MF, including those who also have thrombocytopenia. Pacritinib treatment led to clinically meaningful reduction in spleen size and volume in a substantial proportion of patients with MF in the phase 2 studies. Pacritinib treatment improved disease-associated symptoms. These effects were observed in patients with thrombocytopenia, including those with platelet counts <100,000 /μL, as well as in those with normal platelet counts. These findings warrant phase 3 investigation to confirm the efficacy and safety of pacritinib, both in patients with normal and low platelet counts. For the subgroup of patients with low platelet counts, the currently approved JAK inhibitor requires significant dose reduction and is less effective than in patients with normal platelet counts. Pacritinib may fill a significant unmet need in patients with low platelet counts and also provide effective treatment for nonthrombocytopenic patients with MF.

2.1 Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arm(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

2.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.3 Exploratory Objectives

The exploratory objectives are the evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of RBC transfusion independence (Appendix 1a)
9. Achievement of reduced RBC transfusion dependence (Appendix 1a)
10. Clinical improvement in hemoglobin level (Appendix 2)
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence (Appendix 1b)
13. Clinical improvement in platelet count (Appendix 2)
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4)

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamics (PD) objectives are to assess exposure and exposure response relationships on the safety and efficacy of pacritinib.

3 Study Design

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two-dose schedules of pacritinib in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to one of three treatment arms:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia) and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved

JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT scan at baseline and every 12 weeks thereafter, and at other time points as clinically indicated. MRI is the preferred modality. Imaging should be performed without contrast agents. The analysis of the primary outcome will take place when all randomized patients have completed the Week 24 MRI or CT evaluation, exhibited disease progression, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, OS, PFS, LFS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will monitor the safety of pacritinib. No interim efficacy analysis is planned.

For patients who are no longer taking pacritinib or those in the BAT arm who are no longer receiving study treatment, follow-up for survival and leukemic progression will continue until 3 years past Week 24 or past termination of all study treatment, whichever occurs first. The maximum duration of trial participation for an individual patient will be 3.5 years. The estimated duration of the entire trial is 4.5 years.

3.1 Progression of Disease

Patients may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced, and both should be reported.

Progression of disease is defined as one or more of the following:

- Splenic progression, defined as in increase in splenic volume of ≥25% from baseline, based on centrally read MRI or CT scan
- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
  - Bone marrow blast count ≥20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Although the date of the first event is considered the date of progression of disease, subsequent events must also be reported.

3.2 Criteria for Treatment Continuation After Progression of Disease

To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥25% from baseline on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF.

3.3 Criteria for Crossover from BAT to Pacritinib Treatment

To cross over from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or has progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

Each patient is to receive pacritinib or BAT until progression of disease or the occurrence of unacceptable toxicity, or until the patient no longer derives benefit from treatment (Appendix 11).

Patients on BAT may cross over to pacritinib at any time after splenic progression if leukemic transformation, splenectomy, or splenic irradiation have not occurred, or after completing 24 weeks of treatment with or without progression. Patients may continue on active (drug) study treatment after disease progression, as detailed below.

Patients on BAT who have splenic progression but do not wish to cross over to pacritinib will be followed for safety, survival, and leukemic transformation, but not splenic progression as long as they continue the BAT treatment they were taking at the time of progression. Note that patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will be followed for leukemic transformation and survival.

Patients crossing over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment. If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT must be completed within 30 days prior to the start of pacritinib treatment. This will define the crossover baseline

spleen volume, and patients will be subsequently followed for a second, post-crossover event of splenic progression.

Patients who cross over from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT.

4 Patient Selection and Withdrawal

4.1 Target Population

4.1.1 Inclusion Criteria

1. Intermediate-1 or -2 or high-risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the LCM in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF-TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years old
7. ECOG performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion-dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 x ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)
15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study. Women of childbearing potential must use highly effective methods (defined as those resulting in a failure rate of <1% per year when used consistently and correctly) for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release). Males must use a condom for the duration of the study and for 90 days after the last dose of study treatment. When abstinence is used as a method of birth control, only true abstinence is acceptable, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.
17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument

19. Able to understand and willing to sign the informed consent form.

4.1.2 Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or pacritinib
4. More than 6 months of cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplantation (ASCT) or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion with the approval of the medical monitor if the arrhythmias are stable, asymptomatic and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450 ms, or other factors that increase the risk for QT prolongation (eg, heart failure, hypokalemia [defined as serum potassium < 3.0 mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

4.2 Criteria for Withdrawal of Patients

4.2.1 Withdrawal from Study Treatment

Patients may discontinue or be withdrawn from treatment at any time. All reasonable efforts should be made to retain patients who discontinue treatment in the study and to conduct all follow-up assessments required by the protocol, including MRI or CT scanning and follow-up for progressive disease, leukemic

transformation, and survival. Reasons for discontinuing treatment may include but are not limited to the following:

- Documented disease progression, defined as:
  - Splenic progression, defined as an increase in splenic volume of ≥25% from baseline based on centrally read MRI or CT scan
  - Splenic irradiation
  - Splenectomy
  - Leukemic transformation, defined as one or more of the following:
    - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
    - Bone marrow blast count ≥20%
- Unrelated intercurrent illness that, in the judgment of the principal investigator, will affect assessments of clinical status to a significant degree
- Pregnancy
- Patient's decision
- Patient noncompliance with study drug
- Clinical need for concomitant therapy that is not permitted in the study
- Decision on the part of the investigator or Cell Therapeutics' medical monitor that it is in the patient's best interest to withdraw from study treatment
- Death

4.2.2 Withdrawal from Study Procedures

Patients will be withdrawn from study procedures for the following reasons:

- Withdrawal of consent for study procedures
- Decision on the part of the investigator or Cell Therapeutics' medical monitor that it is in the patient's best interest to withdraw from study procedures

For patients who discontinue treatment and study procedures, all reasonable efforts should be made to maintain the patient in the study and continue follow-up for OS and LFS.

4.2.3 Withdrawal from the Study

Patients will be withdrawn from the study, including follow-up, for the following reasons:

- Withdrawal of consent
- Lost to follow-up
- Death
- Sponsor decision to terminate the study

5 Method of Treatment Assignment and Blinding

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT using a central interactive web response system or interactive voice response system.

Randomization will be stratified by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The first qualifying platelet value after informed consent and the most recent platelet count obtained prior to randomization will be the basis for determining platelet rebound stratification. For patients who receive any platelet transfusions, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization. If necessary due to ROW enrollment and regulatory strategies, the ROW stratum may be divided into 2 or more strata as appropriate.

A patient's treatment assignment will be known to the investigator, site personnel, the patient, clinical monitors, and pharmacovigilance personnel. The sponsor will remain blinded until the database lock for primary analysis. Independent radiographic assessors will remain blinded throughout the study.

6 Study Treatment

6.1 Study Drug Administration

Patients taking pacritinib will be supplied with 100 mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib once a day, at the same time of day, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib twice each day at the same times of day, with or without food (Table--7).

Patients receiving BAT will be treated on a schedule commensurate with the therapy chosen by the investigator.

Table--7
Study Treatment Schedule

Treatment	Dose/Regimen
Pacritinib (QD)	Pacritinib 400 mg (4 capsules) once a day orally, at the same time of day, with or without food.
Pacritinib (BID)	Pacritinib 200 mg (2 capsules) twice each day orally, at the same time of day, with or without food
Best Available Therapy (BAT)	Physician's choice of treatment for PMF, PPV-MF, or PET-MF

6.2 Study Drug Description and Storage

Pacritinib for oral administration is supplied in capsules containing 100 mg (as the free base) in red cap/gray body size 0 opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000.

Each capsule contains 146 mg of pacritinib citrate which is equivalent to 100 mg pacritinib free base.

Pacritinib capsules should not be opened or crushed. Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water.

Pacritinib capsules should be stored at controlled room temperature 20º to 25ºC or 68º to 77º F, with excursions allowed from 15° to 30ºC or 59° to 86ºF. All pacritinib supplies must be kept in a restricted-access area.

BAT may include any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

6.3 Dose, Route, and Mode of Administration

Patients in the pacritinib arms will be supplied with 100-mg capsules of pacritinib. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally, once a day, at the same time of day, with or without food. If assigned to the BID dosing arm, patients will take 200 mg (2 capsules) of pacritinib twice each day orally, at the same times of day, with or without food. On days when PK samples are to be obtained, pacritinib will be administered in the clinic.

6.4 Compliance with Treatment

At every study visit, patients in the pacritinib arm and those who have crossed over to pacritinib arm will return bottles in which pacritinib is supplied with all remaining untaken pacritinib capsules.

6.5 Pacritinib Treatment Adjustments

6.5.1 Treatment Interruption

Safety parameters including AEs, hematology, and serum chemistry will be monitored according to the protocol. Pacritinib treatment may be withheld for up to 2 weeks due to drug-related toxicities. A longer recovery period may be allowed based on the toxicity, but must be agreed upon between the investigator and medical monitor.

After treatment interruption, patients may resume the pacritinib treatment at the same dose level or at a reduced dose level. No dose re-escalation is allowed.

6.5.2 Pacritinib Dose Management Guidelines for QTc Interval Prolongation

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 by CTCAE Version 4.0 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in this section. Dose management for QTc interval prolongation is summarized in Table--8.

For grade 3 QTc prolongation, hold treatment until toxicity resolves to grade ≤1. If, within 7 days, toxicity resolves to grade ≤1, restart pacritinib at 200 mg/day. When restarted, pacritinib dosing will be 200 mg QD for the 400 mg QD arm and 100 mg BID for the 200 mg BID arm. No dose re-escalation is allowed.

If grade 3 toxicity does not resolve to grade ≤1 within 7 days, discontinue all treatment with pacritinib. If grade 3 toxicity recurs despite dose reduction to 200 mg/day, discontinue all treatment with pacritinib.

For grade 4 QTc prolongation, discontinue all treatment with pacritinib.

Table--8
Treatment Toxicity and Dose Management: QTc Interval Prolongation

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3 (first occurrence)	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 within 7 days, treatment may be resumed at 200 mg daily. ▪ Toxicity that does not resolve to grade ≤ 1 within 7 days requires treatment discontinuation.
3 (second occurrence)	▪ Discontinue treatment.
4	▪ Discontinue treatment.

6.5.3 Pacritinib Dose Management Guidelines for Pacritinib-related Nonhematologic Toxicities other than QTc Prolongation

A maximum of 2 dose reductions is allowed. The first dose reduction will be a 100 mg reduction from the original dose. For patients taking 400 mg QD, the dose will be reduced to 300 mg QD. For patients taking 200 mg BID, the dose will be reduced to 200 mg Q AM and 100 mg Q PM.

The second dose reduction will be another 100 mg reduction. For patients taking 300 mg QD, the dose will be reduced to 200 mg/day. For patients taking 200 mg Q AM and 100 mg Q PM, the dose will be reduced to 100 mg BID.

Once the dose is reduced, no re-escalation is allowed.

Dose management for nonhematologic toxicities is summarized in Table--9.

The lowest dose of pacritinib used in the study will be 200 mg/day. If toxicity persists despite dose reduction to 200 mg/day, the patient should be discontinued from treatment.

Table--9
Treatment Toxicity and Dose Management: Pacritinib-Related Nonhematologic Toxicities

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed at the same level or the next lower dose, at the discretion of the investigator after discussion with the sponsor. ▪ Toxicity that does not resolve to grade ≤ 1 or to the baseline grade within 7 days requires dose reduction to the next lower dose level.

Table--9 Treatment Toxicity and Dose Management: Pacritinib-Related Nonhematologic Toxicities	
CTCAE Toxicity Grade	**Management/ Action**
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed, but dose will be reduced by one dose level from the level at which the toxicity was observed. ▪ If grade 4 toxicity occurs at the lowest dose of 200 mg/day, the patient should be discontinued from the study.

6.5.4 Dose Management Guidelines for Hematologic Toxicities

Myelosuppression is an expected event in patients with MF. However, myelosuppression with associated complications such as fever, infection, or bleeding or myelosuppression that worsens during treatment (based on local laboratory values) must be reported as an AE.

Patients with myelosuppression may receive supportive care including transient use of granulocyte-colony stimulating factor for the treatment of febrile neutropenia and transfusion as clinically indicated. Patients receiving pacritinib are not allowed to receive hematopoietic growth factors such as erythropoietin for the treatment of anemia.

Patients with clinically significant worsening of myelosuppression (as judged by the investigator and based on local laboratory values) for more than 7 days or myelosuppression associated with infection or bleeding should have pacritinib dosing interrupted. Pacritinib may be restarted at a reduced dose once the toxicity has resolved to ≤ grade 2 or to the baseline grade and the complications of myelosuppression such as infection or hemorrhage have resolved.

6.6 Concomitant and Excluded Therapies

BAT will include any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved inhibitors of Janus kinases, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

Patients taking pacritinib, including those randomized to pacritinib and those who have crossed over from BAT to pacritinib, may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF during the study.

Patients should receive full supportive care, including transfusions of blood and blood products, antidiarrheal and antiemetic agents (see below), and antibiotics when appropriate.

All concomitant medications and blood products administered during the patient's participation in the study must be recorded in the source documents and electronic case report forms (eCRFs).

Patients may not receive other investigational agents during the study.

Patients may not receive treatment with any potent CYP3A4 inhibitors for 1 week prior to administration of pacritinib and during treatment with pacritinib. Some BAT therapies also have CYP3A4 interactions and/or other drug-drug interactions. Prescribing instructions should always be consulted to ensure adherence to administration guidelines for each prescribed BAT. See Appendix 9 for a list of common potent CYP3A4 inhibitors.

6.6.1 Management of Gastrointestinal Toxicity

The need for managing GI effects of pacritinib, particularly diarrhea, should be anticipated. A careful baseline evaluation of bowel habits (frequency and consistency of bowel movements) should be obtained at baseline for all patients.

The site will contact all patients by telephone during the first week (on Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to pacritinib) and at the beginning of Week 3 (of initial treatment or after crossover to pacritinib) to evaluate GI toxicity and assess the need for modifying the treatment of GI side effects. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any changes in frequency or consistency of bowel movements after starting study treatment.

Early intervention for diarrhea should be initiated for patients with increases of one grade or more in diarrhea (Appendix 12). At the investigator's discretion, prophylactic use of anti-diarrheals may be initiated for patients or populations in whom it is judged necessary to enhance patient safety. Standard supportive care measures to control symptoms of GI toxicity such as diarrhea, constipation, and nausea should be provided.

6.7 BAT Treatment Adjustments

Patients on the BAT arm who are being treated with ruxolitinib must be dosed according to the instructions in the current labeling recommendations.

7 Study Assessments

7.1 Criteria for Evaluation

7.1.1 Efficacy

7.1.1.1 Spleen Volume

Spleen volume measurement by MRI or CT scan will be performed at screening and every 12 weeks thereafter, or at other time points if spleen size progression is suspected by other assessments (eg, physical examination). Unscheduled imaging studies can be performed at physician discretion if he/she considers disease related symptoms to be worsening. All images generated as part of unscheduled evaluations must be submitted by the investigator for central review. MRI is the preferred modality; CT scan will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement. A spleen response is defined as a reduction in spleen volume of ≥35% at any time.

7.1.1.2 Spleen Size Assessment by Physical Examination

Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

7.1.1.3 Disease-Related Signs and Symptoms

Patients will complete the MPN-SAF TSS 2.0 (Appendix 7) daily for 7 to 10 consecutive days prior to starting treatmentand then daily through Week 48, as long as the patient is receiving study treatment.

The pain medication log will be completed daily by patients, as long as they continue to complete the daily MPN-SAF TSS 2.0. The patient global impression assessment will be completed by patients while they continue to complete the daily MPN-SAF TSS 2.0.

7.1.1.4 Survival

Patients will be followed for survival and for transformation to AML (as assessed by the investigator, investigator-obtained records, or if these are not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

7.1.1.5 Quality of Life

The EQ-5D-5L and EORTC-QLQ-C30 version 3.0 will be completed at baseline, Week 8, Week 16, Week 24, and then every 12 weeks during study treatment. Patients will discontinue quality of life assessments after Week 48 is completed or at termination of study treatment, whichever comes first.

7.1.1.6 Other Assessments

Patients will also be followed for leukemic transformation, frequency of RBC and platelet transfusions, and other exploratory endpoints.

Bone marrow slides obtained at or prior to baseline as required for study eligibility and those obtained at Week 24 may be evaluated by central pathology, in addition to local pathology review.

Bone marrow biopsy evaluation (aspirate and core) obtained per protocol will be performed per local standards of care. Bone marrow biopsy sample should be evaluated for myeloblast percentage. In addition, routine and specific evaluations for myelofibrosis should be done, including (but not limited to), the following assessments: cell count and differential, megakaryocyte proliferation and atypia, reticulin and collagen staining and staging, bone marrow cellularity, granulocytic proliferation, decreased erythropoiesis, and cytogenetic analysis (including *JAK2V617F*).

7.1.2 Safety

7.1.2.1 AEs

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. For screened patients who are not

randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

7.1.2.2 Hematology

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Hematology parameters (CBC with differential and platelet count) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local standards of care. Similarly, unscheduled CBC with differential and platelet count may be performed locally and/or centrally whenever clinically indicated.

7.1.2.3 Blood Chemistry

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Blood chemistry parameters (ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin [total, direct, and indirect], creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local standards of care. Similarly, unscheduled chemistries may be performed locally and/or centrally whenever clinically indicated

7.1.2.4 ECG Assessment

All patients will have a single 12-lead ECG at screening. Screening ECGs should be performed at least 1 week after the end of prior therapy. For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study.

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.

7.1.3 Pharmacokinetics

PK samples (five) for assessment of systemic exposure will be collected from approximately 70 patients taking pacritinib at a prespecified subset of sites at the following time points:

- Day 1 of Week 1: at 4 hours postdose
- Day 1 of Week 3: predose (Hour 0) and at 4 hours postdose

- Week 12 and Week 24: predose (Hour 0)

PK samples (two) for assessment of systemic exposure will be collected from approximately 130 patients taking pacritinib at the remaining sites at the following time points:

- Week 12 and Week 24: predose (Hour 0)

On the day prior to PK blood sampling, the patient must record the time of dosing and report it the following day. On the day of PK blood sampling, patients must not take the daily dose of pacritinib prior to the clinic visit.

Results will be used to evaluate the relationship between drug exposure and safety and efficacy.

PK samples will not be collected from patients crossing over from BAT to pacritinib.

7.1.4 Pharmacodynamics

PD samples for assessment of pSTAT3 levels, an established PD marker for JAK-STAT signaling pathway inhibition, will be collected from patients taking pacritinib at a prespecified subset of sites, the same approximate 70 patient, five-sample PK cohort as described above in Section 7.1.3, at the following time points:

- Day 1 of Week 1 and Week 3: predose (Hour 0) and at 4 hours postdose
- Week 12 and Week 24: predose (Hour 0)

7.1.5 *JAK2* Mutation Burden

JAK2V617F mutation burden will be assessed by a central laboratory in all patients at screening, at Week 12, and every 12 weeks thereafter and at termination of study treatment in patients who have the mutation at screening.

7.2 Informed Consent and Washout of Prior Therapies, 35 to 7 Days Before Beginning Study Treatment

Informed consent must be obtained before any study-specific washout. The informed consent process should be documented in the patient's medical chart. Informed consent should be obtained between 35 and 7 days prior to the start of treatment. Washout may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and MF treatments), or 7 days (potent CYP3A4 inhibitors). Patients not requiring washout may sign informed consent at any time prior to screening procedures. The informed consent process should be documented in the patient's medical chart. Eligibility platelet count may be obtained at any time within this window.

7.3 Screening Procedures, 5 to 14 Days Before Beginning Study Treatment

Informed consent must be obtained before study procedures, and screening evaluations are performed unless those evaluations are performed as part of standard of care. Patients who do not meet eligibility criteria at screening may be rescreened at a later date.

The screening evaluations listed below are to be carried out **between 14 and 5 days prior to the start of treatment**. Laboratory assessments and ECGs should be performed at least 1 week after the end of prior

therapy, except eligibility platelet count which may be obtained between 35 and 7 days before beginning study treatment.

- Medical history
- *JAK2V617F* mutation status (for baseline pharmacodynamic assessment; in addition, collect medical and disease history of mutation status if documentation is available)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including height, clinical signs and symptoms, and spleen measurement
- GI assessment
- 12-lead ECG
- ECOG performance status
- Hematology: CBC with differential and platelet count
- BM biopsy within 24 weeks of randomization (may be obtained any time before Day -3)
- Serum chemistry, including ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid
- Serum pregnancy test for women of childbearing potential
- AEs
- Concomitant medications
- Transfusion history
- Assess for leukemic transformation

7.4 Symptom Assessment and Screening MRI Visit, 4 to 10 Days Before Beginning Study Treatment

- Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment
- Pain medication log will begin when MPN-SAF TSS 2.0 symptom reporting begins
- MRI or CT scan (without contrast) for measurement of spleen volume

7.4.1 Randomization, Up to 3 Days Before Beginning Study Treatment

Randomization: Patient must first sign informed consent, then complete all screening procedures, and meet all eligibility criteria. Note that screening procedures include at least two platelet counts to determine 1) the first qualifying platelet value after informed consent and 2) the platelet rebound count for stratification.

Platelet count obtained during the the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for the platelet rebound stratification determination. Should patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion obtained before randomization.

7.4.2 Beginning of Week 1, Study Day 1

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples patients in the pacritinib arm at PK sites: Hour 4 (postdose)
- PD samples for patients in the pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)
- Dispense prescription for antidiarrheal drug and instruct patient to fill it and to begin taking it at onset of gastrointestinal symptoms
- Dispense pacritinib or begin treatment with BAT
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.3 Week 1, Study Day 4 (± 1 d)

- The site (either the investigator or a surrogate) is to contact the patient by telephone to assess the need for modifying the treatment of any GI side effects.
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.4 Beginning of Week 2, Study Day 8 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement

- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.5 Beginning of Week 3, Study Day 15 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- GI assessment
- 12-lead ECG (1 only for BAT patients; 2 for pacritinib patients; predose and at 4 hours postdose) ECOG performance status
- PK samples for patients in pacritinib arm at PK sites: Hour 0 (predose) and Hour 4 (postdose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.6 End of Week 4, Study Day 28 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log

- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.7 End of Week 8, Study Day 56 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.8 End of Week 12, Study Day 84 (± 3 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)

- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.9 End of Week 16, Study Day 112 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.10 End of Week 20, Study Day 140 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Dispense pacritinib
- Pacritinib accountability

- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.11 End of Week 24, Study Day 168 (± 7 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Bone marrow biopsy
- Serum chemistry
- MRI or CT without contrast to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.12 End of Week 36, Study Day 252 (± 7 d), and Every 12 Weeks Thereafter

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry

- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.13 Termination of Study Treatment (up to 7 days after completion of all study drug treatment)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Patient-reported symptoms on MPN-SAF TSS 2.0
- Pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.14 Post-Termination (30 $\pm$ 3 days after study treatment termination)

- AEs: Last time point for collection and follow-up of nonserious AEs and SAEs deemed not related to study treatment or procedures. Please refer to Follow-up section for more details.
- Concomitant medications

7.4.15 Follow-up

SAEs assessed as related to study treatment or study procedures will be collected from the time of signing informed consent through the patient's last day of study participation, and followed until the event resolves, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever comes first. SAEs assessed as unrelated to study drug or study procedures and non-serious AEs will be collected from the time of signing informed consent through the last day of study participation and followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.

Patients will be followed for survival and for transformation to AML (as assessed by investigator, investigator-obtained records, or if not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

8 Pharmacokinetic Analysis and *JAK2* Mutation Burden

8.1 Blood Sample Collection, Handling, and Shipping

Blood samples for PK and *JAK2* mutation burden analyses should be collected in appropriate blood collection tubes as defined in the study manuals. On the days when blood samples for PK analysis are collected, patients should be instructed not to take pacritinib at home. The time/date when the prior dose was administered must be recorded on the appropriate CRF page. At minimum, tubes are to be labeled with the patient number, study number, and specimen identification number.

The sponsor will provide the investigator with a manual containing details for the preparation of blood samples to be collected. Shipment and analysis instructions will be provided to the investigator in a separate manual.

8.2 Pharmacokinetic, Pharmacodynamic, and *JAK2* Mutation Burden Assessments

Blood samples for PK and PD analyses will be collected predose and postdose on the specified study days for patients in the pacritinib arm per the two prespecified subsets of the clinical sites.

Blood samples will be collected for central analysis of *JAK2V617F* mutation burden in all patients at screening, and then only in mutation-positive patients at subsequent time points.

9 Assessment of Safety

9.1 Adverse Events

9.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Examples of AEs include, but are not limited to:

- Any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, medical diagnosis, or concomitant disease temporally associated with the use of the study drug, whether considered related to study drug or not
- Abnormalities observed during the study that meet any of the criteria below
  - Any laboratory or other test result that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring
  - Requires discontinuation, dose reduction, or delay of study drug
  - Requires that the patient receive specific corrective or supportive therapy
  - Clinically significant changes noted during physical examinations, ECGs, imaging studies, biopsies, and other safety assessments, whether or not these procedures were required by the protocol

Progressive disease is not an AE, unless it is the primary cause of death. If the primary cause of death is progressive disease, the primary AE term should be reported as "progressive myelofibrosis." Signs and symptoms associated with disease progression may be recorded as secondary AE terms.

9.1.2 Reporting Adverse Events

All baseline conditions and AEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation.

For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of the patient, or may be detected through a clinically meaningful procedure. To prevent bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

The following information should be captured for all AEs: date of onset and resolution, severity per Common Terminology Criteria for Adverse Events (CTCAE), seriousness, the investigator's assessment of relationship to study drug, event outcome, and action taken with study medication due to the reported event. If concomitant treatment is given for the AE, this information should be captured on the appropriate eCRF. If the AE is an abnormal local laboratory value or test result, this information should also be captured on the appropriate eCRF.

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF and symptoms of the illness or disorder should not be reported as separate AEs with the exception of progressive disease, as discussed above. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting investigator (eg, "anemia" versus "low hemoglobin value").

If an AE results in early termination of the patient's study treatment period, "AE" should be selected as the reason for discontinuation on the eCRF. However, if the AE that resulted in early termination was a sign or symptom of progressive disease, "progressive myelofibrosis" should be selected as the reason for discontinuation on the eCRF.

Special Considerations

- Elective procedures or routinely scheduled treatments are not AEs. However, any untoward medical event occurring during a prescheduled elective procedure or routinely scheduled treatment should be documented as an AE.
- Baseline conditions are not AEs; however, worsening of a baseline condition following study drug administration is an AE.
- Death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. However, sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

If progressive disease is the primary cause of death, the term "progressive myelofibrosis" should be reported as the AE term. All AEs ongoing at the time of death that are not the primary cause of death will remain not resolved on the eCRFs.

9.1.3 Criteria for Assessing Adverse Events

9.1.3.1 Severity

The term "severe" is a measure of intensity; a severe event is not necessarily serious.

The National Cancer Institute (NCI) CTCAE version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities identified as AEs. A copy of these criteria is provided in the study manual, however minor version updates (ie, 4.01, 4.02 and above) may be used at the discretion of the sponsor.

9.1.3.2 Relationship

The relationship of an AE to the study treatment(s) will be assessed using the guidelines described below. If an AE is deemed related to study treatment(s) (eg, for BAT) but the investigator cannot attribute the relationship solely to a single treatment, the investigator should indicate that the AE is related to all possible agents. Any AE for which there is no assessed causal relationship shall be assessed by the sponsor as related, and will require immediate follow up with the site to determine the investigator's assessment.

Definite

There is a reasonable causal relationship between the study treatment and the event, and the event occurred within a plausible time relationship to treatment administration, and the event cannot be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge.

Probable

There is reasonable causal relationship between the event and the study treatment, the event occurred within a plausible time relationship to treatment administration, and the event is unlikely to be attributed to the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event follows a clinically reasonable response on withdrawal of study treatment.

Possible

There is a reasonable causal relationship between the event and study treatment, the event occurred within a plausible time relationship to study treatment administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. Dechallenge information is lacking or unclear.

Unlikely

There is a temporal relationship of the event to study treatment but not a reasonable causal relationship, or there is no temporal relationship to study treatment administration or the condition under study, concurrent disease, other drugs or chemicals, or other circumstances provide a plausible explanation for the event.

Unrelated

There is no temporal relationship between the event and study treatment administration (study treatment given too early or late or study drug not administered). There is no reasonable causal relationship between the event and the study treatment. The condition under study, concurrent disease, other drugs or chemicals, or other circumstances provides a plausible explanation for the event.

9.1.3.3 Outcome

AEs will be characterized according to the outcomes described in Table--10

Table--10
Outcomes of Adverse Events

Outcome	Description
Recovered/Resolved	One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated
Recovered/Resolved with Sequelae	One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury
Recovering/Resolving	One of the possible results of an adverse event outcome that indicates the event is improving
Not Recovered/Not Resolved	One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated
Fatal	The termination of life as a result of an adverse event
Unknown	Not known, not observed, not recorded, or refused

9.1.3.4 Action Taken with Study Drug

Action taken with the study drug in relation to the AE will be characterized as follows:

- Dose increased
- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn

- Not applicable
- Unknown

9.1.4 Serious Adverse Events

9.1.4.1 Definition of a Serious Adverse Event

An SAE is an AE that, at any dose, suggests a significant hazard or side effect, regardless of its relationship to the study drug. An AE is serious if it meets any of the criteria below:

1 Results in death
2 Is life-threatening: in the view of the investigator, the event placed the patient at immediate risk of death. This does not include an AE that, had it occurred in a more severe form, might have caused death
3 Requires inpatient hospitalization or prolongation of an existing hospitalization (see Exceptions below)
4 Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
5 Is a congenital anomaly/birth defect
6 Is an important medical event that is not fatal, life threatening, or requiring hospitalization, but may be considered serious if, based on appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above (1 - 5)
7 Cancer/overdose: All cases of new cancers and drug overdose (defined as accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. Determination of seriousness will be reached in consultation with the Safety Physician, CTI Global Pharmacovigilance US Headquarters or designee

9.1.4.2 Exceptions

Hospitalizations not reported as SAEs include admissions for:

1 Planned, nonlife-threatening medical/surgical procedures
2 Routine health assessments requiring admission for health status documentation (eg, routine gastroscopy, colonoscopy, etc)
3 Other life circumstances that have no bearing on health status and require no medical/surgical intervention (eg, lack of housing, family circumstances, etc.)
4 Administration of study medication

9.1.4.3 Reporting Serious Adverse Events to the Sponsor

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. All SAEs, irrespective of causal relationship, must be recorded on a paper SAE Report Form and reported to the Sponsor within 24 hours of becoming aware of the event via either Fax or e-mail.

Fax (US Only): 1-508-416-2654 Fax (outside the US): +44 870 7107157 Email: safety@aptivsolutions.com

Special Considerations:

- SAEs considered to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the investigator or Sponsor shall be followed until the event resolves, stabilizes or the patient is lost to follow up.
- SAEs assessed as unrelated to study drug or study procedures shall be followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.
- For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported.
- All SAEs for randomized patients must have a corresponding AE recorded on the eCRF with an exact match to the event term or description.
- An SAE form should be completed for any event for which doubt exists regarding its seriousness.
- If an ongoing SAE changes in intensity, relationship to study drug, or as new information becomes available and/or known for the event, a follow-up SAE Report form should be completed and sent to the Sponsor within 24 hours of the change in SAE assessment.
- Any SAE that occurs after study completion and is considered by the investigator to be related to pacritinib should be reported to the sponsor.

A narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted by revising the SAE Report Form as soon as the information becomes available.

Source documents should be submitted only in English. If source documents are not in English, the investigator must summarize the source documents and provide a complete English narrative that includes a description of the event as it evolved the results of all diagnostic procedures performed and treatments administered, and the outcome of the event.

9.1.4.4 Reporting Serious Adverse Events to the Regulatory Agencies, Institutional Review Boards and/or Ethics Committees

The Sponsor will evaluate reported SAEs for expedited reporting as assessed against the most current approved version of the Investigator Brochure for pacritinib SAEs, or against the local Summary of Product Characteristics (SPC) for BAT SAEs. If a brand name for a BAT product is unknown or unavailable, the SPC of the local market leader will be used to assess the suspect product(s) for regulatory reporting purposes. Until an AE is identified in the Investigator Brochure, it is considered unexpected, regardless of whether the AE has been submitted previously as an expedited report.

Expedited reporting will be performed by the Sponsor in accordance with local regulation.

Upon receiving an expedited report, the investigator must review and retain the notice with the Investigator Brochure and shall be responsible for submitting expedited reports to their IRB/EC in accordance with institutional guidelines. Regardless of institutional guidelines, investigators shall submit expedited reports to their IRB/EC in the event that the sponsor identifies an expedited report to represent a new and/or unforeseen risk.

In support of required progress reports, the Sponsor will provide the investigator and/or Ethics Committee with a summary of all SAEs reported for the study at predefined intervals (e.g. quarterly) and/or upon request.

Pregnancy

Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment and/or within one month of ending treatment even if the subject is withdrawn from study, this must be reported to the Sponsor immediately on the Pregnancy Reporting Form. The investigator must obtain written authorization (medical records release) from a female partner of a male subject prior to obtaining follow-up.

The investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcome. All pregnancy outcomes will be recorded on the Pregnancy Report Form.

Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will also be recorded in the AE eCRF and on the SAE Report Form. The associated SAE Report Form should be sent to the Sponsor per the procedure and timelines described within Section 9.1.4.3, Reporting Serious Adverse Events to the Sponsor.

Overdose

Overdose is defined as any deviation from the defined or prescribed use of study drug as applicable for the drug and trial design. Occurrences of overdose should be reported to the sponsor on an SAE Report Form. Reports of overdose will be evaluated on a case by case basis. Additional instructions for reporting overdose information will be provided by the Sponsor in the study binder.

Deaths

All deaths that occur during the study must be recorded on the appropriate eCRF. As described in Section 9.1.2 and 9.1.3, death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. Progressive disease is not an AE, except when it is a cause of death. When progressive MF is a cause of death, it should be reported as an AE and SAE as per above.

Sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

9.2 Laboratory Evaluation

All scheduled clinical laboratory test values collected as part of the study will be evaluated by a central laboratory.

The investigator may use local or central laboratory evaluations (as dictated by local standards of care) to facilitate real-time decisions about study treatment administration, eligibility, and dose modifications and for evaluation of signs and symptoms. If any AE is identified, or clinical intervention results from local laboratory tests, the test result and local laboratory normal ranges for that test will be reported on the appropriate eCRF.

Treatment decisions (such as dose delays) and adverse events may be based on either local or central laboratory results.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central lab or independent review panel for study purposes, treatment decisions must be made by the investigator based on his or her clinical assessment of the patient and his or her interpretation of local labs, radiology assessments, and other tests.

9.3 Vital Signs and Physical Examination

Vital signs will be obtained at each study visit. Physical examinations are performed at screening, baseline, every 12 weeks thereafter, and at study termination.

9.4 ECOG Performance Status

ECOG performance status will be assessed at each visit (Appendix 8).

9.5 Safety Surveillance

An IDMC will meet periodically throughout the study (eg, every 6 months), or as described within the IDMC Charter, to review accumulating safety data from the entire clinical trial.

10 Data Management

The CTI Clinical Data Management Department or its designee will prepare guidelines for data entry and data handling, which will include procedures for data verification and electronic edit checks. The complete data management process will be described in the Data Management Plan.

10.1 Data Collection

An electronic data capture (EDC) system will be used for this study. Designated site personnel will enter subject data required by the protocol into eCRFs based on source documents. Personnel will not receive access to the EDC system until they have completed all training requirements. The EDC system will provide an automatic audit trail of all changes made to the clinical database.

10.2 Data Entry and Quality Control

Data items will be entered directly from source documents by designated site personnel using single data entry. Concomitant medications entered into the database will be encoded using the World Health Organization (WHO) Drug Reference Dictionary. AEs, coexisting disease, and other data items will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in a database system maintained by the central vendor. If clinical intervention is performed on the basis of any local laboratory test result, the test result and local laboratory normal ranges will be entered into the EDC system.

CTI staff or designees will review the data on a periodic basis to ensure validity, accuracy and completeness. Data suspected to be discrepant or incomplete will be questioned using data queries. Data queries resulting from these reviews will be sent to the study sites via the EDC system. The staff at the

study sites will respond to the queries in the EDC system and these responses will be reviewed by CTI staff or designee. Only data that do not unblind the Sponsor will be reviewed by the Sponsor.

11 Statistical Analysis Plan

Statistical analysis of the study data will be the responsibility of CTI Biostatistics Department or its designee. This section describes the statistical methodology used in the primary analysis of the co-primary endpoints. Analysis of the exploratory endpoints and other supportive, sensitivity, or subgroup analyses will be specified in a separate statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of the clinical database.

11.1 Endpoints

11.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of the study are:

- the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT and,
- the proportion of patients with a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

11.1.2 Exploratory Endpoints

The exploratory endpoints are:

1 Overall survival (OS)
2 Progression-free survival (PFS)
3 Leukemia-free survival (LFS)
4 Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥35% reduction from baseline in spleen volume
6 Best response in spleen volume by MRI or CT
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)
9 Achievement of reduced RBC transfusion dependence (Appendix 1a)
10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4).

Details for the definition and analysis of the exploratory endpoints are provided in the Statistical Analysis Plan.

11.2 Hypotheses

11.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in:

- a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and
- a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0

than treatment with BAT.

11.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

11.3 Analysis Populations

11.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. This population will be used for the primary analysis of the efficacy endpoints.

11.3.2 Evaluable Population

The evaluable population for each endpoint is defined as all randomized patients who have an evaluable baseline and follow-up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for the supportive analyses of the efficacy endpoints.

11.3.3 Per-Protocol Population

The per-protocol (PP) population is defined as all randomized patients who receive any study treatment, have a baseline assessment, complete relevant follow-up assessments, and have no major protocol violations. Patients in this population will be analyzed according to the treatment actually received. The PP population will be used for the supportive analyses of the primary efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

11.3.4 Safety Population

The safety population is defined as all randomized patients who receive any dose of study treatment. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received.

11.3.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK, plasma PD markers or STAT3 phosphorylation analysis. The study pharmacokineticist will review data listings of patient dosing and sample records to identify patients with appropriate samples for the analysis.

11.4 Efficacy Analysis

Efficacy analyses including all hypothesis testing will be performed after the last patient completes the Week 24 assessments or experiences progressive disease, whichever comes first. Analysis of long-term safety and efficacy will be performed as supportive analyses as specified in the Statistical Analysis Plan.

11.4.1 Reduction in Spleen Volume

The primary analysis of the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT will be based on the IRF assessments. The analysis will be performed using the ITT population. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be presented by the 3 treatment arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression or drop out of the study before Week 24 will be considered to have not achieved the ≥35% reduction. The numbers and percentages for each reason for not achieving the ≥ 35% reduction will be presented by treatment arm. The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the appropriate confidence intervals based on the Agresti-Caffo method will be provided.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤ 100,000/μL versus > 100,000/μL). The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata.

The primary analysis will be repeated using other post-baseline reduction in spleen volume (Week 12, Week 36, and Week 48). The mean or median reduction in spleen volume over time will be evaluated. More details will be provided in the SAP.

11.4.2 Improvement in Total Symptom Score

All the analyses outlined in Section 11.4.1 will be repeated using the proportion of patients with a ≥ 50% reduction from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

The TSS endpoint is obtained as follows:

- The daily TSS is the sum of the individual symptom scores for tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side. Daily TSS is set to missing if one of these individual symptom scores is missing.
- The baseline TSS is the mean of the daily TSS over the 7 consecutive days immediately prior to randomization. Baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to randomization.
- The Week 24 TSS is the mean of the daily TSS over the 28 consecutive days prior to the Week 24 visit. The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to the Week 24 visit. Patients with a missing Week 24 TSS, including those who meet the criteria for disease progression or drop out of the study before Week 24, will be considered to have not achieved the ≥ 50% reduction.
- The percent reduction in TSS from baseline to Week 24 is then computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 24 TSS} - \text{Baseline TSS}}{\text{Baseline TSS}}\right) * 100$$

A sensitivity analysis will be conducted using the average of the 7 daily TSS prior to the Week 24 visit as the Week 24 TSS. The details of the analysis will be described in the SAP.

In addition, exploratory analyses of the correlation of Week 24 TSS with Week 24 spleen size, STAT3 phosphorylation, and patient global impression assessment will be performed. Details are provided in the SAP.

11.4.3 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1 The primary hypothesis will be tested at $\alpha = 0.05$ (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on:
   a. the difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24, and
   b. the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24

   individually.

   The study reaches its primary objective (claimed to be successful) when both endpoints reach statistical significance ($\alpha = 0.05$, 2-sided).

2 If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in a) the QD arm versus the BAT arm and b) the BID arm versus the BAT arm at the 2-sided 0.025 α-level.
   a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be tested at a 2-sided $\alpha = 0.025$.
   b. If the p-value is less than α, the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24 will be tested at a 2-sided $\alpha = 0.025$.

11.5 Safety Analysis

The assessment of safety will be based mainly on the frequency of AEs and the number of laboratory values that fall outside of predetermined ranges.

Treatment-emergent AEs will be coded using MedDRA version 16.0 and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients with an event. The following subsets of treatment-emergent AEs will also be summarized by treatment arm: AEs related to study treatment, CTCAE grade 3 or 4 AEs, AEs leading to treatment discontinuation, deaths, and SAEs. Ongoing AEs in patients who cross over to pacritinib will be assessed at the time of the crossover, and the CTCAE grade at the time of crossover will be considered the new baseline.

Clinical laboratory data will be summarized with descriptive statistics by treatment and timepoint. Each patient's data will be classified by the CTCAE grade, where possible, and be summarized in shift tables comparing the worst post-baseline visit to baseline.

11.6 Determination of Sample Size

A sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. Based on previous studies, it is assumed that the proportion of patients achieving a $\geq$ 35% reduction in spleen volume at Week 24 is 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. It is also assumed that the proportion of patients achieving a $\geq$ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm.

For primary hypotheses (pooled QD/BID vs BAT), a sample size of 300 patients provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for the secondary hypothyses testing independently; i.e., comparing QD pacritinib arm with the BAT arm and comparing the endpoint in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is $\geq$ 93% power to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

11.7 Interim Analyses

No interim analyses are planned for this study.

12 Pharmacokinetic and Pharmacodynamic Analyses

The PK parameters will be summarized with descriptive statistics. The relationship between exposure and the efficacy and safety of pacritinib will be evaluated. Population PK analysis will be performed.

13 Independent Data Monitoring Committee

An IDMC will be chartered to monitor and evaluate the safety of all patients in this trial. The IDMC will periodically review summaries of trial data, including all safety data, identifying any clinically relevant trends, and making recommendations as to whether the study should continue. The IDMC Charter will include operational and logistical procedures for the IDMC.

14 Study Administration and Investigator Obligations

For studies conducted outside the United States under a US IND, the principal investigator must comply with US FDA IND regulations and with those of relevant national and local health authorities.

14.1 Study Drug Accountability

Cell Therapeutics, Inc. will provide pacritinib. The recipient will acknowledge receipt of the drug by returning the appropriate shipping receipt form according to the study-specific pharmacy manual. Damaged supplies will be replaced.

Accurate records of all pacritinib dispensed from and returned to the study site should be recorded by using the Drug Inventory Log (refer to study-specific pharmacy manual).

Pacritinib will be disposed of at the study site according to institutional standard operating procedures after study monitors have completed the drug inventory reconciliation. The method of destruction must be documented. A copy of the destruction certification along with the inventory of destroyed clinical material will be provided to Cell Therapeutics, Inc.

14.2 Informed Consent

Cell Therapeutics, Inc. will provide a sample ICF to each site. Cell Therapeutics, Inc. or its designee must review any proposed deviations from the sample ICF. Patients must be re-consented to the most current version of the ICF during their participation in the study. The investigator must provide the final local IRB/REB/IEC approved informed consent form to Cell Therapeutics, Inc. for regulatory purposes.

The patient or the patient's legally authorized representative must sign the ICF before his or her participation in the study. The source record for each patient shall document that informed consent was obtained prior to participation in the study. A copy of each signed ICF or Addendum to an existing ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed consent forms must remain in each patient's study file and must be available for verification by the study monitor at any time.

14.3 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, Cell Therapeutics, Inc., its designees and the IRB/IEC/REB for each study site, if appropriate.

14.4 Case Report Forms

Cell Therapeutics, Inc. will provide eCRFs, which should be completed in accordance with instructions from Cell Therapeutics, Inc.

14.5 Study Monitoring

Representatives of Cell Therapeutics, Inc. or their designee must be allowed to visit all study site locations at appropriate intervals to assure compliance with Good Clinical Practice (GCP), satisfactory enrollment rate, data recording, and protocol adherence. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The investigator agrees to cooperate with the monitor to ensure any problems detected in the course of these monitoring visits are resolved. In addition to these visits, Cell Therapeutics, Inc. will routinely monitor each site by phone to keep abreast of patient status and to answer questions.

In order for the investigator to participate in this trial, the trial monitor must have direct access to source data for data verification. This will be done by comparing data from the eCRFs with data from the patient's clinic or hospital records (permission will be sought from the patient as part of the consent process).

In addition, Cell Therapeutics, Inc. internal auditors and government inspectors may evaluate the study. They must be allowed access to eCRFs, source documents, and other study files. Cell Therapeutics, Inc. audit reports will be kept confidential.

The investigator should promptly notify Cell Therapeutics, Inc. of an audit scheduled by any regulatory authority, and promptly forward copies of audit reports.

14.6 Record Retention

US FDA regulations (21CFR§312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that the principal investigator retain records and documents pertaining to the conduct of the study and distribution of investigational drug, including eCRFs, consent forms, laboratory test results, radiographic assessments, and medication inventory records for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. Cell Therapeutics, Inc. will notify the principal investigator of these events.

No records should be disposed of without the written approval of Cell Therapeutics, Inc.

15 Ethics

15.1 Good Clinical Practice

The investigator and sponsor will ensure that this study is conducted in full compliance with Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines, US FDA regulations 21 CFR Parts 50, 56, and 312, and with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient.

15.2 Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC)

The appropriate IRB, REB, or IEC must approve in writing the protocol and ICF for this study in accordance with the laws and regulation of the country in which the research is conducted prior to any patient being registered in this study.

Before the investigational drug will be shipped to the investigator, the investigator must provide Cell Therapeutics, Inc. with a copy of the IRB or REB or IEC approval letter stating that the study protocol and informed consent form have been reviewed and approved. Original US FDA Form 1572 (for all studies conducted under US IND regulations) signed by the principal investigator, and a copy of the CV for the principal investigator, and a copy of an IRB/REB/IEC approved informed consent form are also required.

The investigator must also report all serious and medically significant AEs to the IRB/REB/IEC according to the local regulation.

Error! Reference source not found. lists the responsibilities of the investigator.

16 Termination of Study

Cell Therapeutics, Inc. will retain the right to terminate the study and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory enrollment with regard to quality or quantity
- Deviations from GCP
- Deviation from protocol requirements, without prior approval from Cell Therapeutics, Inc.
- Inaccurate and/or incomplete data recording on a recurrent basis
- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

In terminating the study, Cell Therapeutics, Inc. and the investigator will assure adequate consideration to the protection of the patients' interest.

17 Study Amendments

Changes in any portion of this protocol must be documented in the form of an amendment from Cell Therapeutics, Inc. and must be approved by the site's IRB/REB/IEC before the amendment can be implemented at the site. The IRB/REB/IEC chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions.

18 Use of Information and Publication

Cell Therapeutics, Inc. recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The Clinical Study Agreement will describe the details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial.

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Appendix 1a - Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	$\geq$ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al, 2011	

Appendix 1b – Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

Appendix 2 - International Working Group Consensus Criteria for Treatment Response in Myelofibrosis with Myeloid Metaplasia

Clinical Improvement	
Hemoglobin	A minimum 20g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100g/L) for 8 weeks or more
Platelet count	A minimum 100% increase in platelet count and an absolute platelet count of at least 50,000/μL (applicable only for patients with baseline platelet count below 50,000/μL) for 8 weeks or more
Tefferi et al 2006	

Appendix 3 - EQ-5D-5L Health Questionnaire

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

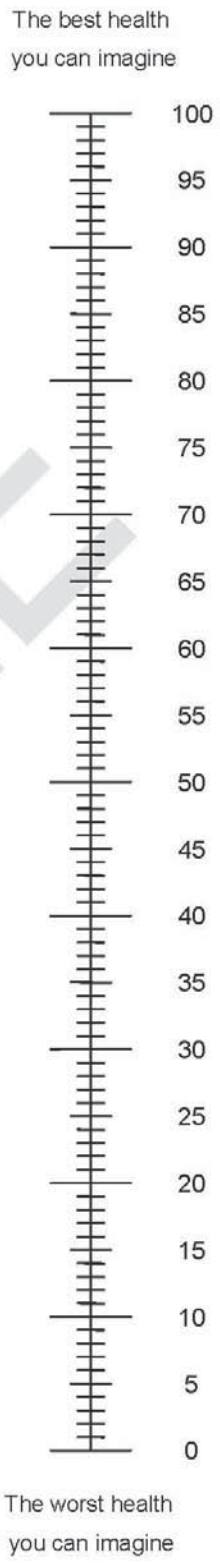
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



3

Appendix 4 - EORTC QLQ-C30 Version 3

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5 - Dynamic International Prognostic Scoring System in Primary Myelofibrosis (Passamonti et al, 2010)

Prognostic Variable	Value		
	0	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, x 10^9/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

Risk Category	
Low	0
Intermediate-1	1-2
Intermediate-2	3-4
High	5-6

Appendix 6 - Diagnostic Criteria for Primary Myelofibrosis, Post-Polycythemia Myelofibrosis and Post-Essential Thrombocythemia Myelofibrosis

	Major Criteria	Minor/Additional Criteria
Primary myelofibrosis (PMF) Diagnosis requires meeting all 3 major criteria and at least 2 minor criteria[1]	1. Megakaryocyte proliferation and atypia[3] accompanied by either reticulin and/or collagen fibrosis **or** 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) 2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm 3. Demonstration of JAK2V617F or other clonal marker **or** No evidence of reactive marrow fibrosis	1. Leukoerythroblastosis 2. Increased serum LDH 3. Anemia 4. Palpable splenomegaly
Post-polycythemia vera myelofibrosis (PPV-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5cm (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 degrees C)
Post-essential thrombocythemia myelofibrosis (PET-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] and a ≥2 mg ml^{-1} 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

	Major Criteria	Minor/Additional Criteria
		margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5 degrees C)

Abbreviations:
WHO - World Health Organization
MDS - myelodysplastic syndrome
CML - chronic myelogenous leukemia
LDH - lactate dehydrogenase

[1] Tefferi A, Vardiman, JW 2008
[2] Barosi G, Mesa RA, Thiele J, et al. 2008
[3] Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering
[4] Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain) (see WHO criteria)
[5] Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis (see WHO criteria)
[6] Below the reference range for appropriate age, sex, gender and altitude considerations

Appendix 7 – Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (Version 2.0)

Symptom	0 to 10 Ranking
Select the one number that describes the worst severity you have experienced with each of the following in the past 24 hours:	
Tiredness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Pain under ribs on the left side	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix 8 - Eastern Cooperative Oncology Group Performance Status Scale Grade Description (Oken et al 1982)

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 9 - Selected Potent Inhibitors of CYP3A4

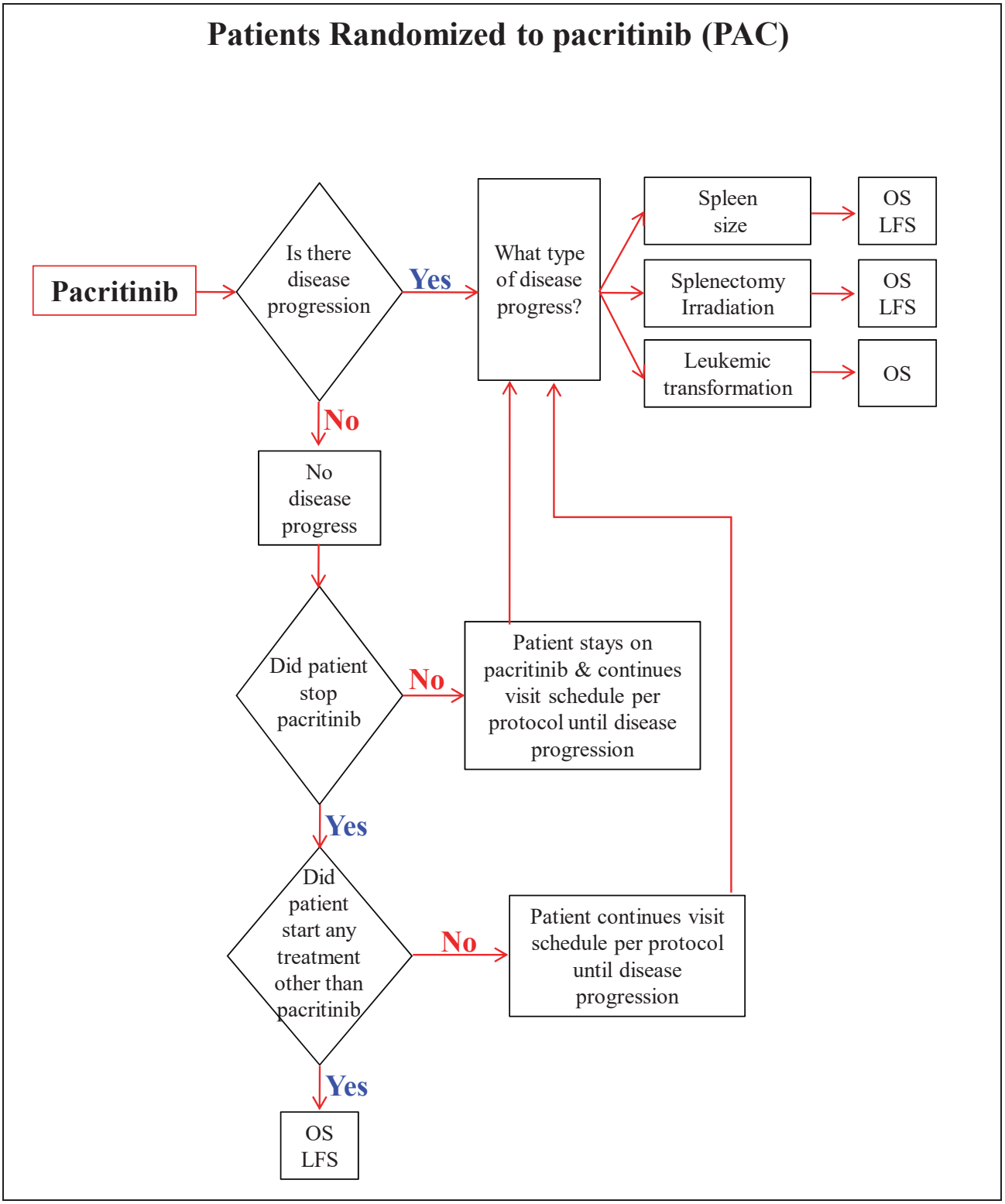
boceprevir	nefazodone
ciprofloxacin	nelfinavir
clarithromycin	norfloxacin
conivaptan	posaconazole
erythromycin	quinidine
fluconazole	ritonavir
grapefruit	saquinavir
grapefruit juice	Seville oranges
indinavir	star fruit
itraconazole	telaprevir
ketoconazole	telithromycin
lopinavir	troleandomycin
mibefradil	voriconazole
This list is not comprehensive. When considering using an agent that could be a potential CYP3A4 inhibitor/inducer, please discuss this with the medical monitor. Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://wwwpharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.	

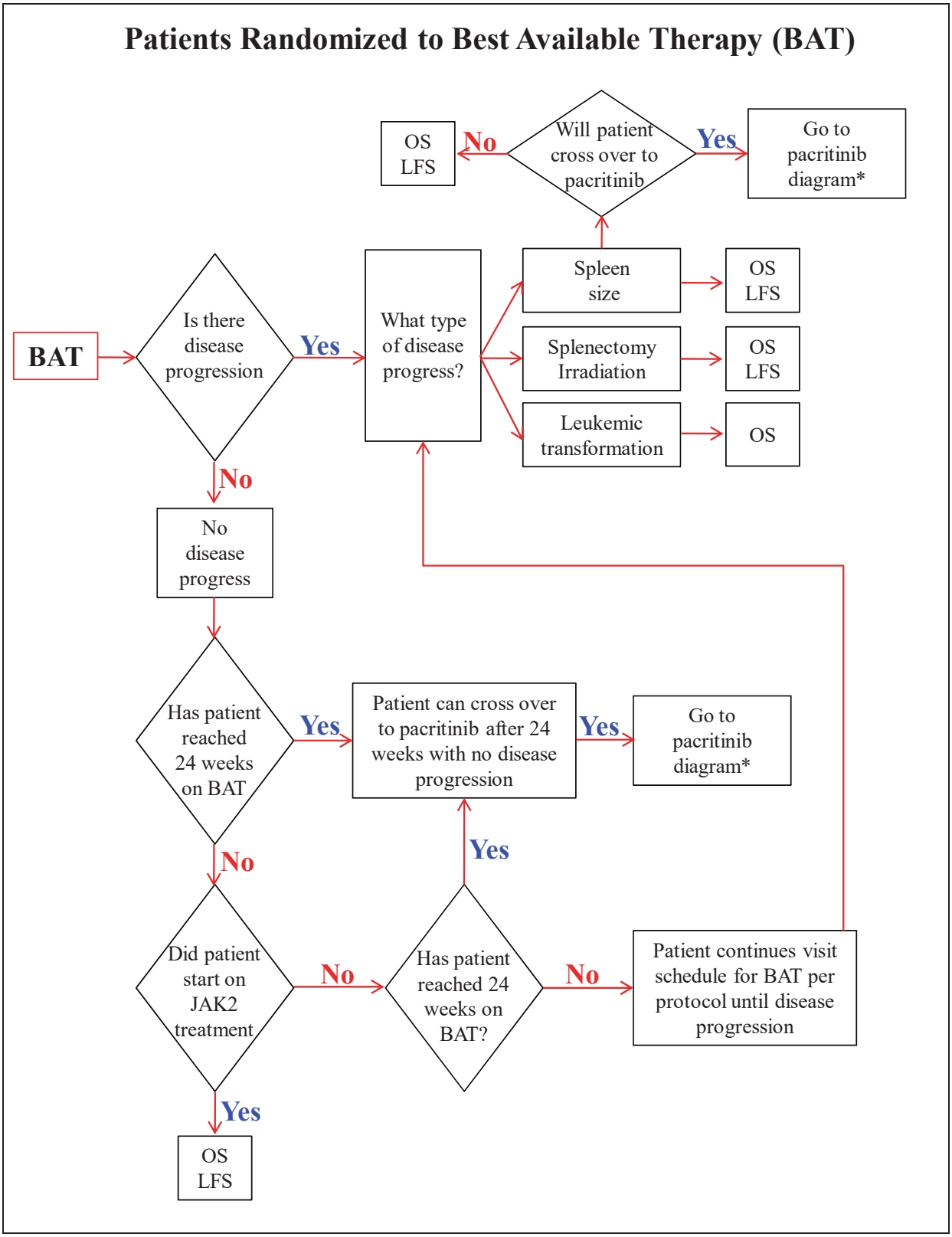
Appendix 10 - The Stages of Heart Failure, New York Heart Association (NYHA) Classification

To determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
Source: Dolgin et al.	

Appendix 11 – Study Flowchart




Patients Randomized to Best Available Therapy (BAT)
BAT
Is there disease progression
Yes
No
What type of disease progress?
Spleen size
OS LFS
Splenectomy Irradiation
OS LFS
Leukemic transformation
OS
Will patient cross over to pacritinib
No
OS LFS
Yes
Go to pacritinib diagram*
No disease progress
Has patient reached 24 weeks on BAT
Yes
Patient can cross over to pacritinib after 24 weeks with no disease progression
Yes
Go to pacritinib diagram*
No
Yes
Did patient start on JAK2 treatment
No
Has patient reached 24 weeks on BAT?
No
Patient continues visit schedule for BAT per protocol until disease progression
Yes
OS LFS

Appendix 12 - Common Terminology Criteria for Adverse Events: Diarrhea (Version 4.03)

Definition: A Disorder Characterized by Frequent and Watery Bowel Movements.	
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Appendix 13 - Responsibilities of the Investigator

For a complete list of investigator responsibilities refer to the ICH guideline for GCP, Section 4.0; *Investigator*. The responsibility of the investigator includes but is not limited to the following criteria:

1. To provide the qualifications of the investigator(s) by Curriculum Vitae and/or other documentation to the sponsor or regulatory authorities upon request.
2. To be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator Brochure, in the product information, and in other information sources provided by the sponsor.
3. To comply with GCP and applicable regulatory requirements.
4. To permit monitoring and auditing by the sponsor, access to all relevant trial documents, and inspection by appropriate regulatory authorities.
5. To maintain a list of qualified persons to whom the investigator has delegated significant trial-related duties.
6. To be able to demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.
7. To have sufficient time to properly conduct and complete the trial within the agreed trial period.
8. To have available adequate facilities and qualified staff to conduct the trial properly and safely for the foreseen duration of the trial, and to ensure that other trials do not divert essential patients or facilities away from the trial.
9. To ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
10. To ensure that adequate medical care is provided to a patient for any adverse experiences, related to the trial, during and following his/her participation in a trial.
11. To inform a patient when medical care is needed for inter-current illness of which the investigator becomes aware.
12. To inform (if possible) the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
13. To secure written and dated IRB/IEC/REB approval prior to initiating a trial for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements), and any other written information to be provided to patients.
14. To provide the IRB/IEC/REB with all trial-relevant documents for review.
15. To conduct the trial in compliance with the protocol as approved by the IRB/IEC/REB and agreed to by the sponsor and applicable regulatory authorities.
16. To sign the protocol (with the sponsor), or an alternative contract, to confirm their agreement on conducting the trial.
17. To not implement any deviation from, or changes of, the protocol without agreement by the sponsor and approval from the IRB/IEC/REB of an amendment, except where necessary to eliminate an immediate risk to trial patients, or when the changes involve only logistical or administrative aspects of the trial, and to document and explain any such deviations. If a deviation or change in the protocol was implemented by the investigator to eliminate an immediate hazard(s) to patients without prior IRB/IEC approval/favorable opinion; the deviation (and reason for) or proposed change must be submitted as soon as possible:
    - To the IRB/IEC/REB for review and approval/favorable opinion;
    - To the sponsor for agreement and, if required;

- To the regulatory authority(ies).

18. To assume full responsibility for investigational products at the trial site (whether through personal supervision or through assignment of these duties to a qualified health care professional). This includes responsibility for usage, accountability (including all necessary documentation), storage and handling, instruction and supervision of any personnel authorized in the usage of the investigational product, and disposition of supplies upon completion of the trial.
19. To follow all randomization procedures and protect the integrity of the blind (if used). In the event of premature unblinding in a blinded trial, the investigator is to promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse experience) of the investigational products.
20. To ensure that the confidentiality of all information about patients and information supplied by the sponsor is respected by all persons involved in the trial.
21. In regards to data collection and management:
    - To collect and record data properly and ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports;
    - To ensure that data reported on the eCRFs, which are derived from source documents, are consistent with the source documents, and that all discrepancies are explained;
    - To follow the sponsor's guidance in making changes or corrections to eCRFs;
    - To maintain the essential trial documents as required by the applicable regulatory requirements, until notification by the sponsor.
22. To provide all requested reports or notification of changes affecting the conduct of the trial, and/or increasing the risk to patients to the sponsor, IRB/IEC, investigative institution, or applicable regulatory agency.
23. To report all deaths, serious adverse experiences, adverse experiences and laboratory abnormalities to the sponsor according to the procedures specified in the protocol.
24. To promptly inform the trial patients in the event that the trial is terminated prematurely or suspended for any reason, and to provide appropriate therapy and follow-up procedures. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator is to inform the institution, where required by the applicable regulatory requirements, and the investigator/institution is to promptly inform the sponsor and the IRB/IEC, and provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
25. To promptly notify the sponsor and investigative institution (with detailed written explanation) of any change or retraction of IRB/IEC approval, where applicable.
26. To provide, upon completion of the trial, all required reports and/or summaries to the sponsor, the IRB/IEC and applicable regulatory authorities.

Cell Therapeutics, Inc.

PERSIST-2 Protocol

PAC326

Pacritinib

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

IND 78,406
EUDRA CT 2013-004000-19

Amendment 1
January 30, 2014

Sponsor:
Cell Therapeutics, Inc.
3101 Western Avenue, Suite 600
Seattle, WA 98121

Medical Monitor
Mary S. Campbell, MD
Associate Medical Director
206-282-7100

Table of Contents

List of Tables

Investigator Responsibilities, Required Documentation, and Signature

Cell Therapeutics, Inc. will select the investigator(s) on the basis of their expertise in the field of clinical studies in hematologic oncology and in the care and treatment of patients with chronic myeloproliferative diseases. Investigators will also be selected on the appropriateness of their facility to conduct a research study of this nature, and the characteristics of the patient population treated at the institution. The investigator will:

- Obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol and amendments to the protocol and Informed Consent Form before initiation of the protocol or any amendments for the study, and obtain annual IRB or IEC renewal, as required.
- Ensure that current FDA and/or ICH-E6 regulations are followed.
- Select all patients in accordance with the selection criteria outlined in the study protocol.
- Treat and follow patients as described in this research protocol. Complete all electronic case report forms (eCRFs) in a timely manner and review eCRFs for accuracy and completeness. Provide the original clinical source documents to verify all data entered on eCRFs or SAE reports and all data that document the course of the patient throughout their participation on the study. Provide a clinical summary to the sponsor's clinical research monitor.
- Report all adverse events to Cell Therapeutics, Inc., or designee, as required by the protocol.
- Ensure that the investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing information is recorded and all drug can be accounted for at all times.
- Before initiation of the study, each participating investigator will submit to CTI:
  - FDA Form 1572 and, if applicable, other ministry of health required forms
  - Copies of the medical licenses of principal investigators and subinvestigators
  - Addresses and descriptions of all clinical laboratory facilities to be used
  - Laboratory certification and expiration dates
  - Normal ranges and effective dates for all required laboratory tests
  - IRB/IEC approval letter referencing the protocol (and amendments, if applicable).
  - IRB/IEC Membership List: A list of the IRB/EC members, their respective titles or occupations, and their institutional affiliations.
  - A sample copy of the IRB/IEC-approved Informed Consent Form
  - Curricula vitae: Curricula vitae for the principal investigator and all subinvestigators
  - Financial disclosure for the principal investigator and all subinvestigators
  - Protocol signature page, signed by the principal investigator

Investigator Statement and Signature:

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

_____

Principal Investigator Signature Date

_____

Principal Investigator Name, Printed Date

Protocol Synopsis

Study Title	A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis
Protocol Number	PAC326
Version	Amendment 1
Sponsor	Cell Therapeutics, Inc.
Clinical Phase	Phase 3

Objectives

Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arms(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan and the proportion of patients achieving a ≥ 50% reduction in total symptom score (TSS) from baseline to Week 24 as measured by the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

Secondary Objectives

The secondary objectives are:

1 To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2 To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1 Overall survival (OS)
2 Progression-free survival (PFS)
3 Leukemia-free survival (LFS)
4 Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥ 35% reduction in spleen volume from baseline
6 Best response in spleen volume by MRI or CT scan
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)
9 Achievement of reduced RBC transfusion dependence (Appendix 1a)

10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4)

Pharmacokinetic and Pharmacodynamic Objectives
The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on the safety and efficacy of pacritinib.

Study Design

This study is a multicenter, randomized, controlled, phase 3 study. It will compare the efficacy and safety of two dose schedules of pacritinib in pooled and individual group analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter. The analysis of the primary outcome of spleen response will be performed when all randomized patients have completed the Week 24 MRI or CT evaluation, met progressive disease criteria, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

Number of Centers

Approximately 100 centers is planned to enroll patients over an estimated period of 11 months.

Number of Patients

The study will randomize approximately 300 patients, with approximately one-third of patients randomized to pacritinib dosed QD, one-third to pacritinib dosed BID, and one-third to BAT.

Randomization

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT. Randomization will be stratified by geographic region (US versus Canada versus Europe versus rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. The most recent platelet count obtained prior to randomization on Days -3 to 1 will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pretransfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification.

Diagnosis and Inclusion Criteria

1. Intermediate-1, intermediate -2, or high risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤ 100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the lower costal margin (LCM) in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 × ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)
15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study
17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcome instrument

19. Able to understand and willing to sign the Informed Consent Form

Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
4. More than 6 months of cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplant (ASCT), or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion, with the approval of the medical monitor, if the arrhythmias are stable, asymptomatic, and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450ms, or other factors that increase the risk for QT interval prolongation (eg, heart failure, hypokalemia [defined as serum potassium <3.0mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

Study Drug, Dose, and Mode of Administration

Patients taking pacritinib will be supplied with 100-mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally once a day at the same time of day, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib orally twice each day at the same times of day, with or without food.

Duration of Study Treatment, Continuation of Treatment, and Crossover to Pacritinib

Each patient is to receive pacritinib or BAT until progression of disease (defined in the Study Treatment and Follow-up synopsis section), the occurrence of unacceptable toxicity, or the patient no longer derives

benefit from treatment.

Patients on BAT may cross over to pacritinib at the time of splenic progression (defined in the Study Treatment and Follow-up synopsis section), at any time after splenic progression (if leukemic transformation, splenectomy, and splenic irradiation have not occurred), or after completing 24 weeks of treatment, with or without progression. When it is decided that a patient will crossover from BAT to pacritinib treatment, the investigator will also specify the patient's pacritinib dose schedule (QD or BID); this dose schedule will not be changed again for the duration of study treatment. Patients may continue on active (drug) study treatment after progression of disease (see Study Treatment and Follow-up synopsis section).

Patients who crossover from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT. Spleen size at the time of crossover will be the new baseline for subsequent determination of progression.

Patients on BAT who have splenic progression, but do not wish to crossover to pacritinib, will be followed for safety, survival, and leukemic transformation; they will not be followed for splenic progression, as long as they continue the BAT treatment they were taking at the time of progression. Patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will not be followed for safety, but will be followed for leukemic transformation and survival.

Patients on pacritinib may continue pacritinib treatment with an unchanged dose schedule after splenic progression, if they are still deriving benefit from treatment and not experiencing excessive drug toxicity. Patients on pacritinib who have splenic progression, but wish to continue taking pacritinib will be followed for spleen volume, safety, survival, and leukemic transformation (but not for splenic progression) until they discontinue taking pacritinib.

Study Treatment and Follow-up

Progression of Disease
A patient may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced and both should be reported.

Progression of disease **is defined as one or more of the following:**

- Splenic progression, defined as an increase in splenic volume of ≥ 25% from baseline, based on centrally read MRI or CT scan
- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥ 20%, sustained for ≥ 8 weeks
  - Bone marrow blast count ≥ 20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Criteria for Treatment Continuation After Progression of Disease

To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥ 25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF

Criteria for Crossover from BAT to Pacritinib Treatment

To crossover from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

A patient who crosses over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment.

If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT scan must be completed within 30 days prior to the start of pacritinib treatment. This scan serves as a new baseline spleen volume; the patient will be followed for a second, post-crossover event of splenic progression relative to the new baseline measurement.

Study Assessments

All patients will be followed for response, splenic and leukemic progression, survival, and other endpoints according to **Table--1** the Study Assessments Calendar.

Special Cases - Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on the criteria for crossover (described in this section) will follow the Study Assessments Calendar, starting at *Start of Week 1 (BL)*, except that no PK or PD assessments will be performed.

Patients who continue an active BAT despite splenic progression will be followed per the Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT scan. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in the Study Assessments Calendar if they opt to not crossover to pacritinib.

Patients who continue pacritinib despite splenic progression will continue to be followed per the Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only*

Follow-up column in the Study Assessments Calendar.

Patients who discontinue pacritinib, but have not progressed, will continue to be followed per the Study Assessments Calendar until progression occurs. After progression, these patients will be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

Patients who undergo splenic irradiation or splenectomy or initiate any non-protocol-directed anti-MF treatment will subsequently be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

All patients will be followed per the Study Assessments Calendar for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

Evaluation

Efficacy

Spleen Volume Assessment by MRI or CT - Spleen volume measurement by MRI or CT will be performed at screening and every 12 weeks thereafter, until progression of disease or withdrawal from study. MRI is the preferred modality; CT will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Imaging for spleen volume assessment may be performed at other time points, if progressive disease is suspected by palpation or as indicated by the treating physician. All scans should be submitted for central reading. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement.

Spleen Size Assessment by Physical Examination - Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

Disease-Related Signs and Symptoms - The MPN-SAF TSS 2.0 will be completed daily for 7 to 10 consecutive days prior to starting treatment and then daily through Week 48 of the study or until the patient discontinues study treatment, whichever occurs first. The pain medication log will be completed daily as long as the MPN-SAF TSS 2.0 is being completed. The patient global impression assessment will be completed every 8 weeks through Week 24, and then every 12 weeks, until the patient discontinues study treatment.

Survival - Patients will be followed for survival and for transformation to acute myeloid leukemia (as assessed by the investigator, investigator-obtained records, or, if these are not available, by patient-provided history) until 3 years after the first of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

Quality-of-Life Assessments - The EQ-5D-5L and EORTC-QLQ-C30 will be completed at baseline, every 8 weeks for the first 24 weeks, and then every 12 weeks during study treatment.

Patients will also be followed for frequencies of RBC and platelet transfusions, and other exploratory endpoints.

Safety

Adverse Events - AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. SAEs that the investigator or Sponsor considers related to study drug or study procedure shall be followed until the event resolves, stabilizes or the patient is lost to follow-up, whichever occurs first. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

Hematology - Hematology parameters (complete blood count [CBC] with differential and platelet count) will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final hematology testing will be performed at treatment termination. In addition, unscheduled CBC with differential and platelet counts may be performed locally and/or centrally, when clinically indicated.

Blood Chemistry - Blood chemistry parameters to be evaluated include alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.

These parameters will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final chemistry testing will be performed at treatment termination. In addition, unscheduled chemistries may be performed locally and/or centrally, when clinically indicated.

ECG Assessment - For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening; within 1 hour prior to dosing; at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3; and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening; at baseline; on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing); and as clinically indicated. Local ECG readings will be used throughout the study.

Gastrointestinal Toxicity Management - Patients will be evaluated at baseline to assess usual bowel habits and will be instructed on the need for early intervention for possible GI side effects of treatment. At the baseline visit, all patients will be provided with a prescription for an antidiarrheal drug and instructed to start taking it as soon as diarrhea is noted. The investigator or a surrogate will contact each patient by telephone during Week 1 (Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to pacritinib) and at the beginning of Week 3 of initial treatment or after crossover to pacritinib to evaluate GI toxicity and assess the need for modifying the treatment for GI side effects. Standard supportive care measures should be provided to control symptoms of GI toxicity, such as diarrhea, constipation, nausea and vomiting.

Ruxolitinib Dose Management - Patients on BAT who are being treated with ruxolitinib or other approved JAK2 inhibitors must be dosed according to current local labeling recommendations.

Pharmacokinetic-Pharmacodynamic Assessments

Pharmacokinetics and Pharmacodynamics – PK samples without PD sampling will be collected from approximately 130 patients taking pacritinib at the Week 12 and Week 24 visit days (predose [Hour 0]).

In addition to assessment of pacritinib plasma concentrations, STAT3 phosphorylation (an established pharmacodynamic marker for JAK-STAT signaling pathway inhibition) will be assessed. PK/PD samples for assessment of exposure-response will be collected from the remaining approximately 70 patients taking pacritinib at a prespecified subset of clinical sites at Day 1 of Week 1 (predose [Hour 0] and 4 hours postdose; only a PD sample will be collected at the predose time point), Day 1 of Week 3 (predose [Hour 0] and at 4 hours postdose), and at Week 12 and Week 24 visit days (predose [Hour 0]). The resulting data will be used to assess exposure, and exposure-safety and exposure-efficacy relationships.

JAK2 Mutation Status - JAK2V617F mutation burden will be assessed by a central laboratory in all patients at screening, then at Week 12, and every 12 weeks thereafter in patients who have the mutation.

Statistical Methods

The study has two primary endpoints: the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by MRI or CT scan, and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

The primary hypotheses of the study are to compare the pacritinib arms QD and BID (pooled) versus BAT arm for the two primary endpoints. The study will be claimed to be successful when both endpoints reach statistical significance ($p \leq 0.05$) individually.

The secondary hypotheses are to compare QD vs BAT and BID vs BAT, separately at a significance level of 0.025, on spleen reduction and TSS reduction, the two primary endpoints.

The Fisher Exact test will be used to evaluate both endpoints. Patients who meet the criteria for disease progression or drop out of the study before Week 24 will be considered non-responders.

A total of 300 patients is planned to be randomized (1:1:1) in the study. This sample size provides at least 95% power on the primary hypotheses (QD+BID vs BAT) for both endpoints individually (at an α-level of 0.05, 2-sided), and at least 93% power for each secondary hypothesis (QD vs. BAT; BID vs. BAT) independently (at an α-level of 0.025, 2-sided).

No interim analysis is planned.

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
Patients who continue an active BAT despite splenic progression will continue to be followed per this Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in this calendar.
Patients who continue pacritinib despite splenic progression will continue to follow this Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in this calendar.
Patients who discontinue pacritinib, but have not progressed will continue to follow this Study Assessments Calendar until progression occurs, and then will follow the *Survival-Only Follow-up* column in this calendar. Note: patients who have stopped taking pacritinib must complete a termination visit within 7 days of stopping the drug.
Patients who undergo splenic irradiation, splenectomy, or who initiate any non-protocol-directed anti-myelofibrosis treatment will subsequently be followed per the *Survival-Only Follow-up* follow-up column in this calendar.

Week	**Consent and Platelet Eligibility**	**Screen**[2]	**Symptom Assessment & Screening MRI Visit**	**Randomization** (patient need not be present)	**Start of Wk 1 (BL)**[3]	**Wk 1**[4]	**Start of Wk 2**[5]	**Start of Wk 3**	**End of Wk 4**	**End of Wk 8**	**End of Wk 12**[6]	**End of Wk 16**	**End of Wk 20**	**End of Wk 24**	**End of Wk 36 & q12w**	**Term**[7]	**30 d Post-Term**	**Survival-only** (Off Treatment) Follow-up
Day	-35 to -7	-14 to -5	-10 to -4	-3 to 1	1	4	8	15	28	56	84	112	140	168	252			q 6 mo
Window (+/- d):						1	3	3	3	3	7	7	7	7	7	7	3	30
Informed consent[25]	x	x																
Platelet count[1]	x			x														
Medical history		x																
Vital signs[8]		x			x		x	x	x	x	x	x	x	x	x	x		
Physical exam, including spleen measurement[9]		x			x		x	x	x	x	x	x	x	x	x	x		
GI assessment[4]		x			x	x		x										
12-lead ECG[10]		x			x		x	x										
ECOG performance status		x			x		x	x	x	x	x	x	x	x	x	x		
Hematology[11]		x		x	x			x	x	x	x	x	x	x	x	x		
Chemistry[12]		x			x			x	x	x	x	x	x	x	x	x		
Serum pregnancy test[24]		x									x			x	x			
Spleen volume by MRI or CT[13]			x								x			x	x	x		
Daily patient-reported symptoms: MPN-SAF TSS 2.0 Begin recording after receiving eDiary[14]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Daily pain medication log[15]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
Patients who continue an active BAT despite splenic progression will continue to be followed per this Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in this calendar.
Patients who continue pacritinib despite splenic progression will continue to follow this Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in this calendar.
Patients who discontinue pacritinib, but have not progressed will continue to follow this Study Assessments Calendar until progression occurs, and then will follow the *Survival-Only Follow-up* column in this calendar. Note: patients who have stopped taking pacritinib must complete a termination visit within 7 days of stopping the drug.
Patients who undergo splenic irradiation, splenectomy, or who initiate any non-protocol-directed anti-myelofibrosis treatment will subsequently be followed per the *Survival-Only Follow-up* follow-up column in this calendar.

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Patient global impression assessment[16]					x					x		x		x	x	x		
Quality of life assessments; EORTC-QLQ-C30 EQ-5D-5L					x					x		x		x	x	x		
Pharmacokinetic (PK) assessment[17]					x			x			x			x				
Pharmacodynamic(PD) assessment[18]					x			x			x			x				
JAK2 mutation burden[19]		x									x			x	x			
Bone marrow biopsy[22]		x												x				
Distribute pacritinib					x				x	x	x	x	x	x	x			
Begin pacritinib dosing					x													
Perform pacritinib accountability[23]					x		x	x	x	x	x	x	x	x	x	x		
Toxicity assessments/AEs[20]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Record BAT treatments					x	x	x	x	x	x	x	x	x	x	x	x		
Transfusion history (RBC and platelet)		x			x	x	x	x	x	x	x	x	x	x	x	x		
Leukemic Transformation		x			x			x	x	x	x	x	x	x	x	x		x
Survival Only Follow-up (phone)[21]																		x

Table--1
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Abbreviations:
AEs = adverse events
BAT = best available therapy
BL=baseline
BUN = blood urea nitrogen
CBC = complete blood count
CRF = case report form
CT = computed tomography
d = day(s); ECG = electrocardiogram
ECOG = Eastern Cooperative Oncology Group
eCRF = electronic case report form
GI = gastrointestinal
LDH = lactate dehydrogenase
MRI = magnetic resonance imaging
PD = pharmacodynamic(s)
PET-MF = post-essential thrombocythemia myelofibrosis
PK = pharmacokinetic(s)
PMF = primary myelofibrosis
PPV-MF = post-polycythemia vera myelofibrosis
RBC = red blood cell(s)
Term=study treatment termination visit
Wk = Week

1 Eligibility platelet count may be obtained at any time between Days -35 and -7 prior to randomization. Platelet count obtained during the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value should be used for platelet rebound stratification determination. If more than one such nadir count is obtained prior to randomization, the count obtained closest to randomization will be used for stratification. If patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion performed before randomization.
2 Screening procedures must be completed between Days -14 and -5, before treatment initiation. Clinical laboratory tests collected at screening must be performed at least 7 days after any prior therapy for PMF, PPV-MF, or PET-MF.
3 Day 1 assessments are required to be performed prior to initiation of study treatment. The baseline visit should also be conducted for patients on BAT who have documented disease progression and are planning to cross over to pacritinib if they meet the criteria for continuation or crossover. For these patients, the termination and baseline visits may be combined (all termination procedures plus locally obtained 12-lead ECG and pharmacodynamic assessment). Patients who cross over to pacritinib after Week 24 must complete an MRI within 30 days of starting pacritinib. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any change in frequency or consistency of bowel movements after starting study treatment.
4 The site will contact all patients by telephone on Day 4 ± 1 day to assess the need for modifying supportive treatment of any GI side effects. Patients will also be assessed at the beginning of Week 3 and throughout the study for GI safety.
5 The study visits at Weeks 2, 3, 4, and 8 have a scheduling window of ± 3 d; however, all procedures other than MRI or CT should be performed on the same day's visit.
6 The study visits at Weeks 12 and beyond have a scheduling window of ± 7 d; however, all procedures other than MRI or CT should be performed on the same day's visit.
7 The treatment termination visit is scheduled within 7 d after completing or terminating each study treatment arm. A final visit to assess events is scheduled 30 ± 3 d after the last study treatment day. If termination takes place at a regularly scheduled visit, these procedures may be performed at that time. Patients on BAT who have documented progression of disease and are planning to cross over to pacritinib must complete all baseline procedures except PK and PD procedures (all termination procedures plus local 12-lead ECG and central pharmacodynamic assessment) and record this information on the crossover Week 1 visit CRF. The spleen size at the end of BAT will serve as the new baseline for the patient. For patients on BAT who cross over to pacritinib after Week 24, spleen imaging must be performed within 30 days prior to starting pacritinib, and the spleen size at that time will serve as the new baseline.
8 Vital signs include blood pressure, pulse, respiratory rate, temperature, and body weight.
9 Height should be measured only on Day 1. Measurement of spleen by physical examination will be performed during screening, at baseline, and at each visit until study termination.
10 For patients assigned to pacritinib or those who have crossed over to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours post dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2 and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study. QTc interval prolongation identified on automated ECG calculations that is ≥grade 1 should be manually recalculated using the same method for any given patient. The manual recalculation should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.
11 Hematology: CBC, differential count, and platelet count. The most recent hematology evaluation obtained prior to randomization must be used to stratify the patient by baseline DIPSS risk category. Screening hematology assessments used to identify strata for randomization may be performed by local laboratories, but screening samples will also be sent for central laboratory evaluation.
12 Eligibility may be based on local laboratory values. Central blood chemistry values will include: ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect) creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.
13 Spleen volume by MRI or CT will be reviewed centrally by an independent radiology facility. The screening MRI or CT must be performed prior to randomization between Days -10 to -4. Imaging should be performed without

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contrast agents. MRI or CT will be performed at the end of Week 12 ± 7 d and every 12 weeks thereafter, and at the termination of treatment. For each patient, the same imaging modality should be used throughout the study. Unscheduled imaging studies may be performed at the physician's discretion, if he/she considers disease-related symptoms to be worsening. Splenic progression will be followed for patients who discontinue treatment, but have not progressed. Patients with progressive disease documented prior to Week 24 who opt to continue on study treatment will not undergo Week 24 imaging if the date of progression is at or later than Week 20. For patients who cross over after Week 24, an MRI must be performed within 30 days prior to the start of pacritinib treatment.

14 Daily patient-reported disease-related symptoms assessed after receiving an eDiary and throughout treatment. Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment and daily through Week 48 of the study or until patient discontinues study treatment, whichever occurs first.

15 Patients will complete the pain medication log daily as long as the patient is completing the MPN-SAF TSS 2.0.

16 Patient global impression assessment and Quality of Life Assessments will be done every 8 weeks through Week 24, and then every 12 weeks thereafter until patient discontinues study treatment.

17 Five PK samples from patients in the pacritinib arm(s) will be collected from approximately 70 patients at a prespecified subset of clinical sites. Blood samples will be collected postdose (Hour 4) on Day 1, Week 1, predose (Hour 0) and postdose (Hour 4) on Day 1, Week 3 and predose (Hour 0) on the visit day of Weeks 12 and 24. Two PK samples will be collected from approximately 130 patients taking pacritinib at the remaining sites predose (Hour 0) on the visit day of Week 12 and Week 24.

18 PD assessment for patients in the pacritinib arm will be collected from patients at a prespecified subset of of clinical sites. Blood samples will be collected predose (Hour 0) and postdose (Hour 4) on Day 1 of Weeks 1 and 3 and predose (Hour 0) on the visit day of Weeks 12 and 24.

19 Samples for central analysis of *JAK2* mutation burden will be collected at screening, Week 12, and every 12 weeks thereafter in patients who have the mutation.

20 Toxicity assessments/AEs: Patients will be evaluated from the time of signing the Informed Consent Form through 30 d after the last study treatment. However, each SAE assessed as related to study treatment or study procedures will be collected through the patient's last day of study participation the event will be followed until it is resolved, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever occurs first.

21 Survival-only follow-up for each patient will continue for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

22 Bone marrow biopsy must be obtained within 24 weeks prior to randomization and may be obtained any time before Day -3. Bone marrow biopsy will also be performed at Week 24. Patients who discontinue study treatment prior to Week 24 do not need another bone marrow biopsy.

23 At time of dispensing, the lot number for capsules dispensed and the number of capsules in bottle(s) should be recorded. Instruct patient to bring bottle to every visit. When a patient returns one or more bottles, count the remaining capsules in all bottle(s).

24 All women of child-bearing potential must have a pregnancy test at screening. Additional pregnancy tests every 12 weeks while on study treatment may be mandated as a country-specific requirement.

25 Informed consent must be obtained before any study-specific washout. This may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and standard MF treatments), or 7 days (potent CYP 3A4 inhibitors). Patients not requiring washout may sign the Informed Consent Form at any time prior to screening procedures.

Abbreviations	
Abbreviation	**Full Term**
AE	adverse event
ALT	alanine aminotransferase (syn: see SGPT)
AML	acute myeloblastic leukemia (or acute myeloid leukemia)
ANC	absolute neutrophil count
ASCT	allogeneic stem cell transplantation
AST	aspartate aminotransferase (syn: see SGOT)
BAT	best available therapy
BID	twice daily
BL	baseline
BUN	blood urea nitrogen
CBC	complete blood count
CI	clinical improvement
CMH	Cochran-Mantel-Haenszel
CR	complete remission or complete response
CRF(s)	case report form(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
d	day, days
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESA	erythropoiesis-stimulating agent
ET	essential thrombocythemia
FDA	Food and Drug Administration
FLT3	fms-like receptor tyrosine kinase 3
GCP	Good Clinical Practice
GI	gastrointestinal
h	hour, hours
HIV	human immunodeficiency virus
IC_{50}	50% inhibitory concentration

Abbreviations	
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Us
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
IRF	independent radiology facility
ITT	intent-to-treat
IWG	International Working Group
JAK2	Janus kinase 2
L	liter(s)
LCM	lower costal margin
LDH	lactate dehydrogenase
LFS	leukemia-free survival
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent(s)
mo	month(s)
MPD	myeloproliferative disease
MPN-SAF TSS 2.0	Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0
MRI	magnetic resonance imaging
ms	millisecond(s)
MTD	maximum tolerated dose
NCI	National Cancer Institute
nM	nanomolar
NYHA	New York Heart Association
OS	overall survival
^{32}P	phosphorus-32
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os, oral(ly)
PMF	primary myelofibrosis

Abbreviations	
PPV-MF	post-polycythemia vera myelofibrosis
PV	polycythemia vera
QD	daily
QTc	corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
ROC	receiver operating characteristic curve
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic-oxaloacetic transaminase (syn: see AST)
SGPT	serum glutamic pyruvic transaminase (syn: see ALT)
STAT	signal transducers and activators of transcription
T_{max}	time of maximum concentration
ULN	upper limit of normal
uMPD	unclassifiable myeloproliferative disease
wk	week, weeks

1 Background Information

1.1 JAK2 in Hematologic Malignancies

The Janus kinases (JAK) are a family of cytoplasmic tyrosine kinases consisting of JAK1, JAK2, JAK3, and TYK2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones, and growth factors. Their intracellular substrates include the signal transducer and activator of transcription (STAT) family of proteins. The JAK/STAT pathways, through the proper actions of the ligands, regulate important physiological processes, such as the immune response to viruses, hematopoiesis, lactation, and lipid homeostasis. However, dysfunctional signaling caused by a myriad of factors results in pathological conditions, such as allergies, asthma, rheumatoid arthritis, severe combined immune deficiency, and hematological malignancies. In particular, mutations in the *JAK2* gene have been associated with myeloproliferative disorders (MPDs), including polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF).

The incidence of the *JAK2V617F* mutation, as determined by allele-specific polymerase chain reaction in granulocytes from patients with MPDs, occurs in 35% to 50% of patients with primary MF (PMF), 32% to 57% of patients with ET, and 74% to 97% of patients with PV. This mutation, however, can also be found on rare occasions in patients with other chronic myeloid diseases, including myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative diseases (MDS/MPD), and unclassifiable MPD (uMPD). There is strong evidence that the *JAK2* mutation (and corresponding continuously active JAK2 tyrosine kinases) significantly contributes to the existence and progression of the disease. Its inhibition thus presents a suitable target for drug development. Even in patients without *JAK2* mutation, the JAK/STAT pathway may be deregulated, and these patients may also benefit from JAK2 inhibitor therapy.

1.2 Myelofibrosis

1.2.1 Clinical Presentation and Disease-related Symptoms

Myelofibrosis may present as either a primary myeloproliferative disorder or follow a diagnosis of PV or ET. Regardless of the original diagnosis, PMF, PPV-MF, and PET-MF have a common pathophysiological profile, characterized by elevated numbers of CD34-positive cells in the marrow in the early phase of the disease, followed in the later phases by marrow fibrosis, with decreasing numbers of CD34 cells in the marrow and a corresponding increase in splenic and liver engorgement by CD34 cells.

PMF, PPV-MF and PET-MF usually present with a white blood cell (WBC) count < 30,000/mm^3, prominent teardrops on peripheral smear, normocellular or hypocellular marrow with moderate to marked fibrosis, an absence of the Philadelphia chromosome or the BCR-ABL translocation, and frequent positivity for the *JAK2* mutation (Campbell et al 2006). In addition to the clonal proliferation of a multipotent hematopoietic progenitor cell, an event common to all chronic MPDs, these disorders are characterized by colonization of extramedullary sites, such as the spleen or liver (Barosi 1999, Tefferi 2000).

About 70% of patients with MF are symptomatic at presentation. The main physical findings are splenomegaly and hepatomegaly. Other symptoms include those secondary to a hypercatabolic state (fever, weight loss, and night sweats) and peripheral blood abnormalities (fatigue and dyspnea resulting from anemia and bleeding, and petechiae resulting from thrombocytopenia and/or abnormal platelet function). Gout and renal stones secondary to hyperuricemia are also common [4] (Ahmed et al, 2006). Other clinical manifestations of the disease include thromboembolic episodes, hemorrhage, splenic pain, early satiety, anemia, and bone pain.

PMF, PPV-MF, and PET-MF have similar types and distributions of bone marrow cytogenetic abnormalities (Tefferi, Mesa et al 2001), and they are known to harbor a common mutant allele, *JAK2V617F* (James et al 2005).

Transformation from PV to PPV-MF significantly worsens survival. *JAK2* mutations are almost always present in patients with PV and PPV-MF. Common clinical and laboratory findings in PPV-MF include a hyperproliferative bone marrow, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) Grade 2 to 3 marrow fibrosis, anemia, splenomegaly, and constitutional symptoms (Passamonti et al 2008).

Diagnostic tools for PMF, PPV-MF, and PET-MF include complete blood count (CBC), bone marrow aspiration and biopsy, cytogenetic analysis, peripheral blood smear analysis for teardrop-shaped RBCs, the number and kinds of WBCs, platelet count, and the presence of blast cells.

1.2.2 Current Strategies for Treating PMF, PPV-MF, and PET-MF

Currently, as no therapeutic strategy has been efficacious at reducing overall mortality, medical therapy for PMF, PPV-MF, and PET-MF is administered with supportive intent. Treatment is aimed at improving quality of life through palliation of symptoms and control of peripheral blood counts (Arana-Yi et al 2006). Therapeutic interventions usually are used only in symptomatic patients with MF, since asymptomatic patients demonstrate prolonged survival (Barosi 1999, Dupriez et al 1996).

At present, allogeneic stem cell transplantation (ASCT) is the only available method for altering the natural history of PMF, PPV-MF, or PET-MF (Passamonti et al 2008, Rondelli et al 2005). ASCT can completely reverse the fibrosis in bone marrow (Ni et al 2005) and restore normal hematopoiesis. However, while ASCT is potentially curative for patients with PMF, PPV-MF, and PET-MF, this form of treatment is largely limited to young patients with negligible comorbidities (Arana-Yi et al 2006). The International Working Group – Myelofibrosis Research and Treatment considers it "…reasonable to recommend ASCT for high- or intermediate-risk 2 patients" (Cervantes et al 2009). Thus far, no therapy has proven effective in prolonging overall survival (OS) in PMF, PPV-MF, or PET-MF (Arana-Yi et al 2006).

Current treatment approaches are aimed at mitigating specific disease symptoms, such as anemia. Transfusion therapy is the core strategy for treatment of disease-related anemia, and it is also used to manage thrombocytopenia. Long-term RBC transfusion therapy should be accompanied by oral iron chelation therapy to avoid long-term consequences of iron overload. Disease-associated anemia occasionally responds to erythropoietin, hydroxyurea, cladribine, thalidomide, lenalidomide, or interferon treatment (Ahmed et al 2006). These and other agents have been used to correct cytopenias, halt the progression of splenomegaly, or reduce the size of a site of extramedullary hematopoiesis in patients with PMF, PPV-MF, and PET-MF.

Danazol, a synthetic attenuated anabolic steroid with androgenic activity, has been used to treat anemia in PMF, PPV-MF, and PET-MF. Erythropoietin has been administered to patients with these diseases for palliation of constitutional symptoms and anemia (Arana-Yi et al 2006). The use of interferon-α can result in hematologic responses, including reduction in spleen size, but many patients do not tolerate this medication (Sacchi 1995, Gilbert 1998). Antiangiogenic and immunomodulatory drugs, such as thalidomide and lenalidomide, have shown activity in patients with MF (Gilbert 1998, Barosi et al 2002, Marchetti et al 2004, Tefferi, Cortes et al 2006, Mesa et al 2004, Strupp et al 2004), but they are not routinely used for the indications proposed in this study of pacritinib.

Other antiangiogenic agents, such as vatalanib and sorafenib, have been studied in PMF, PPV-MF, and PET-MF, but the data are not promising. Etanercept has been evaluated, but it was not superior to the combination of thalidomide and prednisone (Arana-Yi et al 2006).

The use of signal transduction inhibitors, such as imatinib, have resulted in an increase in the number of clonogenic megakaryocytic progenitors in bone marrow, suggesting they may be an effective treatment for thrombocytopenia in patients with MF (le Bousse-Kerdiles et al 2005).

For patients with PMF, PPV-MF, or PET-MF who have painful splenomegaly and no other treatment options, splenectomy may be performed. The decision to perform splenectomy involves weighing the benefits (long-term improvement in symptomatic splenomegaly, anemia, portal hypertension, and severe thrombocytopenia in 30% to 70% of patients) versus the risks (10% postoperative mortality, and 30% postoperative morbidity caused by infection, bleeding, or thrombosis; additionally, some investigators have reported accelerated progression to blast crisis).

1.2.3 Targeted Therapy for Myeloproliferative Disease

In 2011, JAK 1/2 inhibitor ruxolitinib received approval in the United States for the treatment of patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF based on the COMFORT I and II randomized controlled trials showing that treatment with ruxolitinib decreased spleen size and symptom score (Verstovsek et al 2012; Harrison et al 2012). Entry criteria for both studies was limited to patients with platelet counts >100,000/μL. The median platelet counts at entry for the two studies were 262,000/μL and 244,000/μL, respectively.

Ruxolitinib causes significant dose-related thrombocytopenia, and the dose must be adjusted in patients with platelet counts < 200,000/μL. In patients taking ruxolitinib who develop a platelet count < 50,000/μL, withholding all dosing is recommended until the platelet count recovers to 50,000/μL. In clinical trials, patients taking ruxolitinib who had pretreatment platelet counts between 100,000/μL and 200,000/μL had a higher frequency of grade 3 or 4 thrombocytopenia (16.7%) than patients with higher initial platelet counts (7.2%).

The incidence of thrombocytopenia (all grades) during randomized treatment in COMFORT I was 69.7% in the ruxolitinib arm compared with 30.5% in the placebo arm. The dose of ruxolitinib was adjusted downward for patients with platelet counts <100,000/μL and withheld for those with platelet counts <50,000/μL. In COMFORT II, protocol-specified dose modifications for thrombocytopenia were more frequent in the ruxolitinib arm than the best available therapy arm (41% vs. 1%).

Median time to recovery of platelet counts to above 50,000/μL was 14 days in patients requiring interruption of treatment due to thrombocytopenia (Jakafi label).

1.3 Pacritinib

Pacritinib is a novel JAK2/FLT3 inhibitor that has demonstrated promising antitumor activity in two mouse models of human malignancies. Preclinical toxicology studies have identified a safe starting dose for clinical trials. The potential indications that may be targeted include: (i) PV, ET, and MF, all of which are MPDs with a high frequency of a *JAK2V617F* mutation; (ii) certain leukemias and lymphomas where other forms of JAK aberrations have been reported; and (iii) acute myeloid leukemia (AML), in which FLT3 inhibitors have shown preliminary clinical promise.

1.3.1 Pharmacology

Pacritinib is a potent, selective inhibitor of JAK2 and FLT3 kinase activities (IC_{50} = 23 nM and 22 nM, respectively), as well as JAK2V617F mutant kinase activity (IC_{50} = 19 nM). Pacritinib is also a potent inhibitor of cellular proliferation in human leukemia and lymphoma cell lines selected for their dependence on the target kinases (cellular IC_{50} ranges from 0.03 to 0.24 μM). Consistent with these activities, exposure to pacritinib resulted in the reduction of phospho-JAK2, phospho-STAT3, or phospho-STAT5 in the relevant cell lines.

The therapeutic effects of pacritinib were assessed in an orthotopic model of MPD induced with Ba/F3-JAK2V617F cells. Pacritinib treatment at 150 mg/kg po bid significantly ameliorated symptoms, with 60% normalization of spleen weight and 92% normalization of liver weight. It was also very well tolerated.

1.3.2 Pharmacokinetics in Animals

PK following single intravenous or oral administration of pacritinib was evaluated in mice, rats, and dogs. Following oral administration, pacritinib showed rapid absorption in mice (T_{max} from 0.5 to 1.3 hours) and moderately fast absorption in rats and dogs (T_{max} ~ 4 hours). The oral terminal half-lives were 2.2, 5.7 and 4.4 h in mice, rats, and dogs respectively. As measured by liver blood flow, the systemic clearance of pacritinib from plasma was high in mice (8 L/h/kg) and dogs (1.6 L/h/kg) and moderate in rats (1.6 L/h/kg). The i.v. terminal half-lives were 5.6, 6, and 4.6 hours in mice, rats, and dogs, respectively. The oral bioavailability of pacritinib was 39% in mice, 10% in rats, and 24% in dogs.

1.3.3 Preclinical Toxicology

The adverse effects of pacritinib were evaluated in 30-day repeated oral dose toxicity studies with 14-day recovery in both mice and dogs, and in 26- and 39-week chronic toxicity studies in mice and dogs, respectively. Key findings included dose-dependent leukopenia accompanied by neutropenia (dog) and neutrophilia (mice) that partially reversed during recovery. Mice also showed dose-dependent but reversible thrombocytosis and anemia. In the chronic toxicity studies, low-magnitude decreases in neutrophils and red blood cell parameters were observed. No treatment-related hepatic changes were observed with the exception of increased AST (to +109%, male dogs) and increased triglycerides (to +57%, male and female dogs).

In the 30-day study in dogs, animals receiving mid and high doses of pacritinib experienced vomiting and diarrhea that increased in severity despite treatment with antiemetic and antidiarrheal medication. Similarly, in the 39-week study in dogs, an increased incidence of nausea and vomiting was observed at doses of 20 mg/kg/day and higher. Periods of low food consumption in individual animals receiving 40 and 50 mg/kg/day were accompanied by rapid weight loss (which was controlled and reversed with subcutaneous fluid and supplemental food) and were considered treatment related and adverse.

Based on these studies, the no observed adverse effect level was determined to be 100 mg/kg bid in mice and 10 mg/kg bid in dogs.

1.3.4 Summary of Clinical Pharmacology and Phase I Studies with Healthy Volunteers with Pacritinib

To date, CTI has completed two PK studies for pacritinib in healthy volunteers, including a food-effect study (SB1518-2010-006) characterizing the effects of a high calorie, high fat meal on the bioavailability and PK of pacritinib and a study assessing inter- and intra-individual variability of oral pacritinib in

healthy volunteers under fasted conditions at 100 mg, 200 mg and 400 mg doses (SB1518-2010-004). In addition, the single and multiple dose population PK of pacritinib has been characterized following multiple dose administration of pacritinib in two trials (SB1518-2007-001 and SB1518-2008-003) in patients with advanced myeloid malignancies.

After administration of single doses of pacritinib in a randomized, three-treatment, three-period crossover study in healthy volunteers under fasting conditions in study SB1518-2010-004, peak plasma concentrations were reached at a median T_{max} ranging from 4.5 h to 5.5 hours across the 100-400 mg dose range. While between-subject variability was relatively high (28-45%), the within-subject variability was low (13-15%), highlighting the consistent systemic exposure for pacritinib in individual subjects. The mean elimination half-life was approximately 34 hours and was not dependent on dose. The systemic exposure of pacritinib is healthy volunteers was comparable to that in patients. After oral administration of single 200-mg doses (2×100 mg capsules) of pacritinib under fed and fasted conditions in study SB1518-2010-006, the 90% confidence intervals for the geometric mean ratios (fed to fasted) for C_{max}, AUC_{0-t}, and AUC_{inf} were between 80% and 125%, demonstrating lack of an effect of food on absorption. Given this data, pacritinib can be orally administered without regard to timing of meals.

Pooled analyses of PK assessments from the two completed clinical trials in patients at pacritinib dose levels up to 600 mg QD showed slow absorption (T_{max} 4-6 hrs) and dose-related increases in systemic exposure up to 400 mg QD. Beyond the 400 mg QD dose level, there was minimal increase in exposure with doses up to 600 mg QD suggesting involvement of a saturable process in oral absorption of pacritinib. In addition, the results demonstrated a prolonged elimination half-life (mean Day 1 $t_{1/2}$ = 47 hrs), supporting a QD regimen of pacritinib in clinical development. Comparison of systemic exposure of pacritinib on Days 1 and 15 showed a 1.5- to 2-fold increase in systemic exposure at steady-state.

Pacritinib is not a PgP substrate at clinical exposure levels. While in vitro metabolism studies suggest that pacritinib is a potential substrate for CYP3A4 isozyme, the results of a mouse mass balance ADME study demonstrate that pacritinib is overwhelmingly eliminated by biliary excretion with minimal involvement of metabolism or renal excretion in the systemic clearance of pacritinib. Overall, the preclinical in vitro and in vivo data suggest limited liability of pacritinib in metabolic and PgP-related drug interactions.

At a pacritinib 100 mg QD regimen, mean steady-state plasma levels of pacritinib exceeded the in vitro IC_{50} values for inhibition of targeted kinases (JAK2/FLT3) and inhibition of whole cell proliferation (BaF3-JAK2 and MV4-11 cells). Pacritinib potently inhibited the proliferation of only a few tumor cell lines at submicromolar concentrations, consistent with its target selectivity. The most sensitive cell lines were either JAK2-dependent or mutant FLT3-dependent, including murine 32D (IC_{50} = 160 nM), human Karpas 1106P (IC_{50} = 240 nM), and mutant FLT3-dependent MV4-11 cells (IC_{50} = 32 nM). In a study using ex vivo expanded erythroid progenitors (EPs) treated with pacritinib, phos-STAT5 levels were inhibited in a dose-dependent manner (IC_{50} < 200 nM) and reduced the viability of expanded EPs from both normal volunteers with JAK2wt (IC_{50} = 260 nM) and PV patients with JAK2V617F (IC_{50} = 230 nM), with no significant differences observed between arms. Moreover, pacritinib treatment had no effect on the JAK2V617F allele frequency in EPs from PV patients, indicating similar drug sensitivity for EPs from the same patient, regardless of the presence of JAK2 mutation. A study to assess the effects of pacritinib on intracellular JAK2 signaling showed that phos-STAT3 was reduced in a dose-dependent manner in both Karpas 1106P and 32D cells.

1.3.5 Overview of Clinical Studies of Pacritinib in Patients with Myelofibrosis

Patients with MF have been studied in two clinical trials of pacritinib. Both phase 1/2 trials included dose-finding PK portions and safety and efficacy portions. SB1518-2007-001 enrolled patients with advanced myeloid malignancies, and SB1518-2008-003 enrolled patients with chronic idiopathic MF.

1.3.6 SB1518-2007-001: Phase 1/2 Study in Patients with Advanced Myeloid Malignancies

1.3.6.1 Phase 1

During the phase 1 portion of SB1518-2007-001, cohorts of 3 to 6 patients with advanced myeloid malignancies were enrolled into one of a series of escalating doses of pacritinib, ranging from 100 to 600 mg/day. Treatment was administered orally once a day for 28 d (defined as one cycle). Preliminary data were presented in 2009 (Verstovsek et al 2009).

Dose-limiting toxicities (DLTs) included grade 3 QTc prolongation in 1 patient with AML taking 150 mg and grade 3 diarrhea in 1 patient at 300 mg. At the 600-mg dose level, 1 patient reported grade 3 GI toxicity and 1 patient reported grade 2 blurred vision, dizziness, and unsteady gait. No DLTs were reported at 400 mg or 500 mg. Thus, the 500 mg dose level was determined to be the maximum tolerated dose (MTD).

Diarrhea and general GI toxicities, the most common toxicities that affected dosing, often resulted in dose interruption and dose reduction. On the basis of the safety and efficacy observations during long-term dosing, 400 mg/day was chosen as the recommended dose for the phase 2 study. The most commonly reported treatment-emergent events (> 20%) were diarrhea, nausea, vomiting, constipation, dyspnea, fatigue, and peripheral edema. Most events were mild to moderate in severity. Grade 3 or greater anemia and thrombocytopenia were each reported in 16% of patients and were the only events of grade 3 or higher severity that occurred in more than 10% of patients. Sixteen of the 43 patients (37%) had grade 3 (25,000 – 50,000/μL) or grade 4 (< 25,000/μL) thrombocytopenia at baseline.

Of the 36 patients with MF enrolled in the phase 1 portion, 25 had baseline splenomegaly ≥ 5 cm below the left costal margin. Eighteen of these 25 patients had at least 25% reduction in spleen size; these 18 patients included 6 patients whose spleens became nonpalpable.

PK analysis showed that pacritinib was rapidly absorbed, with T_{max} ranging from 3 to 5 hours. The estimated terminal half-life was 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations, measured by inhibition of STAT3 and STAT5 phosphorylation, were achieved at the starting dose of 100 mg/day.

1.3.6.2 Phase 2

The primary objective of this portion of the study was to assess spleen response rate as measured by the change in spleen volume between baseline, Day 1 of Cycle 4, and Day 1 of Cycle 7. Response was defined as a decrease of at least 35% in MRI-determined spleen volume any time between baseline and Week 24. Secondary objectives included spleen response by physical examination, duration of spleen response, safety, and tolerability.

Thirty-one patients were enrolled and received at least one dose of study drug (Table--2). Of these 31 patients, 13 had a history of either PV (11 patients) or ET (2 patients). Twenty-seven patients had received prior treatment for MF, and all had baseline splenomegaly that measured at least 5 cm below the LCM.

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
Age (yr)	
N	31
Mean (SD)	65.4 (8.62)
Median	67
25 - 75 percentile	60 - 72
Range	47 - 83
Gender	
N	31
Female	9 (29%)
Male	22 (71%)
Race	
N	31
American Indian or Alaska Native	0
Asian	0
Black or African American	1 (3%)
Native Hawaiian or Other Pacific Islander	0
White	30 (97%)
Other	0
Time Since Last Cancer Treatment (mo)	
N	31
Mean (SD)	121.1 (241.40)
Median	2
25 - 75 percentile	1 - 30
Range	1 - 606
ECOG Performance Status	
N	31
0	6 (19%)
1	17 (55%)
2	8 (26%)
>2	0
JAK 2 Mutation	

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
N	31
No	6 (19%)
Yes	25 (81%)
Type of JAK 2 Mutation	
N	25
V617F	25 (100%)
Other	0
FLT 3 Mutation	
N	23
No	23 (100%)
Yes	0
Baseline Hemoglobin (g/dL)	
N	31
Mean (SD)	9.845 (2.6000)
Median	9.000
25 - 75 percentile	8.10 - 11.80
Range	3.70 - 14.40
Baseline Platelet Count (10^3/µL)	
N	31
Mean (SD)	172.61 (130.924)
Median	126.00
25 - 75 percentile	62.0 - 260.0
Range	28.0 - 494.0
Baseline Platelet Count Category N(%)	
N	31
<50,000/µL	4 (12.9)
50,000 – 100,000/µL	9 (29.0)
≥100,000/µL	18 (58.1)
Baseline WBC (10^3/µL)	
N	31
Mean (SD)	12.180 (9.2365)
Median	8.910

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
25 - 75 percentile	4.40 - 18.00
Range	1.50 - 38.20
Baseline Absolute Neutrophil Count (10^3/µL)	
N	31
Mean (SD)	8.86 (6.989)
Median	6.98
25 - 75 percentile	3.0 - 13.3
Range	0.9 - 29.4

Source: Table 2 (t02_demog 2012-02-29), Table 14 (t14_hema 2012-02-29), Table 1 (t_base_platelet_ph2_myel).
Abbreviations:
µL = microliter(s) ECOG = Eastern Cooperative Oncology Group FLT3 = fms-like receptor tyrosine kinase 3
g/dL = gram(s) per deciliter JAK2 = Janus kinase 2 N = number
SD = standard deviation WBC = white blood cell(s) yr = year(s).

Reasons for study drug discontinuation were lack of response (8 patients), disease progression (4 patients), withdrawal of consent (3 patients), adverse event (2 patients), and death (2 patients).

The most common treatment emergent adverse events (AEs) were diarrhea (90%), fatigue (58%), nausea (52%), and vomiting (35%). Most of these AEs were mild to moderate in severity (Table--3). Grade 3 AEs reported by more than one patient were anaemia (10%), thrombocytopenia (6%), cardiac failure congestive (10%), diarrhea (16%), abdominal pain (10%), fatigue (13%), pneumonia (6%), hypokalaemia (6%), and bone pain (13%). Grade 4 AEs were anemia (6%), thrombocytopenia (3%), pancytopenia (3%) fatigue (3%), hyperuricemia (6%), failure to thrive (3%), hyperglycaemia (3%), pain in extremity (3%), and muscular weakness (3%). Two serious adverse events (SAEs) were thought to be possibly related to treatment: grade 3 diarrhea in 1 patient and grade 3 dehydration in another. Both resolved without sequelae. No treatment-related deaths occurred and no SAE was reported in more than one patient.

Table--3 Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001						
SOC/Preferred Term	**Phase II (N = 31)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Subjects with any Event	2 (6%)	7 (23%)	12 (39%)	6 (19%)	4 (13%)	31 (100%)
Blood and Lymphatic System Disorders	0	0	6 (19%)	3 (10%)	0	9 (29%)
Anaemia	0	1 (3%)	3 (10%)	2 (6%)	0	6 (19%)
Thrombocytopenia	0	0	2 (6%)	1 (3%)	0	3 (10%)
Cardiac Disorders						
Cardiac failure congestive	0	0	3 (10%)	0	0	3 (10%)
Gastrointestinal Disorders	9 (29%)	9 (29%)	13 (42%)	0	0	31 (100%)
Diarrhoea	14 (45%)	9 (29%)	5 (16%)	0	0	28 (90%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nausea	9 (29%)	6 (19%)	1 (3%)	0	0	16 (52%)
Vomiting	7 (23%)	3 (10%)	1 (3%)	0	0	11 (35%)
Abdominal pain	3 (10%)	3 (10%)	3 (10%)	0	0	9 (29%)
Constipation	5 (16%)	0	0	0	0	5 (16%)
Abdominal pain upper	2 (6%)	0	1 (3%)	0	0	3 (10%)
Ascites	0	2 (6%)	1 (3%)	0	0	3 (10%)
General Disorders and Administration Site Conditions	6 (19%)	13 (42%)	5 (16%)	1 (3%)	0	25 (81%)
Fatigue	2 (6%)	11 (35%)	4 (13%)	1 (3%)	0	18 (58%)
Oedema peripheral	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Asthenia	4 (13%)	1 (3%)	0	0	0	5 (16%)
Pyrexia	4 (13%)	0	0	0	0	4 (13%)
Chills	2 (6%)	1 (3%)	0	0	0	3 (10%)
Infections and Infestations	1 (3%)	4 (13%)	7 (23%)	0	1 (3%)	13 (42%)
Upper respiratory tract infection	2 (6%)	1 (3%)	0	0	0	3 (10%)
Urinary tract infection	0	2 (6%)	1 (3%)	0	0	3 (10%)
Investigations	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Cardiac murmur	0	4 (13%)	0	0	0	4 (13%)
Weight decreased	4 (13%)	0	0	0	0	4 (13%)
Metabolism and Nutrition Disorders	5 (16%)	2 (6%)	3 (10%)	2 (6%)	1 (3%)	13 (42%)
Hyperuricaemia	2 (6%)	0	0	2 (6%)	0	4 (13%)
Hyperkalaemia	2 (6%)	1 (3%)	0	0	0	3 (10%)
Hypoalbuminaemia	1 (3%)	2 (6%)	0	0	0	3 (10%)
Hypokalaemia	1 (3%)	0	2 (6%)	0	0	3 (10%)
Musculoskeletal and Connective Tissue Disorders	7 (23%)	5 (16%)	4 (13%)	2 (6%)	0	18 (58%)
Bone pain	1 (3%)	1 (3%)	4 (13%)	0	0	6 (19%)
Pain in extremity	3 (10%)	2 (6%)	0	1 (3%)	0	6 (19%)
Back pain	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Muscle spasms	3 (10%)	0	0	0	0	3 (10%)
Nervous System Disorders	5 (16%)	2 (6%)	1 (3%)	0	0	8 (26%)
Neuropathy peripheral	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Psychiatric Disorders	6 (19%)	5 (16%)	1 (3%)	0	0	12 (39%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Insomnia	7 (23%)	2 (6%)	0	0	0	9 (29%)
Respiratory, Thoracic and Mediastinal Disorders	9 (29%)	1 (3%)	5 (16%)	0	0	15 (48%)
Dyspnoea	4 (13%)	0	1 (3%)	0	0	5 (16%)
Cough	3 (10%)	0	0	0	0	3 (10%)
Dyspnoea exertional	3 (10%)	0	0	0	0	3 (10%)
Skin and Subcutaneous Disorders	10 (32%)	10 (32%)	2 (6%)	0	0	22 (71%)
Pruritus	4 (13%)	4 (13%)	1 (3%)	0	0	9 (29%)
Night sweats	4 (13%)	3 (10%)	0	0	0	7 (23%)
Rash	2 (6%)	1 (3%)	1 (3%)	0	0	4 (13%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations: N = number; SOC = system organ class.

Grade 4 thrombocytopenia was reported in 1 patient (923), a 59-year-old male with a prior diagnosis of PV. His baseline platelet count was 30,000/μL (grade 3) and his on-study nadir was 22,000/μL (grade 4). Associated splenic volume change was -20%.

Grade 3 thrombocytopenia was reported in 2 patients (907 and 916). Patient 907, a 76-year-old male with a prior diagnosis of PV, had a baseline platelet count of 59,000/ μL (grade 2) and an on-study nadir of 41,000/μL (grade 3). Associated splenic volume change was -26%. Patient 916, a 71-year-old male, had a baseline platelet count of 58,000/ μL (grade 2) and an on-study nadir of 54,000/μL (grade 2). Associated splenic volume change was -35%.

Among the 3 patients reporting grade 3 anemia, 2 had grade 2 anemia and one had grade 4 anemia at baseline. Both of the 2 patients reporting grade 4 anemia had grade 3 anemia at baseline.

Myelosuppression has been uncommon, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with normal platelet counts and those with baseline thrombocytopenia have tolerated pacritinib and responded equally well.

By MRI assessments, 17 patients (55%) experienced a spleen volume decrease of ≥ 25% from baseline through Week 24, and 5 patients (16%) experienced a spleen volume decrease of ≥ 35% from baseline through Week 24. According to organ measurement by physical examination, 12 patients (39%) experienced a spleen size decrease of ≥ 50% from baseline through Week 24 (data derived from T5.2-A_spleen_ALL.2012-02-29 using ITT denominator of 31). Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

A patient-reported outcome related to MF symptoms was assessed in this study using the myelofibrosis symptom assessment form (MFSAF) form (Mesa RA et al 2009). The study did not include a control arm, so it is not possible to evaluate the actual effect of pacritinib treatment on disease symptoms. However, on Day 1 of Cycle 7, patients who had a baseline score of ≥ 4 showed improvement in all symptoms most relevant to MF; a mean score change of ≥ 2 was experienced in abdominal pain, bone pain, early satiety, inactivity, night sweats, pruritus, and fatigue.

1.3.7 SB1518-2008-003: Phase 1/2 Study in Patients with Chronic Idiopathic Myelofibrosis

1.3.7.1 Phase 1

During the phase 1 portion of SB1518-2008-003, cohorts of 3 to 6 patients with MF were enrolled into one of a series of escalating doses of pacritinib ranging from 100 to 600 mg/day. DLTs were observed in 2 of 4 patients at the 600 mg dose level: 1 experienced grade 3 diarrhea and 1 experienced grade 3 nausea, fatigue, and dehydration. The safety findings in this study were similar to those in SB1518-2007-001. The MTD based on first cycle data was determined to be 500 mg/day, and the recommended dose for phase 2 study, based on multicycle safety and efficacy data, was 400 mg/day.

The most commonly reported treatment-emergent AEs (> 20%) were diarrhea, nausea, vomiting, fatigue, constipation, abdominal pain, dizziness, ALT increased, anorexia, cough, pain in extremity, abdominal distension, peripheral edema, bone pain, headache, and rash. Most AEs were mild to moderate in severity. The only AEs of grade 3 or greater severity that occurred in more than 10% of patients were anemia, diarrhea, thrombocytopenia, and fatigue, each of which occurred in 15% of patients.

PK analysis showed a T_{max} of 3 to 7 hours and a terminal half-life of 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations were achieved at the starting dose of 100 mg on Day 1. No drug accumulation occurred upon repeated dosing over several cycles.

1.3.7.2 Phase 2

The objectives of the phase 2 portion of this study included spleen response rate, duration of spleen response, safety, and tolerability. Spleen response rate was defined as the proportion of patients achieving an MRI-determined reduction in spleen volume of 35% or more between baseline and Week 24.

Data are available for 34 patients in this trial (Table--4). Twenty-nine patients were previously treated for MF, and all enrolled patients had baseline splenomegaly that measured at least 5 cm below the LCM. Seven patients discontinued the study for the following reasons: AE (1 patient each for hyperbilirubinemia, allergic reaction, thrombocytopenia, and subdural hematoma), disease progression (1 patient), lack of response (1 patient), and withdrawal of consent (1 patient).

Table--4
Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003

Demographic/Baseline Characteristics	MRI Phase II (N=34)
Age (yr)	
N	34
Mean (SD)	66.6 (10.44)
Median	69
25 - 75 percentile	60 - 72
Range	44 - 84
Gender	
N	34
Female	9 (26%)

Table--4 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003	
Demographic/Baseline Characteristics	**MRI Phase II (N=34)**
Male	25 (74%)
Ethnicity	
N	34
Hispanic or Latino	2 (6%)
Not Hispanic or Latino	32 (94%)
Race	
N	34
American Indian or Alaska Native	0
Asian	1 (3%)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	33 (97%)
Other	0
ECOG Performance Status	
N	32
0	9 (28%)
1	21 (66%)
2	2 (6%)
>2	0
Number of Prior Systemic Therapies	
N	34
Mean (SD)	1.9 (1.60)
Median	1
25 - 75 percentile	1 - 2
Range	0 - 6
Initial Stage of Disease	
N	34
MF0	1 (3%)
MF1	1 (3%)
MF2	7 (21%)
MF3	9 (26%)
Unknown or N/A	16 (47%)
Baseline Hemoglobin (g/dL)	
N	33
Mean (SD)	10.142 (1.8755)

Table--4
Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518 -2008-003

Demographic/Baseline Characteristics	MRI Phase II (N=34)
Median	10.200
25 - 75 percentile	8.90 - 11.40
Range	5.50 - 14.10
Baseline Platelet Count (10^3/µL)	
N	33
Mean (SD)	167.39 (168.857)
Median	119.00
25 - 75 percentile	53.0 - 214.0
Range	15.0 - 859.0
Baseline Platelet Count Category	
<50,000/µL	7 (21.2)
50,000 – 100,000/µL	8 (24.2)
≥100,000/µL	18 (54.9)
Baseline WBC (10^3/µL)	
N	33
Mean (SD)	18.204 (19.5116)
Median	10.800
25 - 75 percentile	6.10 - 22.45
Range	1.14 - 89.60
Baseline Absolute Neutrophil Count (10^3/µL)	
N	34
Mean (SD)	12.21 (11.963)
Median	7.92
25 - 75 percentile	4.0 - 20.1
Range	0.3 - 56.4

Source: Table 2 (t02_demog 27FEB2012), Table 3 (t03_disease 27FEB2012), Table 14 (t14_hema 27FEB2012), Table 1 (t_base_platelet_ph2_myel).
Abbreviations:
µL = microliter(s) ECOG = Eastern Cooperative Oncology Group g/dL = gram(s) per deciliter
MRI = magnetic resonance imaging N = number SD = standard deviation
WBC = white blood cells yr = year(s).

Most AEs were mild to moderate in severity (Table--5). The most frequently occurring treatment emergent AEs were diarrhea (79%), nausea (41%), anemia (38%), fatigue (35%), abdominal pain (26%), pruritus (24%), and thrombocytopenia (24%). Grade 3 AEs reported by more than one patient were anemia (18%), thrombocytopenia (15%), fatigue (15%), diarrhea (9%), abdominal pain (6%), GI hemorrhage (6%), pneumonia (6%), AST increased (6%), QT prolongation (6%), dehydration (6%), and iron overload (6%). Grade 4 AEs were anemia (9%), thrombocytopenia (6%), hyponatremia (6%), atrial fibrillation (6%), neutropenia (3%), leukopenia (3%), fatigue (3%), cellulitis (3%), septic shock (3%),

blood uric acid increased (3%), hyperuricemia (3%), and renal cell cancer (3%). Grade 5 AEs were septic shock (3%), sepsis (3%), and subdural hematoma (3%). The only death considered related to treatment was the subdural hematoma. The only SAE reported in more than one patient was septic shock (2 patients, 6%). Ten SAEs reported in 6 patients were thought to be related to treatment; each SAE was reported in a single patient: grade 3 febrile neutropenia, grade 3 hyperbilirubinemia, grade 3 dehydration, grade 4 thrombocytopenia, grade 4 myocardial infarction, grade 4 septic shock, grade 4 hyperuricemia, grade 4 hyponatremia, and grade 5 subdural hematoma.

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Subjects with any Event	3 (9%)	3 (9%)	15 (44%)	9 (26%)	3 (9%)	33 (97%)
Blood and Lymphatic System Disorders	2 (6%)	5 (15%)	9 (26%)	5 (15%)	0	21 (62%)
Anaemia	0	4 (12%)	6 (18%)	3 (9%)	0	13 (38%)
Thrombocytopenia	1 (3%)	0	5 (15%)	2 (6%)	0	8 (24%)
Gastrointestinal Disorders	17 (50%)	9 (26%)	5 (15%)	0	0	31 (91%)
Diarrhoea	15 (44%)	9 (26%)	3 (9%)	0	0	27 (79%)
Nausea	13 (38%)	1 (3%)	0	0	0	14 (41%)
Vomiting	8 (24%)	3 (9%)	0	0	0	11 (32%)
Abdominal pain	5 (15%)	2 (6%)	2 (6%)	0	0	9 (26%)
Flatulence	6 (18%)	0	0	0	0	6 (18%)
Constipation	3 (9%)	1 (3%)	0	0	0	4 (12%)
General Disorders and Administration Site Conditions	10 (29%)	5 (15%)	5 (15%)	1 (3%)	0	21 (62%)
Fatigue	3 (9%)	3 (9%)	5 (15%)	1 (3%)	0	12 (35%)
Asthenia	2 (6%)	1 (3%)	1 (3%)	0	0	4 (12%)
Pyrexia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Investigations	9 (26%)	2 (6%)	4 (12%)	1 (3%)	0	16 (47%)
Aspartate aminotransferase increased	3 (9%)	0	2 (6%)	0	0	5 (15%)
Metabolism and Nutrition Disorders	6 (18%)	5 (15%)	7 (21%)	2 (6%)	0	20 (59%)
Dehydration	1 (3%)	3 (9%)	2 (6%)	0	0	6 (18%)
Anorexia	2 (6%)	3 (9%)	0	0	0	5 (15%)
Hyperuricaemia	3 (9%)	0	1 (3%)	1 (3%)	0	5 (15%)
Hypomagnesaemia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Musculoskeletal and Connective Tissue Disorders	12 (35%)	3 (9%)	0	0	0	15 (44%)
Musculoskeletal pain	2 (6%)	2 (6%)	0	0	0	4 (12%)
Nervous System Disorders	10 (29%)	1 (3%)	1 (3%)	0	0	12 (35%)
Dizziness	5 (15%)	1 (3%)	0	0	0	6 (18%)

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518 -2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dysgeusia	4 (12%)	0	0	0	0	4 (12%)
Headache	3 (9%)	0	1 (3%)	0	0	4 (12%)
Psychiatric Disorders	4 (12%)	2 (6%)	0	0	0	6 (18%)
Insomnia	4 (12%)	0	0	0	0	4 (12%)
Respiratory, Thoracic and Mediastinal Disorders	5 (15%)	8 (24%)	4 (12%)	0	0	17 (50%)
Dyspnoea	1 (3%)	3 (9%)	0	0	0	4 (12%)
Skin and Subcutaneous Disorders	15 (44%)	4 (12%)	1 (3%)	0	0	20 (59%)
Pruritus	6 (18%)	1 (3%)	1 (3%)	0	0	8 (24%)
Alopecia	4 (12%)	0	0	0	0	4 (12%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations: N = number; SOC = system organ class.

Among the patients reporting grade 3 anemia, all had grade 2 or grade 3 anemia at baseline. Among the 3 patients reporting grade 4 anemia, 1 had grade 3 anemia, 1 had grade 1 anemia, and 1 had no lab value at baseline.

Myelosuppression has been relatively infrequent, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with severe baseline hematologic abnormalities, including those with platelet counts <150,000/μL, appear to tolerate pacritinib as well as patients with normal and lesser degrees of abnormal hematopoiesis.

By MRI assessments, 12 patients (35%) experienced a decrease in spleen volume of at least 25% from baseline through Week 24, and 8 patients (24%) experienced a decrease in spleen volume of at least 35% from baseline through Week 24 (data derived from Table 5.2-A [t05.2-A_spleen_ALL.27FEB2012 using ITT denominator of 34]). According to organ measurement by physical examination, 14 patients (41%) experienced a decrease in spleen size of at least 50% from baseline through Week 24. Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

Patients completed the MFSAF (Mesa RA et al 2009) at baseline and throughout the trial. Intra- and inter-patient symptom severity varied widely at baseline. On Day 1 of Cycle 4, patients who had a baseline score of ≥4 showed improvement in some symptoms, with mean decreases of ≥2 in early satiety, abdominal pain, night sweats, and pruritus.

1.3.8 Phase 1 and 2 Experience with Pacritinib in Myelofibrosis: Summary and Conclusions

- Fifty-six patients with MF have been treated with escalating doses of pacritinib in the phase 1 portions of studies SB1518-2007-001 and SB1518-2008-003. An additional 65 patients have been treated in the phase 2 portions of these studies in Australia and the US.
- A total of 36 patients with starting platelet counts ≤150,000/μL have been treated, with an apparent response rate similar to those with higher platelet counts and no consistent treatment-related platelet suppression.

- Pacritinib did not appear to increase anemia or RBC transfusion requirements.
- Pacritinib has a favorable safety profile and is generally well tolerated in patients with MF, including those with PMF, PPV-MF, and PET-MF. Side effects are predominantly GI and are readily managed with symptomatic treatment and/or study drug interruption or dose reduction. AEs associated with myelosuppression are uncommon, and pacritinib is well tolerated and active in patients with cytopenias-particularly thrombocytopenia.
- Median baseline platelet counts in patients treated with pacritinib in phase 2 studies were 126,000/μL and 119,000/μL, approximately half of those in the ruxolitinib studies (262,000/μL and 244,000/μL).
- The overall incidence of all grades of thrombocytopenia reported as adverse events in efficacy and safety trials with pacritinib was 17%. Twelve percent of patients experienced a 2-grade or greater shift in platelet counts from baseline to worst platelet count, and 5% experienced a 2-grade or greater shift in platelet counts from baseline to end of study (Table--6).
- In comparison, the incidence of all grades of thrombocytopenia was 69% in the COMFORT I trial, and the incidence of thrombocytopenia requiring dose adjustment was 41% in the COMFORT II trial.

Table--6
Shift from Baseline Platelet Count by CTC Grade in Phase 2 of SB1518-2007-001 and SB1518-2008-003

	Baseline Platelet Count CTC Grade (N = 65)				
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nadir Platelet Count CTC Grade (N = 64)					
0	16 (25.0%)	0	0	0	0
1	11 (17.2%)	3 (4.7%)	0	0	0
2	0	4 (6.3%)	5 (7.8%)	0	0
3	1 (1.6%)	5 (7.8%)	6 (9.4%)	4 (6.3%)	0
4	1 (1.6%)	0	1 (1.6%)	5 (7.8%)	2 (3.1%)
End of Study Platelet Count CTC Grade (N = 64)					
0	20 (31.3%)	4 (6.3%)	0	0	0
1	7 (10.9%)	2 (3.1%)	2 (3.1%)	0	0
2	0	5 (7.8%)	6 (9.4%)	1 (1.6%)	0
3	1 (1.6%)	1 (1.6%)	4 (6.3%)	6 (9.4%)	1 (1.6%)
4	1 (1.6%)	0	0	2 (3.1%)	1 (1.6%)

Source: (t_platelet_shift_from_base_ph2_myel).
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number

- A notable proportion of the 65 patients with MF who were treated with pacritinib experienced a reduction in splenomegaly on both MRI and physical examination assessments. Among 49 patients with post-baseline follow-up evaluations, 29 (59%) had a 25% or greater reduction in MRI-assessed spleen volume and 13 (27%) had a 35% or greater reduction in MRI-assessed spleen volume. Twenty-six (41%) of 63 evaluable patients had at least a 50% reduction in physical examination-assessed spleen size as a best response. Patients with thrombocytopenia showed similar treatment effects.
- Clinical experience through phase 2 has demonstrated the safety and activity of pacritinib in patients with MF and warrants phase 3 trials to confirm the efficacy and safety of this drug in this patient population.

1.3.9 PERSIST-1: Phase 3 Study of Pacritinib versus Best Available Therapy in Patients with PMF, PPV-MF, or PET-MF

This ongoing phase 3 study will compare the efficacy of pacritinib with that of BAT in patients with PMF, PPV-MF, or PET-MF. The primary objective is to assess the proportion of patients in each arm achieving a ≥35% reduction in spleen volume from baseline to Week 24. The secondary objective is to assess the proportion of patients in each arm with ≥50% reduction from baseline to Week 24 on the MPN-SAF TSS 2.0.

A total of 351 patients at approximately 100 centers in the US, Europe, Russia, and Oceania will be randomized in a 2:1 allocation to pacritinib or BAT. BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, with the exclusion of JAK2 inhibitors. BAT also includes watchful waiting (no treatment). Spleen volume will be measured at baseline and every 12 weeks thereafter. Patients previously treated with JAK2 inhibitors are excluded. There are no exclusion criteria based on platelet count.

2 Rationale for Study

Two phase 2 studies of pacritinib have been conducted in patients with MF. Data from these trials show that pacritinib can be safely administered to patients with MF, including those who also have thrombocytopenia. Pacritinib treatment led to clinically meaningful reduction in spleen size and volume in a substantial proportion of patients with MF in the phase 2 studies. Pacritinib treatment improved disease-associated symptoms. These effects were observed in patients with thrombocytopenia, including those with platelet counts < 100,000 /μL, as well as in those with normal platelet counts. These findings warrant phase 3 investigation to confirm the efficacy and safety of pacritinib, both in patients with normal and low platelet counts. For the subgroup of patients with low platelet counts, the currently approved JAK inhibitor requires significant dose reduction and is less effective than in patients with normal platelet counts. Pacritinib may fill a significant unmet need in patients with low platelet counts and also provide effective treatment for nonthrombocytopenic patients with MF.

2.1 Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arm(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

2.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.3 Exploratory Objectives

The exploratory objectives are the evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of RBC transfusion independence (Appendix 1a)
9. Achievement of reduced RBC transfusion dependence (Appendix 1a)
10. Clinical improvement in hemoglobin level (Appendix 2)
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence (Appendix 1b)
13. Clinical improvement in platelet count (Appendix 2)
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4)

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamics (PD) objectives are to assess exposure and exposure response relationships on the safety and efficacy of pacritinib.

3 Study Design

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two-dose schedules of pacritinib in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to one of three treatment arms:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia) and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved

JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT scan at baseline and every 12 weeks thereafter, and at other time points as clinically indicated. MRI is the preferred modality. Imaging should be performed without contrast agents. The analysis of the primary outcome will take place when all randomized patients have completed the Week 24 MRI or CT evaluation, exhibited disease progression, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, OS, PFS, LFS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will monitor the safety of pacritinib. No interim efficacy analysis is planned.

For patients who are no longer taking pacritinib or those in the BAT arm who are no longer receiving study treatment, follow-up for survival and leukemic progression will continue until 3 years past Week 24 or past termination of all study treatment, whichever occurs first. The maximum duration of trial participation for an individual patient will be 3.5 years. The estimated duration of the entire trial is 4.5 years.

3.1 Progression of Disease

Patients may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced, and both should be reported.

Progression of disease is defined as one or more of the following:

- Splenic progression, defined as in increase in splenic volume of ≥25% from baseline, based on centrally read MRI or CT scan
- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
  - Bone marrow blast count ≥20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Although the date of the first event is considered the date of progression of disease, subsequent events must also be reported.

3.2 Criteria for Treatment Continuation After Progression of Disease

To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥25% from baseline on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF.

3.3 Criteria for Crossover from BAT to Pacritinib Treatment

To cross over from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or has progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

Each patient is to receive pacritinib or BAT until progression of disease or the occurrence of unacceptable toxicity, or until the patient no longer derives benefit from treatment (Appendix 11).

Patients on BAT may cross over to pacritinib at any time after splenic progression if leukemic transformation, splenectomy, or splenic irradiation have not occurred, or after completing 24 weeks of treatment with or without progression. Patients may continue on active (drug) study treatment after disease progression, as detailed below.

Patients on BAT who have splenic progression but do not wish to cross over to pacritinib will be followed for safety, survival, and leukemic transformation, but not splenic progression as long as they continue the BAT treatment they were taking at the time of progression. Note that patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will be followed for leukemic transformation and survival.

Patients crossing over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment. If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT must be completed within 30 days prior to the start of pacritinib treatment. This will define the crossover baseline

spleen volume, and patients will be subsequently followed for a second, post-crossover event of splenic progression.

Patients who cross over from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT.

4 Patient Selection and Withdrawal

4.1 Target Population

4.1.1 Inclusion Criteria

1. Intermediate-1 or -2 or high risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the LCM in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF-TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years old
7. ECOG performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion-dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 x ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)
15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study. Women of childbearing potential must use highly effective methods (defined as those resulting in a failure rate of <1% per year when used consistently and correctly) for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release). Males must use a condom for the duration of the study and for 90 days after the last dose of study treatment. When abstinence is used as a method of birth control, only true abstinence is acceptable, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.
17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument

19. Able to understand and willing to sign the informed consent form.

4.1.2 Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or pacritinib
4. More than 6 months of cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplantation (ASCT) or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion with the approval of the medical monitor if the arrhythmias are stable, asymptomatic and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450 ms, or other factors that increase the risk for QT prolongation (eg, heart failure, hypokalemia [defined as serum potassium < 3.0 mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

4.2 Criteria for Withdrawal of Patients

4.2.1 Withdrawal from Study Treatment

Patients may discontinue or be withdrawn from treatment at any time. All reasonable efforts should be made to retain patients who discontinue treatment in the study and to conduct all follow-up assessments required by the protocol, including MRI or CT scanning and follow-up for progressive disease, leukemic

transformation, and survival. Reasons for discontinuing treatment may include but are not limited to the following:

- Documented disease progression, defined as:
  - Splenic progression, defined as an increase in splenic volume of ≥25% from baseline based on centrally read MRI or CT scan
  - Splenic irradiation
  - Splenectomy
  - Leukemic transformation, defined as one or more of the following:
    - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
    - Bone marrow blast count ≥20%
- Unrelated intercurrent illness that, in the judgment of the principal investigator, will affect assessments of clinical status to a significant degree
- Pregnancy
- Patient's decision
- Patient noncompliance with study drug
- Clinical need for concomitant therapy that is not permitted in the study
- Decision on the part of the investigator or Cell Therapeutics' medical monitor that it is in the patient's best interest to withdraw from study treatment
- Death

4.2.2 Withdrawal from Study Procedures

Patients will be withdrawn from study procedures for the following reasons:

- Withdrawal of consent for study procedures
- Decision on the part of the investigator or Cell Therapeutics' medical monitor that it is in the patient's best interest to withdraw from study procedures

For patients who discontinue treatment and study procedures, all reasonable efforts should be made to maintain the patient in the study and continue follow-up for OS and LFS.

4.2.3 Withdrawal from the Study

Patients will be withdrawn from the study, including follow-up, for the following reasons:

- Withdrawal of consent
- Lost to follow-up
- Death
- Sponsor decision to terminate the study

5 Method of Treatment Assignment and Blinding

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT using a central interactive web response system or interactive voice response system.

Randomization will be stratified by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The first qualifying platelet value after informed consent and the most recent platelet count obtained prior to randomization will be the basis for determining platelet rebound stratification. For patients who receive any platelet transfusions, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization. If necessary due to ROW enrollment and regulatory strategies, the ROW stratum may be divided into 2 or more strata as appropriate.

A patient's treatment assignment will be known to the investigator, site personnel, the patient, clinical monitors, and pharmacovigilance personnel. The sponsor will remain blinded until the database lock for primary analysis. Independent radiographic assessors will remain blinded throughout the study.

6 Study Treatment

6.1 Study Drug Administration

Patients taking pacritinib will be supplied with 100 mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib once a day, at the same time of day, orally, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib twice each day at the same times of day, orally, with or without food (Table--7).

Patients receiving BAT will be treated on a schedule commensurate with the therapy chosen by the investigator.

Table--7
Study Treatment Schedule

Treatment	Dose/Regimen
Pacritinib (QD)	Pacritinib 400 mg (4 capsules) once a day orally, at the same time of day, with or without food.
Pacritinib (BID)	Pacritinib 200 mg (2 capsules) twice each day orally, at the same time of day, with or without food
Best Available Therapy (BAT)	Physician's choice of treatment for PMF, PPV-MF, or PET-MF

6.2 Study Drug Description and Storage

Pacritinib for oral administration is supplied in capsules containing 100 mg (as the free base) in red cap/gray body size 0 opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000.

Each capsule contains 146 mg of pacritinib citrate which is equivalent to 100 mg pacritinib free base.

Pacritinib capsules should not be opened or crushed. Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water.

Pacritinib capsules should be stored at controlled room temperature 20º to 25ºC or 68º to 77º F, with excursions allowed from 15° to 30ºC or 59° to 86ºF. All pacritinib supplies must be kept in a restricted-access area.

BAT may include any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

6.3 Dose, Route, and Mode of Administration

Patients in the pacritinib arms will be supplied with 100-mg capsules of pacritinib. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally, once a day, at the same time of day, with or without food. If assigned to the BID dosing arm, patients will take 200 mg (2 capsules) of pacritinib twice each day orally, at the same times of day, with or without food. On days when PK and/or PD samples are to be obtained, pacritinib will be administered in the clinic.

6.4 Compliance with Treatment

At every study visit, patients in the pacritinib arm and those who have crossed over to pacritinib arm will return bottles in which pacritinib is supplied with all remaining untaken pacritinib capsules.

6.5 Pacritinib Treatment Adjustments

6.5.1 Treatment Interruption

Safety parameters including AEs, hematology, and serum chemistry will be monitored according to the protocol. Pacritinib treatment may be withheld for up to 2 weeks due to drug-related toxicities. A longer recovery period may be allowed based on the toxicity, but must be agreed upon between the investigator and medical monitor.

After treatment interruption, patients may resume the pacritinib treatment at the same dose level or at a reduced dose level. No dose re-escalation is allowed.

6.5.2 Pacritinib Dose Management Guidelines for QTc Interval Prolongation

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 by CTCAE Version 4.0 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in this section. Dose management for QTc interval prolongation is summarized in Table--8.

For grade 3 QTc prolongation, hold treatment until toxicity resolves to grade ≤1. If, within 7 days, toxicity resolves to grade ≤1, restart pacritinib at 200 mg/day. When restarted, pacritinib dosing will be 200 mg QD for the 400 mg QD arm and 100 mg BID for the 200 mg BID arm. No dose re-escalation is allowed.

After restart of pacritinib, QTc monitoring should follow this schedule with EKGs obtained on:

- Restart Day 1 at 4 hours (± 1 hour) after ingestion of the first reduced dose
- Restart Day 7 (± 2 days) 4 hours after dosing (± 1 hour)
- Restart Day 14 (± 2 days) 4 hours after dosing (± 1 hour)
- Restart Day 28 (± 2 days) at any time relative to dosing
- Restart Day 56 (± 7 days) at any time relative to dosing

If grade 3 toxicity does not resolve to grade ≤1 within 7 days, discontinue all treatment with pacritinib. If grade 3 toxicity recurs despite dose reduction to 200 mg/day, discontinue all treatment with pacritinib.

For grade 4 QTc prolongation, discontinue all treatment with pacritinib.

Table--8
Treatment Toxicity and Dose Management: QTc Interval Prolongation

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3 (first occurrence)	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 within 7 days, treatment may be resumed at 200 mg daily (for QD dosing arm patients) or 100 mg twice daily (for BID dosing arm patients). In patients who resume pacritinib treatment, follow-up EKGs should be obtained to monitor QTc intervals at the following time points after resumption of pacritinib treatment: ▪ Restart Day 1 at 4 hours (± 1 hour) after ingestion of the first reduced dose ▪ Restart Day 7 (± 2 days) 4 hours (± 1 hour) after dosing ▪ Restart Day 14 (± 2 days) 4 hours (± 1 hour) after dosing ▪ Restart Day 28 (± 2 days) at any time relative to dosing ▪ Restart Day 56 (± 7 days) at any time relative to dosing ▪ Toxicity that does not resolve to grade ≤ 1 within 7 days requires treatment discontinuation.
3 (second occurrence)	▪ Discontinue treatment.
4	▪ Discontinue treatment.

6.5.3 Pacritinib Dose Management Guidelines for Pacritinib-Related Nonhematologic Toxicities other than QTc Prolongation

A maximum of 2 dose reductions is allowed. The first dose reduction will be a 100 mg reduction from the original dose. For patients taking 400 mg QD, the dose will be reduced to 300 mg QD. For patients taking 200 mg BID, the dose will be reduced to 200 mg Q AM and 100 mg Q PM.

The second dose reduction will be another 100 mg reduction. For patients taking 300 mg QD, the dose will be reduced to 200 mg/day. For patients taking 200 mg Q AM and 100 mg Q PM, the dose will be reduced to 100 mg BID.

Once the dose is reduced, no re-escalation is allowed.

Dose management for nonhematologic toxicities is summarized in Table--9.

The lowest dose of pacritinib used in the study will be 200 mg/day. If toxicity persists despite dose reduction to 200 mg/day, the patient should be discontinued from treatment.

Table--9
Treatment Toxicity and Dose Management: Pacritinib-Related Nonhematologic Toxicities

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed at the same level or the next lower dose, at the discretion of the investigator after discussion with the sponsor. ▪ Toxicity that does not resolve to grade ≤ 1 or to the baseline grade within 7 days requires dose reduction to the next lower dose level.
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed, but dose will be reduced by one dose level from the level at which the toxicity was observed. ▪ If grade 4 toxicity occurs at the lowest dose of 200 mg/day, the patient should be discontinued from the study.

6.5.4 Dose Management Guidelines for Hematologic Toxicities

Myelosuppression is an expected event in patients with MF. However, myelosuppression with associated complications such as fever, infection, or bleeding or myelosuppression that worsens during treatment (based on local laboratory values) must be reported as an AE.

Patients with myelosuppression may receive supportive care including transient use of granulocyte-colony stimulating factor for the treatment of febrile neutropenia and transfusion as clinically indicated. Patients receiving pacritinib are not allowed to receive hematopoietic growth factors such as erythropoietin for the treatment of anemia.

Patients with clinically significant worsening of myelosuppression (as judged by the investigator and based on local laboratory values) for more than 7 days or myelosuppression associated with infection or bleeding should have pacritinib dosing interrupted. Pacritinib may be restarted at a reduced dose once the toxicity has resolved to grade ≤ 2 or to the baseline grade and the complications of myelosuppression such as infection or hemorrhage have resolved.

6.6 Concomitant and Excluded Therapies

BAT will include any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved inhibitors of Janus kinases, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

Patients taking pacritinib, including those randomized to pacritinib and those who have crossed over from BAT to pacritinib, may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF during the study.

Patients should receive full supportive care, including transfusions of blood and blood products, antidiarrheal and antiemetic agents (see below), and antibiotics when appropriate.

All concomitant medications and blood products administered during the patient's participation in the study must be recorded in the source documents and electronic case report forms (eCRFs).

Patients may not receive other investigational agents during the study.

Patients may not receive treatment with any potent CYP3A4 inhibitors for 1 week prior to administration of pacritinib and during treatment with pacritinib. Some BAT therapies also have CYP3A4 interactions and/or other drug-drug interactions. Prescribing instructions should always be consulted to ensure adherence to administration guidelines for each prescribed BAT. See Appendix 9 for a list of common potent CYP3A4 inhibitors.

6.6.1 Management of Gastrointestinal Toxicity

The need for managing GI effects of pacritinib, particularly diarrhea, should be anticipated. A careful baseline evaluation of bowel habits (frequency and consistency of bowel movements) should be obtained at baseline for all patients.

The site will contact all patients by telephone during the first week (on Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to pacritinib) and at the beginning of Week 3 (of initial treatment or after crossover to pacritinib) to evaluate GI toxicity and assess the need for modifying the treatment of GI side effects. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any changes in frequency or consistency of bowel movements after starting study treatment.

Early intervention for diarrhea should be initiated for patients with increases of one grade or more in diarrhea (Appendix 12). At the investigator's discretion, prophylactic use of anti-diarrheals may be initiated for patients or populations in whom it is judged necessary to enhance patient safety. Standard supportive care measures to control symptoms of GI toxicity such as diarrhea, constipation, and nausea should be provided.

6.7 BAT Treatment Adjustments

Patients on the BAT arm who are being treated with ruxolitinib must be dosed according to the instructions in the current labeling recommendations.

7 Study Assessments

7.1 Criteria for Evaluation

7.1.1 Efficacy

7.1.1.1 Spleen Volume

Spleen volume measurement by MRI or CT scan will be performed at screening and every 12 weeks thereafter, or at other time points if spleen size progression is suspected by other assessments (eg, physical examination). Unscheduled imaging studies can be performed at physician discretion if he/she considers disease related symptoms to be worsening. All images generated as part of unscheduled evaluations must be submitted by the investigator for central review. MRI is the preferred modality; CT scan will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging

should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement. A spleen response is defined as a reduction in spleen volume of ≥35% at any time.

7.1.1.2 Spleen Size Assessment by Physical Examination

Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

7.1.1.3 Disease-Related Signs and Symptoms

Patients will complete the MPN-SAF TSS 2.0 (Appendix 7) daily for 7 to 10 consecutive days prior to starting treatment and then daily through Week 48 of the study or until the patient discontinues study treatment, whichever occurs first.

The pain medication log will be completed daily by patients, as long as they continue to complete the daily MPN-SAF TSS 2.0. The patient global impression assessment will be completed by patients every 8 weeks through Week 24 and then every 12 weeks until the patient discontinues study treatment.

7.1.1.4 Survival

Patients will be followed for survival and for transformation to AML (as assessed by the investigator, investigator-obtained records, or if these are not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

7.1.1.5 Quality of Life

The EQ-5D-5L and EORTC-QLQ-C30 version 3.0 will be completed at baseline, Week 8, Week 16, Week 24, and then every 12 weeks as long as the patient remains on study treatment. Patients will discontinue quality of life assessments at study treatment termination.

7.1.1.6 Other Assessments

Patients will also be followed for leukemic transformation, frequency of RBC and platelet transfusions, and other exploratory endpoints.

Bone marrow slides obtained at or prior to baseline as required for study eligibility and those obtained at Week 24 may be evaluated by central pathology, in addition to local pathology review.

Bone marrow biopsy evaluation (aspirate and core) obtained per protocol will be performed per local standards of care. Bone marrow biopsy sample should be evaluated for myeloblast percentage. In addition, routine and specific evaluations for myelofibrosis should be done, including (but not limited to), the following assessments: cell count and differential, megakaryocyte proliferation and atypia, reticulin

and collagen staining and staging, bone marrow cellularity, granulocytic proliferation, decreased erythropoiesis, and cytogenetic analysis (including *JAK2V617F*).

7.1.2 Safety

7.1.2.1 AEs

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

7.1.2.2 Hematology

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Hematology parameters (CBC with differential and platelet count) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local standards of care. Similarly, unscheduled CBC with differential and platelet count may be performed locally and/or centrally whenever clinically indicated.

7.1.2.3 Blood Chemistry

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Blood chemistry parameters (ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin [total, direct, and indirect], creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local standards of care. Similarly, unscheduled chemistries may be performed locally and/or centrally whenever clinically indicated

7.1.2.4 ECG Assessment

All patients will have a single 12-lead ECG at screening. Screening ECGs should be performed at least 1 week after the end of prior therapy. For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study.

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.

7.1.3 Pharmacokinetics

PK samples (five) for assessment of systemic exposure will be collected from approximately 70 patients taking pacritinib at a prespecified subset of sites at the following time points:

- Day 1 of Week 1: at 4 hours postdose
- Day 1 of Week 3: predose (Hour 0) and at 4 hours postdose
- Week 12 and Week 24: predose (Hour 0)

PK samples (two) for assessment of systemic exposure will be collected from approximately 130 patients taking pacritinib at the remaining sites at the following time points:

- Week 12 and Week 24: predose (Hour 0)

On the day prior to PK blood sampling, the patient must record the time of dosing and report it the following day. On the day of PK blood sampling, patients must not take the daily dose of pacritinib prior to the clinic visit.

Results will be used to evaluate the relationship between drug exposure and safety and efficacy.

PK samples will not be collected from patients crossing over from BAT to pacritinib.

7.1.4 Pharmacodynamics

PD samples for assessment of pSTAT3 levels, an established PD marker for JAK-STAT signaling pathway inhibition, will be collected from patients taking pacritinib at a prespecified subset of sites, the same approximate 70 patient, five-sample PK cohort as described above in Section 7.1.3, at the following time points:

- Day 1 of Week 1 and Week 3: predose (Hour 0) and at 4 hours postdose
- Week 12 and Week 24: predose (Hour 0)

PD samples will not be collected from patients crossing over from BAT to pacritinib.

7.1.5 *JAK2* Mutation Burden

JAK2V617F mutation burden will be assessed by a central laboratory in all patients at screening, at Week 12, and every 12 weeks thereafter and at termination of study treatment in patients who have the mutation at screening.

7.2 Informed Consent and Washout of Prior Therapies, 35 to 7 Days Before Beginning Study Treatment

Informed consent must be obtained before any study-specific washout. The informed consent process should be documented in the patient's medical chart. Informed consent should be obtained between 35 and 7 days prior to the start of treatment. Washout may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and MF treatments), or 7 days (potent CYP3A4 inhibitors). Patients not requiring washout may sign informed consent at any time prior to screening procedures. The informed consent

process should be documented in the patient's medical chart. Eligibility platelet count may be obtained at any time within this window.

7.3 Screening Procedures, 5 to 14 Days Before Beginning Study Treatment

Informed consent must be obtained before study procedures and screening evaluations are performed unless those evaluations are performed as part of standard of care. Patients who do not meet eligibility criteria at screening may be rescreened at a later date.

The screening evaluations listed below are to be carried out **between 14 and 5 days prior to the start of treatment**. Laboratory assessments and ECGs should be performed at least 1 week after the end of prior therapy, except eligibility platelet count which may be obtained between 35 and 7 days before beginning study treatment.

- Medical history
- *JAK2V617F* mutation status (for baseline pharmacodynamic assessment; in addition, collect medical and disease history of mutation status if documentation is available)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including height, clinical signs and symptoms, and spleen measurement
- GI assessment
- 12-lead ECG
- ECOG performance status
- Hematology: CBC with differential and platelet count
- BM biopsy within 24 weeks of randomization (may be obtained any time before Day -3)
- Serum chemistry, including ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid
- Serum pregnancy test for women of childbearing potential
- AEs
- Concomitant medications
- Transfusion history
- Assess for leukemic transformation

7.4 Symptom Assessment and Screening MRI Visit, 4 to 10 Days Before Beginning Study Treatment

- Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment
- Pain medication log will begin when MPN-SAF TSS 2.0 symptom reporting begins
- MRI or CT scan (without contrast) for measurement of spleen volume

7.4.1 Randomization, Up to 3 Days Before Beginning Study Treatment

Randomization: Patient must first sign informed consent, then complete all screening procedures, and meet all eligibility criteria. Note that screening procedures include at least two platelet counts to determine 1) the first qualifying platelet value after informed consent and 2) the platelet rebound count for stratification.

Platelet count obtained during the the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for the platelet rebound stratification determination. Should patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion obtained before randomization.

7.4.2 Beginning of Week 1, Study Day 1

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples patients in the pacritinib arm at PK sites: Hour 4 (postdose)
- PD samples for patients in the pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)
- Dispense prescription for antidiarrheal drug and instruct patient to fill it and to begin taking it at onset of gastrointestinal symptoms
- Dispense pacritinib or begin treatment with BAT
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.3 Week 1, Study Day 4 (± 1 d)

- The site (either the investigator or a surrogate) is to contact the patient by telephone to assess the need for modifying the treatment of any GI side effects.
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.4 Beginning of Week 2, Study Day 8 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.5 Beginning of Week 3, Study Day 15 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- GI assessment
- 12-lead ECG (1 only for BAT patients; 2 for pacritinib patients; predose and at 4 hours postdose)
- ECOG performance status
- PK samples for patients in pacritinib arm at PK sites: Hour 0 (predose) and Hour 4 (postdose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability

- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.6 End of Week 4, Study Day 28 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.7 End of Week 8, Study Day 56 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

- Assess for leukemic transformation

7.4.8 End of Week 12, Study Day 84 (± 3 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.9 End of Week 16, Study Day 112 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications

- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.10 End of Week 20, Study Day 140 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.11 End of Week 24, Study Day 168 (± 7 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Bone marrow biopsy
- Serum chemistry
- MRI or CT without contrast to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability

- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.12 End of Week 36, Study Day 252 (± 7 d), and Every 12 Weeks Thereafter

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.13 Termination of Study Treatment (up to 7 days after completion of all study drug treatment)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Patient-reported symptoms on MPN-SAF TSS 2.0

- Pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.14 Post-Termination (30 ± 3 days after study treatment termination)

- AEs: Last time point for collection and follow-up of nonserious AEs and SAEs deemed not related to study treatment or procedures. Please refer to Follow-up section for more details.
- Concomitant medications

7.4.15 Follow-up

SAEs assessed as related to study treatment or study procedures will be collected from the time of signing informed consent through the patient's last day of study participation, and followed until the event resolves, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever comes first. SAEs assessed as unrelated to study drug or study procedures and non-serious AEs will be collected from the time of signing informed consent through the last day of study participation and followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.

Patients will be followed for survival and for transformation to AML (as assessed by investigator, investigator-obtained records, or if not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

8 Pharmacokinetic Analysis and *JAK2* Mutation Burden

8.1 Blood Sample Collection, Handling, and Shipping

Blood samples for PK and *JAK2* mutation burden analyses should be collected in appropriate blood collection tubes as defined in the study manuals. On the days when blood samples for PK analysis are collected, patients should be instructed not to take pacritinib at home. The time/date when the prior dose was administered must be recorded on the appropriate CRF page. At minimum, tubes are to be labeled with the patient number, study number, and specimen identification number.

The sponsor will provide the investigator with a manual containing details for the preparation of blood samples to be collected. Shipment and analysis instructions will be provided to the investigator in a separate manual.

8.2 Pharmacokinetic, Pharmacodynamic, and *JAK2* Mutation Burden Assessments

Blood samples for PK and PD analyses will be collected predose and postdose on the specified study days for patients in the pacritinib arm per the two prespecified subsets of the clinical sites.

Blood samples will be collected for central analysis of *JAK2V617F* mutation burden in all patients at screening, and then only in mutation-positive patients at subsequent time points.

9 Assessment of Safety

9.1 Adverse Events

9.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Examples of AEs include, but are not limited to:

- Any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, medical diagnosis, or concomitant disease temporally associated with the use of the study drug, whether considered related to study drug or not
- Abnormalities observed during the study that meet any of the criteria below
  - Any laboratory or other test result that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring
  - Requires discontinuation, dose reduction, or delay of study drug
  - Requires that the patient receive specific corrective or supportive therapy
  - Clinically significant changes noted during physical examinations, ECGs, imaging studies, biopsies, and other safety assessments, whether or not these procedures were required by the protocol

Progressive disease is not an AE, unless it is the primary cause of death. If the primary cause of death is progressive disease, the primary AE term should be reported as “progressive myelofibrosis.” Signs and symptoms associated with disease progression may be recorded as secondary AE terms.

9.1.2 Reporting Adverse Events

All baseline conditions and AEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject’s last day of study participation.

For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of the patient, or may be detected through a clinically meaningful procedure. To prevent bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

The following information should be captured for all AEs: date of onset and resolution, severity per Common Terminology Criteria for Adverse Events (CTCAE), seriousness, the investigator's assessment of relationship to study drug, event outcome, and action taken with study medication due to the reported event. If concomitant treatment is given for the AE, this information should be captured on the appropriate eCRF. If the AE is an abnormal local laboratory value or test result, this information should also be captured on the appropriate eCRF.

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF and symptoms of the illness or disorder should not be reported as separate AEs with the exception of progressive disease, as discussed above. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting investigator (eg, "anemia" versus "low hemoglobin value").

If an AE results in early termination of the patient's study treatment period, "AE" should be selected as the reason for discontinuation on the eCRF. However, if the AE that resulted in early termination was a sign or symptom of progressive disease, "progressive myelofibrosis" should be selected as the reason for discontinuation on the eCRF.

Special Considerations

- Elective procedures or routinely scheduled treatments are not AEs. However, any untoward medical event occurring during a prescheduled elective procedure or routinely scheduled treatment should be documented as an AE.
- Baseline conditions are not AEs; however, worsening of a baseline condition following study drug administration is an AE.
- Death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. However, sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

If progressive disease is the primary cause of death, the term "progressive myelofibrosis" should be reported as the AE term. All AEs ongoing at the time of death that are not the primary cause of death will remain not resolved on the eCRFs.

9.1.3 Criteria for Assessing Adverse Events

9.1.3.1 Severity

The term "severe" is a measure of intensity; a severe event is not necessarily serious.

The National Cancer Institute (NCI) CTCAE version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities identified as AEs. A copy of these criteria is provided in the study manual, however minor version updates (ie, 4.01, 4.02 and above) may be used at the discretion of the sponsor.

9.1.3.2 Relationship

The relationship of an AE to the study treatment(s) will be assessed using the guidelines described below. If an AE is deemed related to study treatment(s) (eg, for BAT) but the investigator cannot attribute the relationship solely to a single treatment, the investigator should indicate that the AE is related to all

possible agents. Any AE for which there is no assessed causal relationship shall be assessed by the sponsor as related, and will require immediate follow up with the site to determine the investigator's assessment.

Definite

There is a reasonable causal relationship between the study treatment and the event, and the event occurred within a plausible time relationship to treatment administration, and the event cannot be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge.

Probable

There is reasonable causal relationship between the event and the study treatment, the event occurred within a plausible time relationship to treatment administration, and the event is unlikely to be attributed to the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event follows a clinically reasonable response on withdrawal of study treatment.

Possible

There is a reasonable causal relationship between the event and study treatment, the event occurred within a plausible time relationship to study treatment administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. Dechallenge information is lacking or unclear.

Unlikely

There is a temporal relationship of the event to study treatment but not a reasonable causal relationship, or there is no temporal relationship to study treatment administration or the condition under study, concurrent disease, other drugs or chemicals, or other circumstances provide a plausible explanation for the event.

Unrelated

There is no temporal relationship between the event and study treatment administration (study treatment given too early or late or study drug not administered). There is no reasonable causal relationship between the event and the study treatment. The condition under study, concurrent disease, other drugs or chemicals, or other circumstances provides a plausible explanation for the event.

9.1.3.3 Outcome

AEs will be characterized according to the outcomes described in Table--10

Table--10
Outcomes of Adverse Events

Outcome	Description
Recovered/Resolved	One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated
Recovered/Resolved with Sequelae	One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury

Table--10 Outcomes of Adverse Events	
Outcome	**Description**
Recovering/Resolving	One of the possible results of an adverse event outcome that indicates the event is improving
Not Recovered/Not Resolved	One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated
Fatal	The termination of life as a result of an adverse event
Unknown	Not known, not observed, not recorded, or refused

9.1.3.4 Action Taken with Study Drug

Action taken with the study drug in relation to the AE will be characterized as follows:

- Dose increased
- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

9.1.4 Serious Adverse Events

9.1.4.1 Definition of a Serious Adverse Event

An SAE is an AE that, at any dose, suggests a significant hazard or side effect, regardless of its relationship to the study drug. An AE is serious if it meets any of the criteria below:

1 Results in death

2 Is life-threatening: in the view of the investigator, the event placed the patient at immediate risk of death. This does not include an AE that, had it occurred in a more severe form, might have caused death.

3 Requires inpatient hospitalization or prolongation of an existing hospitalization (see Exceptions below)

4 Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

5 Is a congenital anomaly/birth defect

6 Is an important medical event that is not fatal, life threatening, or requiring hospitalization, but may be considered serious if, based on appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above (1 - 5)

7 Cancer/overdose: All cases of new cancers, with the exception of disease progression/transformation to acute myeloid leukemia, and drug overdose (defined as accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. Determination of seriousness will be reached in consultation with the Safety Physician, CTI Global Pharmacovigilance US Headquarters or designee.

9.1.4.2 Exceptions

Hospitalizations not reported as SAEs include admissions for:

1 Planned, nonlife-threatening medical/surgical procedures
2 Routine health assessments requiring admission for health status documentation (eg, routine gastroscopy, colonoscopy, etc)
3 Other life circumstances that have no bearing on health status and require no medical/surgical intervention (eg, lack of housing, family circumstances, etc.)
4 Administration of study medication

9.1.4.3 Reporting Serious Adverse Events to the Sponsor

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. All SAEs, irrespective of causal relationship, must be recorded on a paper SAE Report Form and reported to the Sponsor within 24 hours of becoming aware of the event via either Fax or e-mail.

Fax (US Only): 1-508-416-2654 Fax (outside the US): +44 870 7107157 Email: safety@aptivsolutions.com

Special Considerations:

- SAEs considered to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the investigator or Sponsor shall be followed until the event resolves, stabilizes or the patient is lost to follow up.
- SAEs assessed as unrelated to study drug or study procedures shall be followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.
- For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported.
- All SAEs for randomized patients must have a corresponding AE recorded on the eCRF with an exact match to the event term or description.
- An SAE form should be completed for any event for which doubt exists regarding its seriousness.
- If an ongoing SAE changes in intensity, relationship to study drug, or as new information becomes available and/or known for the event, a follow-up SAE Report form should be completed and sent to the Sponsor within 24 hours of the change in SAE assessment.
- Any SAE that occurs after study completion and is considered by the investigator to be related to pacritinib should be reported to the sponsor.

A narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted by revising the SAE Report Form as soon as the information becomes available.

Source documents should be submitted only in English. If source documents are not in English, the investigator must summarize the source documents and provide a complete English narrative that includes a description of the event as it evolved the results of all diagnostic procedures performed and treatments administered, and the outcome of the event.

9.1.4.4 Reporting Serious Adverse Events to the Regulatory Agencies, Institutional Review Boards and/or Ethics Committees

The Sponsor will evaluate reported SAEs for expedited reporting as assessed against the most current approved version of the Investigator Brochure for pacritinib SAEs, or against the local Summary of Product Characteristics (SPC) for BAT SAEs. If a brand name for a BAT product is unknown or unavailable, the SPC of the local market leader will be used to assess the suspect product(s) for regulatory reporting purposes. Until an AE is identified in the Reference Safety Information of the IB or SPC, it is considered unexpected, regardless of whether the AE has been submitted previously as an expedited report.

Expedited reporting will be performed by the Sponsor in accordance with local regulation.

Upon receiving an expedited report, the investigator must review and retain the notice with the Investigator Brochure and shall be responsible for submitting expedited reports to their IRB/EC in accordance with institutional guidelines. Regardless of institutional guidelines, investigators shall submit expedited reports to their IRB/EC in the event that the sponsor identifies an expedited report to represent a new and/or unforeseen risk.

In support of required progress reports, the Sponsor will provide the investigator and/or Ethics Committee with a summary of all SAEs reported for the study at predefined intervals (e.g. quarterly) and/or upon request.

Pregnancy

Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment and/or within one month of ending treatment even if the subject is withdrawn from study, this must be reported to the Sponsor immediately on the Pregnancy Reporting Form. The investigator must obtain written authorization (medical records release) from a female partner of a male subject prior to obtaining follow-up.

The investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcome. All pregnancy outcomes will be recorded on the Pregnancy Report Form.

Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will also be recorded in the AE eCRF and on the SAE Report Form. The associated SAE Report Form should be sent to the Sponsor per the procedure and timelines described within Section 9.1.4.3, Reporting Serious Adverse Events to the Sponsor.

Overdose

Overdose is defined as any deviation from the defined or prescribed use of study drug as applicable for the drug and trial design. Occurrences of overdose should be reported to the sponsor on an SAE Report Form. Reports of overdose will be evaluated on a case by case basis. Additional instructions for reporting overdose information will be provided by the Sponsor in the study binder.

Deaths

All deaths that occur during the study must be recorded on the appropriate eCRF. As described in Section 9.1.2 and 9.1.3.1, death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. Progressive disease is not an AE, except when it is a cause of death. When progressive MF is a cause of death, it should be reported as an AE and SAE as per above.

Sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

9.2 Laboratory Evaluation

All scheduled clinical laboratory test values collected as part of the study will be evaluated by a central laboratory.

The investigator may use local or central laboratory evaluations (as dictated by local standards of care) to facilitate real-time decisions about study treatment administration, eligibility, and dose modifications and for evaluation of signs and symptoms. If any AE is identified, or clinical intervention results from local laboratory tests, the test result and local laboratory normal ranges for that test will be reported on the appropriate eCRF.

Treatment decisions (such as dose delays) and adverse events may be based on either local or central laboratory results.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central lab or independent review panel for study purposes, treatment decisions must be made by the investigator based on his or her clinical assessment of the patient and his or her interpretation of local labs, radiology assessments, and other tests.

9.3 Vital Signs and Physical Examination

Vital signs will be obtained at each study visit. Physical examinations are performed at screening, baseline, every 12 weeks thereafter, and at study termination.

9.4 ECOG Performance Status

ECOG performance status will be assessed at each visit (Appendix 8).

9.5 Safety Surveillance

An IDMC will meet periodically throughout the study (eg, every 6 months), or as described within the IDMC Charter, to review accumulating safety data from the entire clinical trial.

10 Data Management

The CTI Clinical Data Management Department or its designee will prepare guidelines for data entry and data handling, which will include procedures for data verification and electronic edit checks. The complete data management process will be described in the Data Management Plan.

10.1 Data Collection

An electronic data capture (EDC) system will be used for this study. Designated site personnel will enter subject data required by the protocol into eCRFs based on source documents. Personnel will not receive access to the EDC system until they have completed all training requirements. The EDC system will provide an automatic audit trail of all changes made to the clinical database.

10.2 Data Entry and Quality Control

Data items will be entered directly from source documents by designated site personnel using single data entry. Concomitant medications entered into the database will be encoded using the World Health Organization (WHO) Drug Reference Dictionary. AEs, coexisting disease, and other data items will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in a database system maintained by the central vendor. If clinical intervention is performed on the basis of any local laboratory test result, the test result and local laboratory normal ranges will be entered into the EDC system.

CTI staff or designees will review the data on a periodic basis to ensure validity, accuracy and completeness. Data suspected to be discrepant or incomplete will be questioned using data queries. Data queries resulting from these reviews will be sent to the study sites via the EDC system. The staff at the study sites will respond to the queries in the EDC system and these responses will be reviewed by CTI staff or designee. Only data that do not unblind the Sponsor will be reviewed by the Sponsor.

11 Statistical Analysis Plan

Statistical analysis of the study data will be the responsibility of CTI Biostatistics Department or its designee. This section describes the statistical methodology used in the primary analysis of the co-primary endpoints. Analysis of the exploratory endpoints and other supportive, sensitivity, or subgroup analyses will be specified in a separate statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of the clinical database.

11.1 Endpoints

11.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of the study are:

- the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT and,
- the proportion of patients with a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

11.1.2 Exploratory Endpoints

The exploratory endpoints are:

1 Overall survival (OS)
2 Progression-free survival (PFS)

3 Leukemia-free survival (LFS)
4 Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥35% reduction from baseline in spleen volume
6 Best response in spleen volume by MRI or CT
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)
9 Achievement of reduced RBC transfusion dependence (Appendix 1a)
10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4).

Details for the definition and analysis of the exploratory endpoints are provided in the Statistical Analysis Plan.

11.2 Hypotheses

11.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in:

- a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and
- a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0

than treatment with BAT.

11.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

11.3 Analysis Populations

11.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. This population will be used for the primary analysis of the efficacy endpoints.

11.3.2 Evaluable Population

The evaluable population for each endpoint is defined as all randomized patients who have an evaluable baseline and follow-up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for the supportive analyses of the efficacy endpoints.

11.3.3 Per-Protocol Population

The per-protocol (PP) population is defined as all randomized patients who receive any study treatment, have a baseline assessment, complete relevant follow-up assessments, and have no major protocol violations. Patients in this population will be analyzed according to the treatment actually received. The PP population will be used for the supportive analyses of the primary efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

11.3.4 Safety Population

The safety population is defined as all randomized patients who receive any dose of study treatment. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received.

11.3.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK, plasma PD markers or STAT3 phosphorylation analysis. The study pharmacokineticist will review data listings of patient dosing and sample records to identify patients with appropriate samples for the analysis.

11.4 Efficacy Analysis

Efficacy analyses including all hypothesis testing will be performed after the last patient completes the Week 24 assessments or experiences progressive disease, whichever comes first. Analysis of long-term safety and efficacy will be performed as supportive analyses as specified in the Statistical Analysis Plan.

11.4.1 Reduction in Spleen Volume

The primary analysis of the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT will be based on the IRF assessments. The analysis will be performed using the ITT population. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be presented by the 3 treatment arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression or drop out of the study before Week 24 will be considered to have not achieved the ≥35% reduction. The numbers and percentages for each reason for not achieving the ≥ 35% reduction

will be presented by treatment arm. The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the appropriate confidence intervals based on the Agresti-Caffo method will be provided.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤ 100,000/μL versus > 100,000/μL). The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata.

The primary analysis will be repeated using other post-baseline reduction in spleen volume (Week 12, Week 36, and Week 48). The mean or median reduction in spleen volume over time will be evaluated. More details will be provided in the SAP.

11.4.2 Improvement in Total Symptom Score

All the analyses outlined in Section 11.4.1 will be repeated using the proportion of patients with a ≥ 50% reduction from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

The TSS endpoint is obtained as follows:

- The daily TSS is the sum of the individual symptom scores for tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side. Daily TSS is set to missing if one of these individual symptom scores is missing.
- The baseline TSS is the mean of the daily TSS over the 7 consecutive days immediately prior to randomization. Baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to randomization.
- The Week 24 TSS is the mean of the daily TSS over the 28 consecutive days prior to the Week 24 visit. The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to the Week 24 visit. Patients with a missing Week 24 TSS, including those who meet the criteria for disease progression or drop out of the study before Week 24, will be considered to have not achieved the ≥ 50% reduction.
- The percent reduction in TSS from baseline to Week 24 is then computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 24 TSS} - \text{Baseline TSS}}{\text{Baseline TSS}}\right) * 100$$

A sensitivity analysis will be conducted using the average of the 7 daily TSS prior to the Week 24 visit as the Week 24 TSS. The details of the analysis will be described in the SAP.

In addition, exploratory analyses of the correlation of Week 24 TSS with Week 24 spleen size, STAT3 phosphorylation, and patient global impression assessment will be performed. Details are provided in the SAP.

11.4.3 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1 The primary hypothesis will be tested at $\alpha = 0.05$ (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on:

   a. the difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24, and

   b. the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24

   individually.

   The study reaches its primary objective (claimed to be successful) when both endpoints reach statistical significance ($\alpha = 0.05$, 2-sided).

2 If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in a) the QD arm versus the BAT arm and b) the BID arm versus the BAT arm at the 2-sided 0.025 α-level.

   a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be tested at a 2-sided $\alpha = 0.025$.

   b. If the p-value is less than α, the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24 will be tested at a 2-sided $\alpha = 0.025$.

11.5 Safety Analysis

The assessment of safety will be based mainly on the frequency of AEs and the number of laboratory values that fall outside of predetermined ranges.

Treatment-emergent AEs will be coded using MedDRA version 16.0 and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients with an event. The following subsets of treatment-emergent AEs will also be summarized by treatment arm: AEs related to study treatment, CTCAE grade 3 or 4 AEs, AEs leading to treatment discontinuation, deaths, and SAEs. Ongoing AEs in patients who cross over to pacritinib will be assessed at the time of the crossover, and the CTCAE grade at the time of crossover will be considered the new baseline.

Clinical laboratory data will be summarized with descriptive statistics by treatment and timepoint. Each patient's data will be classified by the CTCAE grade, where possible, and be summarized in shift tables comparing the worst post-baseline visit to baseline.

11.6 Determination of Sample Size

A sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. Based on previous studies, it is assumed that the proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24 is 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. It is also assumed that the proportion of patients achieving a ≥ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm.

For primary hypotheses (pooled QD/BID vs BAT), a sample size of 300 patients provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for the

secondary hypothyses testing independently; i.e., comparing QD pacritinib arm with the BAT arm and comparing the endpoint in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is ≥ 93% power to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

11.7 Interim Analyses

No interim analyses are planned for this study.

12 Pharmacokinetic and Pharmacodynamic Analyses

The PK parameters will be summarized with descriptive statistics. The relationship between exposure and the efficacy and safety of pacritinib will be evaluated. Population PK analysis will be performed.

13 Independent Data Monitoring Committee

An IDMC will be chartered to monitor and evaluate the safety of all patients in this trial. The IDMC will periodically review summaries of trial data, including all safety data, identifying any clinically relevant trends, and making recommendations as to whether the study should continue. The IDMC Charter will include operational and logistical procedures for the IDMC.

14 Study Administration and Investigator Obligations

For studies conducted outside the United States under a US IND, the principal investigator must comply with US FDA IND regulations and with those of relevant national and local health authorities.

14.1 Study Drug Accountability

Cell Therapeutics, Inc. will provide pacritinib. The recipient will acknowledge receipt of the drug by returning the appropriate shipping receipt form according to the study-specific pharmacy manual. Damaged supplies will be replaced.

Accurate records of all pacritinib dispensed from and returned to the study site should be recorded by using the Drug Inventory Log (refer to study-specific pharmacy manual).

Pacritinib will be disposed of at the study site according to institutional standard operating procedures after study monitors have completed the drug inventory reconciliation. The method of destruction must be documented. A copy of the destruction certification along with the inventory of destroyed clinical material will be provided to Cell Therapeutics, Inc.

14.2 Informed Consent

Cell Therapeutics, Inc. will provide a sample ICF to each site. Cell Therapeutics, Inc. or its designee must review any proposed deviations from the sample ICF. Patients must be re-consented to the most current version of the ICF during their participation in the study. The investigator must provide the final local IRB/REB/IEC approved informed consent form to Cell Therapeutics, Inc. for regulatory purposes.

The patient or the patient's legally authorized representative must sign the ICF before his or her participation in the study. The source record for each patient shall document that informed consent was

obtained prior to participation in the study. A copy of each signed ICF or Addendum to an existing ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed consent forms must remain in each patient's study file and must be available for verification by the study monitor at any time.

14.3 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, Cell Therapeutics, Inc., its designees and the IRB/IEC/REB for each study site, if appropriate.

14.4 Case Report Forms

Cell Therapeutics, Inc. will provide eCRFs, which should be completed in accordance with instructions from Cell Therapeutics, Inc.

14.5 Study Monitoring

Representatives of Cell Therapeutics, Inc. or their designee must be allowed to visit all study site locations at appropriate intervals to assure compliance with Good Clinical Practice (GCP), satisfactory enrollment rate, data recording, and protocol adherence. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The investigator agrees to cooperate with the monitor to ensure any problems detected in the course of these monitoring visits are resolved. In addition to these visits, Cell Therapeutics, Inc. will routinely monitor each site by phone to keep abreast of patient status and to answer questions.

In order for the investigator to participate in this trial, the trial monitor must have direct access to source data for data verification. This will be done by comparing data from the eCRFs with data from the patient's clinic or hospital records (permission will be sought from the patient as part of the consent process).

In addition, Cell Therapeutics, Inc. internal auditors and government inspectors may evaluate the study. They must be allowed access to eCRFs, source documents, and other study files. Cell Therapeutics, Inc. audit reports will be kept confidential.

The investigator should promptly notify Cell Therapeutics, Inc. of an audit scheduled by any regulatory authority, and promptly forward copies of audit reports.

14.6 Record Retention

US FDA regulations (21CFR§312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that the principal investigator retain records and documents pertaining to the conduct of the study and distribution of investigational drug, including eCRFs, consent forms, laboratory test results, radiographic assessments, and medication inventory records for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. Cell Therapeutics, Inc. will notify the principal investigator of these events.

No records should be disposed of without the written approval of Cell Therapeutics, Inc.

15 Ethics

15.1 Good Clinical Practice

The investigator and sponsor will ensure that this study is conducted in full compliance with Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines, US FDA regulations 21 CFR Parts 50, 56, and 312, and with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient.

15.2 Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC)

The appropriate IRB, REB, or IEC must approve in writing the protocol and ICF for this study in accordance with the laws and regulation of the country in which the research is conducted prior to any patient being registered in this study.

Before the investigational drug will be shipped to the investigator, the investigator must provide Cell Therapeutics, Inc. with a copy of the IRB or REB or IEC approval letter stating that the study protocol and informed consent form have been reviewed and approved. Original US FDA Form 1572 (for all studies conducted under US IND regulations) signed by the principal investigator, and a copy of the CV for the principal investigator, and a copy of an IRB/REB/IEC approved informed consent form are also required.

The investigator must also report all serious and medically significant AEs to the IRB/REB/IEC according to the local regulation.

Appendix 13 lists the responsibilities of the investigator.

16 Termination of Study

Cell Therapeutics, Inc. will retain the right to terminate the study and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory enrollment with regard to quality or quantity
- Deviations from GCP
- Deviation from protocol requirements, without prior approval from Cell Therapeutics, Inc.
- Inaccurate and/or incomplete data recording on a recurrent basis

- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

In terminating the study, Cell Therapeutics, Inc. and the investigator will assure adequate consideration to the protection of the patients' interest.

17 Study Amendments

Changes in any portion of this protocol must be documented in the form of an amendment from Cell Therapeutics, Inc. and must be approved by the site's IRB/REB/IEC before the amendment can be implemented at the site. The IRB/REB/IEC chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions.

18 Use of Information and Publication

Cell Therapeutics, Inc. recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The Clinical Study Agreement will describe the details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial.

19 References

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Appendix 1a - Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	$\geq$ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al, 2011	

Appendix 1b – Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

Appendix 2 - International Working Group Consensus Criteria for Treatment Response in Myelofibrosis with Myeloid Metaplasia

Clinical Improvement	
Hemoglobin	A minimum 20g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100g/L) for 8 weeks or more
Platelet count	A minimum 100% increase in platelet count and an absolute platelet count of at least 50,000/μL (applicable only for patients with baseline platelet count below 50,000/μL) for 8 weeks or more
Tefferi et al 2006	

Appendix 3 - EQ-5D-5L Health Questionnaire

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

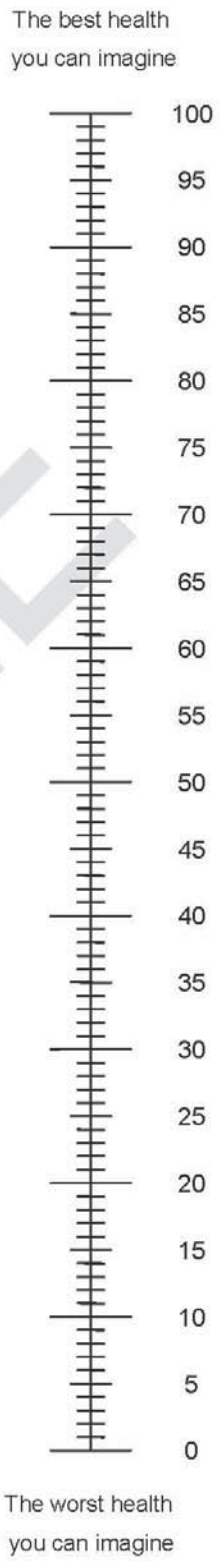
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



3

Appendix 4 - EORTC QLQ-C30 Version 3

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

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

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5 - Dynamic International Prognostic Scoring System in Primary Myelofibrosis (Passamonti et al, 2010)

Prognostic Variable	Value		
	0	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, x 10^9/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

Risk Category	
Low	0
Intermediate-1	1-2
Intermediate-2	3-4
High	5-6

Appendix 6 - Diagnostic Criteria for Primary Myelofibrosis, Post-Polycythemia Myelofibrosis and Post-Essential Thrombocythemia Myelofibrosis

	Major Criteria	Minor/Additional Criteria
Primary myelofibrosis (PMF) Diagnosis requires meeting all 3 major criteria and at least 2 minor criteria[1]	1. Megakaryocyte proliferation and atypia[3] accompanied by either reticulin and/or collagen fibrosis **or** 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) 2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm 3. Demonstration of JAK2V617F or other clonal marker **or** No evidence of reactive marrow fibrosis	1. Leukoerythroblastosis 2. Increased serum LDH 3. Anemia 4. Palpable splenomegaly
Post-polycythemia vera myelofibrosis (PPV-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5cm (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 degrees C)
Post-essential thrombocythemia myelofibrosis (PET-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] and a ≥2 mg ml^{-1} 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

	Major Criteria	Minor/Additional Criteria
		margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5 degrees C)

Abbreviations:
WHO - World Health Organization
MDS - myelodysplastic syndrome
CML - chronic myelogenous leukemia
LDH - lactate dehydrogenase

[1] Tefferi A, Vardiman, JW 2008
[2] Barosi G, Mesa RA, Thiele J, et al. 2008
[3] Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering
[4] Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain) (see WHO criteria)
[5] Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis (see WHO criteria)
[6] Below the reference range for appropriate age, sex, gender and altitude considerations

Appendix 7 – Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (Version 2.0)

Symptom	0 to 10 Ranking
Select the one number that describes the worst severity you have experienced with each of the following in the past 24 hours:	
Tiredness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Pain under ribs on the left side	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix 8 - Eastern Cooperative Oncology Group Performance Status Scale Grade Description (Oken et al 1982)

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 9 - Selected Potent Inhibitors of CYP3A4

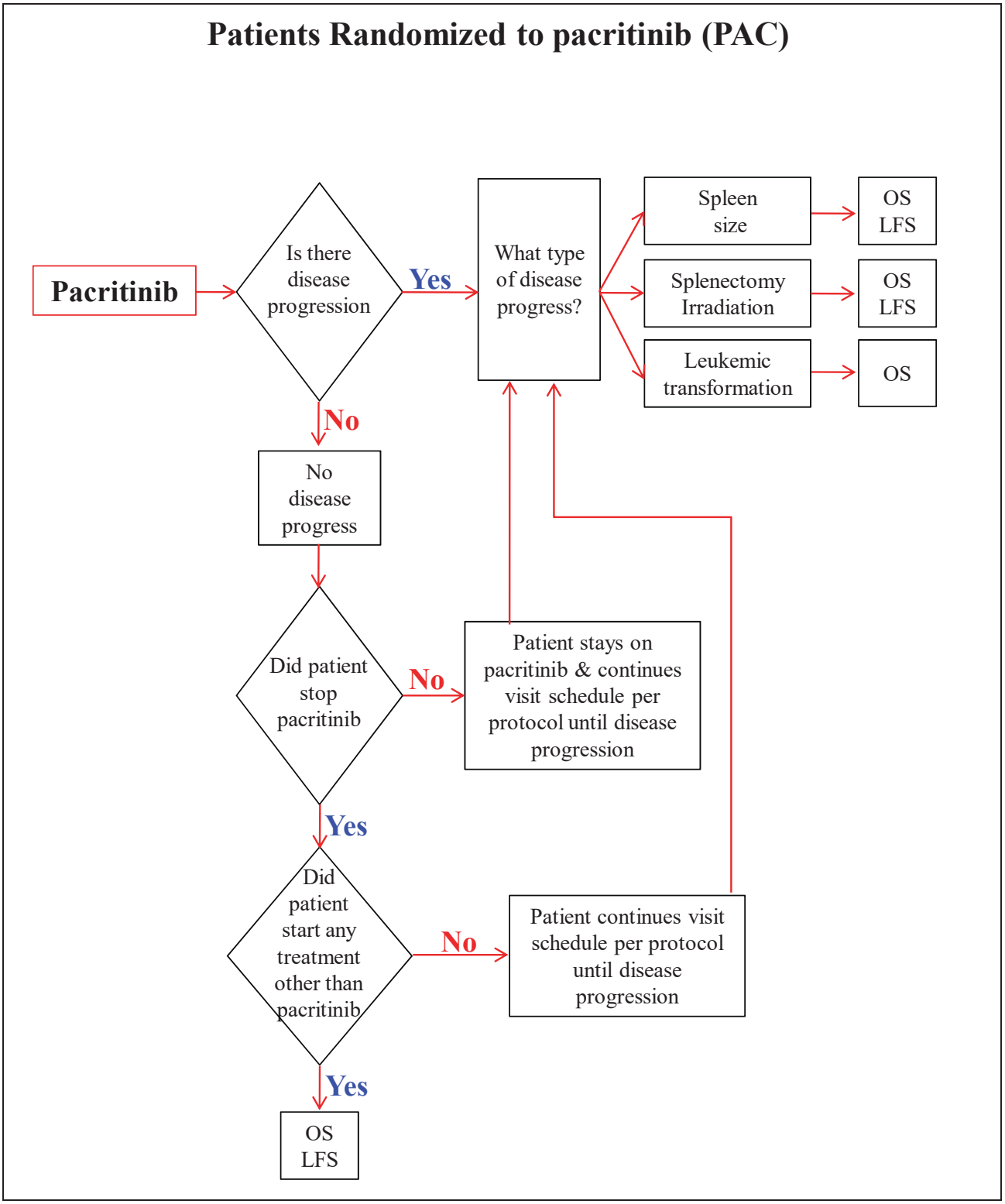
boceprevir	nefazodone
ciprofloxacin	nelfinavir
clarithromycin	norfloxacin
conivaptan	posaconazole
erythromycin	quinidine
fluconazole	ritonavir
grapefruit	saquinavir
grapefruit juice	Seville oranges
indinavir	star fruit
itraconazole	telaprevir
ketoconazole	telithromycin
lopinavir	troleandomycin
mibefradil	voriconazole
This list is not comprehensive. When considering using an agent that could be a potential CYP3A4 inhibitor/inducer, please discuss this with the medical monitor. Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://wwwpharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.	

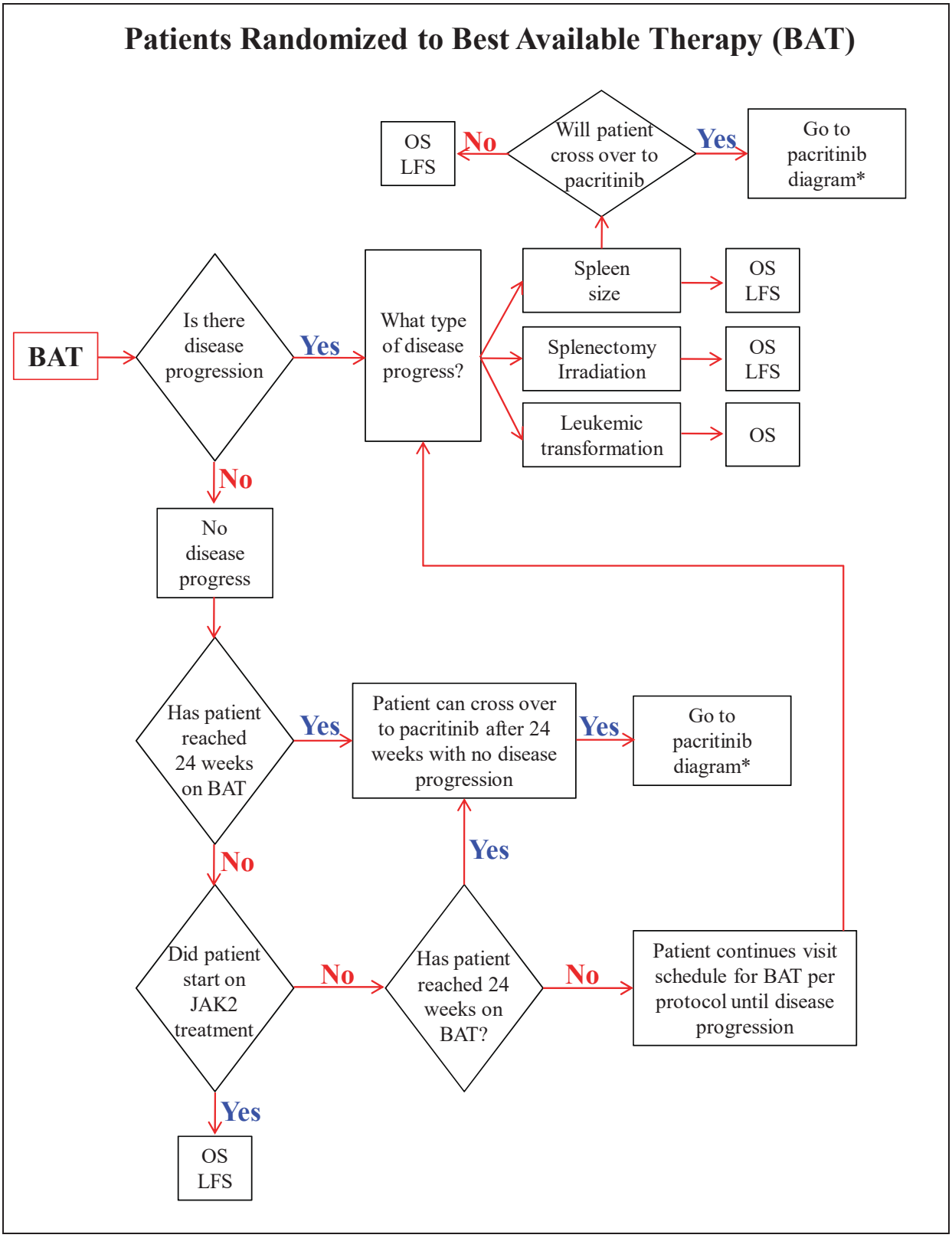
Appendix 10 - The Stages of Heart Failure, New York Heart Association (NYHA) Classification

To determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
Source: Dolgin et al.	

Appendix 11 – Study Flowchart




Patients Randomized to Best Available Therapy (BAT)
BAT
Is there disease progression
Yes
No
What type of disease progress?
Spleen size
Splenectomy Irradiation
Leukemic transformation
OS LFS
OS LFS
OS
Will patient cross over to pacritinib
No
Yes
OS LFS
Go to pacritinib diagram*
No disease progress
Has patient reached 24 weeks on BAT
Yes
Patient can cross over to pacritinib after 24 weeks with no disease progression
Yes
Go to pacritinib diagram*
No
Yes
Did patient start on JAK2 treatment
No
Has patient reached 24 weeks on BAT?
No
Patient continues visit schedule for BAT per protocol until disease progression
Yes
OS LFS

Appendix 12 - Common Terminology Criteria for Adverse Events: Diarrhea (Version 4.03)

Definition: A Disorder Characterized by Frequent and Watery Bowel Movements.	
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Appendix 13 - Responsibilities of the Investigator

For a complete list of investigator responsibilities refer to the ICH guideline for GCP, Section 4.0; *Investigator*. The responsibility of the investigator includes but is not limited to the following criteria:

1. To provide the qualifications of the investigator(s) by Curriculum Vitae and/or other documentation to the sponsor or regulatory authorities upon request.
2. To be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator Brochure, in the product information, and in other information sources provided by the sponsor.
3. To comply with GCP and applicable regulatory requirements.
4. To permit monitoring and auditing by the sponsor, access to all relevant trial documents, and inspection by appropriate regulatory authorities.
5. To maintain a list of qualified persons to whom the investigator has delegated significant trial-related duties.
6. To be able to demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.
7. To have sufficient time to properly conduct and complete the trial within the agreed trial period.
8. To have available adequate facilities and qualified staff to conduct the trial properly and safely for the foreseen duration of the trial, and to ensure that other trials do not divert essential patients or facilities away from the trial.
9. To ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
10. To ensure that adequate medical care is provided to a patient for any adverse experiences, related to the trial, during and following his/her participation in a trial.
11. To inform a patient when medical care is needed for inter-current illness of which the investigator becomes aware.
12. To inform (if possible) the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
13. To secure written and dated IRB/IEC/REB approval prior to initiating a trial for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements), and any other written information to be provided to patients.
14. To provide the IRB/IEC/REB with all trial-relevant documents for review.
15. To conduct the trial in compliance with the protocol as approved by the IRB/IEC/REB and agreed to by the sponsor and applicable regulatory authorities.
16. To sign the protocol (with the sponsor), or an alternative contract, to confirm their agreement on conducting the trial.
17. To not implement any deviation from, or changes of, the protocol without agreement by the sponsor and approval from the IRB/IEC/REB of an amendment, except where necessary to eliminate an immediate risk to trial patients, or when the changes involve only logistical or administrative aspects of the trial, and to document and explain any such deviations. If a deviation or change in the protocol was implemented by the investigator to eliminate an immediate hazard(s) to patients without prior IRB/IEC approval/favorable opinion; the deviation (and reason for) or proposed change must be submitted as soon as possible:
    - To the IRB/IEC/REB for review and approval/favorable opinion;
    - To the sponsor for agreement and, if required;

- To the regulatory authority(ies).

18. To assume full responsibility for investigational products at the trial site (whether through personal supervision or through assignment of these duties to a qualified health care professional). This includes responsibility for usage, accountability (including all necessary documentation), storage and handling, instruction and supervision of any personnel authorized in the usage of the investigational product, and disposition of supplies upon completion of the trial.
19. To follow all randomization procedures and protect the integrity of the blind (if used). In the event of premature unblinding in a blinded trial, the investigator is to promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse experience) of the investigational products.
20. To ensure that the confidentiality of all information about patients and information supplied by the sponsor is respected by all persons involved in the trial.
21. In regards to data collection and management:
    - To collect and record data properly and ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports;
    - To ensure that data reported on the eCRFs, which are derived from source documents, are consistent with the source documents, and that all discrepancies are explained;
    - To follow the sponsor's guidance in making changes or corrections to eCRFs;
    - To maintain the essential trial documents as required by the applicable regulatory requirements, until notification by the sponsor.
22. To provide all requested reports or notification of changes affecting the conduct of the trial, and/or increasing the risk to patients to the sponsor, IRB/IEC, investigative institution, or applicable regulatory agency.
23. To report all deaths, serious adverse experiences, adverse experiences and laboratory abnormalities to the sponsor according to the procedures specified in the protocol.
24. To promptly inform the trial patients in the event that the trial is terminated prematurely or suspended for any reason, and to provide appropriate therapy and follow-up procedures. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator is to inform the institution, where required by the applicable regulatory requirements, and the investigator/institution is to promptly inform the sponsor and the IRB/IEC, and provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
25. To promptly notify the sponsor and investigative institution (with detailed written explanation) of any change or retraction of IRB/IEC approval, where applicable.
26. To provide, upon completion of the trial, all required reports and/or summaries to the sponsor, the IRB/IEC and applicable regulatory authorities.

CTI BioPharma Corp.

PERSIST-2 Protocol

PAC326

Pacritinib

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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Amendment 2
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Sponsor:
CTI BioPharma Corp.
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Seattle, WA 98121

Medical Monitor
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Investigator Responsibilities, Required Documentation, and Signature

Cell Therapeutics, Inc. will select the investigator(s) on the basis of their expertise in the field of clinical studies in hematologic oncology and in the care and treatment of patients with chronic myeloproliferative diseases. Investigators will also be selected on the appropriateness of their facility to conduct a research study of this nature, and the characteristics of the patient population treated at the institution. The investigator will:

- Obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol and amendments to the protocol and Informed Consent Form before initiation of the protocol or any amendments for the study, and obtain annual IRB or IEC renewal, as required.
- Ensure that current FDA and/or ICH-E6 regulations are followed.
- Select all patients in accordance with the selection criteria outlined in the study protocol.
- Treat and follow patients as described in this research protocol. Complete all electronic case report forms (eCRFs) in a timely manner and review eCRFs for accuracy and completeness. Provide the original clinical source documents to verify all data entered on eCRFs or SAE reports and all data that document the course of the patient throughout their participation on the study. Provide a clinical summary to the sponsor's clinical research monitor.
- Report all adverse events to CTI BioPharma Corp. or designee, as required by the protocol.
- Ensure that the investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing information is recorded and all drug can be accounted for at all times.
- Before initiation of the study, each participating investigator will submit to CTI:
  - FDA Form 1572 and, if applicable, other ministry of health required forms
  - Copies of the medical licenses of principal investigators and subinvestigators
  - Addresses and descriptions of all clinical laboratory facilities to be used
  - Laboratory certification and expiration dates
  - Normal ranges and effective dates for all required laboratory tests
  - IRB/IEC approval letter referencing the protocol (and amendments, if applicable).
  - IRB/IEC Membership List: A list of the IRB/EC members, their respective titles or occupations, and their institutional affiliations.
  - A sample copy of the IRB/IEC-approved Informed Consent Form
  - Curricula vitae: Curricula vitae for the principal investigator and all subinvestigators
  - Financial disclosure for the principal investigator and all subinvestigators
  - Protocol signature page, signed by the principal investigator

Investigator Statement and Signature:

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

_____

Principal Investigator Signature Date

_____

Principal Investigator Name, Printed Date

Protocol Synopsis

Study Title	A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis
Protocol Number	PAC326
Version	Amendment 2
Sponsor	CTI BioPharma Corp.
Clinical Phase	Phase 3

Objectives

Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arms(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan and the proportion of patients achieving a ≥ 50% reduction in total symptom score (TSS) from baseline to Week 24 as measured by the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

Secondary Objectives

The secondary objectives are:

1 To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.
2 To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1 Overall survival (OS)
2 Progression-free survival (PFS)
3 Leukemia-free survival (LFS)
4 Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥ 35% reduction in spleen volume from baseline
6 Best response in spleen volume by MRI or CT scan
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)
9 Achievement of reduced RBC transfusion dependence (Appendix 1a)

10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4)

Pharmacokinetic and Pharmacodynamic Objectives
The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on the safety and efficacy of pacritinib.

Study Design

This study is a multicenter, randomized, controlled, phase 3 study. It will compare the efficacy and safety of two dose schedules of pacritinib in pooled and individual group analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter. The analysis of the primary outcome of spleen response will be performed when all randomized patients have completed the Week 24 MRI or CT evaluation, met progressive disease criteria, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

Number of Centers

Approximately 100 centers is planned to enroll patients over an estimated period of 11 months.

Number of Patients

The study will randomize approximately 300 patients, with approximately one-third of patients randomized to pacritinib dosed QD, one-third to pacritinib dosed BID, and one-third to BAT.

Randomization

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT. Randomization will be stratified by geographic region (US versus Canada versus Europe versus rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. The most recent platelet count obtained prior to randomization on Days -3 to 1 will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pretransfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification.

Diagnosis and Inclusion Criteria

1. Intermediate-1, intermediate -2, or high risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤ 100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the lower costal margin (LCM) in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 × ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)
15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study
17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcome instrument

19. Able to understand and willing to sign the Informed Consent Form

Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
4. There is no maximum cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplant (ASCT), or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion, with the approval of the medical monitor, if the arrhythmias are stable, asymptomatic, and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450ms, or other factors that increase the risk for QT interval prolongation (eg, heart failure, hypokalemia [defined as serum potassium <3.0mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

Study Drug, Dose, and Mode of Administration

Patients taking pacritinib will be supplied with 100-mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally once a day at the same time of day, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib orally twice each day at the same times of day, with or without food.

Duration of Study Treatment, Continuation of Treatment, and Crossover to Pacritinib

Each patient is to receive pacritinib or BAT until progression of disease (defined in the Study Treatment and Follow-up synopsis section), the occurrence of unacceptable toxicity, or the patient no longer derives

benefit from treatment.

Patients on BAT may cross over to pacritinib at the time of splenic progression (defined in the Study Treatment and Follow-up synopsis section), at any time after splenic progression (if leukemic transformation, splenectomy, and splenic irradiation have not occurred), or after completing 24 weeks of treatment, with or without progression. When it is decided that a patient will crossover from BAT to pacritinib treatment, the investigator will also specify the patient's pacritinib dose schedule (QD or BID); this dose schedule will not be changed again for the duration of study treatment. Patients may continue on active (drug) study treatment after progression of disease (see Study Treatment and Follow-up synopsis section).

Patients who crossover from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT. Spleen size at the time of crossover will be the new baseline for subsequent determination of progression.

Patients on BAT who have splenic progression, but do not wish to crossover to pacritinib, will be followed for safety, survival, and leukemic transformation; they will not be followed for splenic progression, as long as they continue the BAT treatment they were taking at the time of progression. Patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will not be followed for safety, but will be followed for leukemic transformation and survival.

Patients on pacritinib may continue pacritinib treatment with an unchanged dose schedule after splenic progression, if they are still deriving benefit from treatment and not experiencing excessive drug toxicity. Patients on pacritinib who have splenic progression, but wish to continue taking pacritinib will be followed for spleen volume, safety, survival, and leukemic transformation (but not for splenic progression) until they discontinue taking pacritinib.

Study Treatment and Follow-up

Progression of Disease
A patient may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced and both should be reported.

Progression of disease **is defined as one or more of the following:**

- Splenic progression, defined as an increase in splenic volume of ≥ 25% from baseline, based on centrally read MRI or CT scan
- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥ 20%, sustained for ≥ 8 weeks
  - Bone marrow blast count ≥ 20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Criteria for Treatment Continuation After Progression of Disease

To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥ 25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF

Criteria for Crossover from BAT to Pacritinib Treatment

To crossover from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

A patient who crosses over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment.

If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT scan must be completed within 30 days prior to the start of pacritinib treatment. This scan serves as a new baseline spleen volume; the patient will be followed for a second, post-crossover event of splenic progression relative to the new baseline measurement.

Study Assessments

All patients will be followed for response, splenic and leukemic progression, survival, and other endpoints according to Table--1 the Study Assessments Calendar.

Special Cases - Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on the criteria for crossover (described in this section) will follow the Study Assessments Calendar, starting at *Start of Week 1 (BL)*, except that no PK or PD assessments will be performed.

Patients who continue an active BAT despite splenic progression will be followed per the Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT scan. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in the Study Assessments Calendar if they opt to not crossover to pacritinib.

Patients who continue pacritinib despite splenic progression will continue to be followed per the Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only*

Follow-up column in the Study Assessments Calendar.

Patients who discontinue pacritinib, but have not progressed, will continue to be followed per the Study Assessments Calendar until progression occurs. After progression, these patients will be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

Patients who undergo splenic irradiation or splenectomy or initiate any non-protocol-directed anti-MF treatment will subsequently be followed per the *Survival-Only Follow-up* column in the Study Assessments Calendar.

All patients will be followed per the Study Assessments Calendar for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

Evaluation

Efficacy

Spleen Volume Assessment by MRI or CT - Spleen volume measurement by MRI or CT will be performed at screening and every 12 weeks thereafter, until progression of disease or withdrawal from study. MRI is the preferred modality; CT will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Imaging for spleen volume assessment may be performed at other time points, if progressive disease is suspected by palpation or as indicated by the treating physician. All scans should be submitted for central reading. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement.

Spleen Size Assessment by Physical Examination - Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

Disease-Related Signs and Symptoms - The MPN-SAF TSS 2.0 will be completed daily for 7 to 10 consecutive days prior to starting treatment and then daily through Week 48 of the study or until the patient discontinues study treatment, whichever occurs first. The pain medication log will be completed daily as long as the MPN-SAF TSS 2.0 is being completed. The patient global impression assessment will be completed every 8 weeks through Week 24, and then every 12 weeks, until the patient discontinues study treatment.

Survival - Patients will be followed for survival and for transformation to acute myeloid leukemia (as assessed by the investigator, investigator-obtained records, or, if these are not available, by patient-provided history) until 3 years after the first of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

Quality-of-Life Assessments - The EQ-5D-5L and EORTC-QLQ-C30 will be completed at baseline, every 8 weeks for the first 24 weeks, and then every 12 weeks during study treatment.

Patients will also be followed for frequencies of RBC and platelet transfusions, and other exploratory endpoints.

Safety

Adverse Events - AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. SAEs that the investigator or Sponsor considers related to study drug or study procedure shall be followed until the event resolves, stabilizes or the patient is lost to follow-up, whichever occurs first. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

Hematology - Hematology parameters (complete blood count [CBC] with differential and platelet count) will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final hematology testing will be performed at treatment termination. In addition, unscheduled CBC with differential and platelet counts may be performed locally and/or centrally, when clinically indicated.

Blood Chemistry - Blood chemistry parameters to be evaluated include alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.

These parameters will be evaluated at screening; baseline; beginning of Week 3; completion of Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter. Scheduled laboratory samples will be sent for central evaluation. Final chemistry testing will be performed at treatment termination. In addition, unscheduled chemistries may be performed locally and/or centrally, when clinically indicated.

ECG Assessment - For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening; within 1 hour prior to dosing; at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3; and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening; at baseline; on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing); and as clinically indicated. Local ECG readings will be used throughout the study.

Gastrointestinal Toxicity Management - Patients will be evaluated at baseline to assess usual bowel habits and will be instructed on the need for early intervention for possible GI side effects of treatment. At the baseline visit, all patients will be provided with a prescription for an antidiarrheal drug and instructed to start taking it as soon as diarrhea is noted. The investigator or a surrogate will contact each patient by telephone during Week 1 (Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to pacritinib) and at the beginning of Week 3 of initial treatment or after crossover to pacritinib to evaluate GI toxicity and assess the need for modifying the treatment for GI side effects. Standard supportive care measures should be provided to control symptoms of GI toxicity, such as diarrhea, constipation, nausea and vomiting.

Ruxolitinib Dose Management - Patients on BAT who are being treated with ruxolitinib or other approved JAK2 inhibitors must be dosed according to current local labeling recommendations.

Pharmacokinetic-Pharmacodynamic Assessments

Pharmacokinetics and Pharmacodynamics – PK samples without PD sampling will be collected from approximately 130 patients taking pacritinib at the Week 12 and Week 24 visit days (predose [Hour 0]).

In addition to assessment of pacritinib plasma concentrations, STAT3 phosphorylation (an established pharmacodynamic marker for JAK-STAT signaling pathway inhibition) will be assessed. PK/PD samples for assessment of exposure-response will be collected from the remaining approximately 70 patients taking pacritinib at a prespecified subset of clinical sites at Day 1 of Week 1 (predose [Hour 0] and 4 hours postdose; only a PD sample will be collected at the predose time point), Day 1 of Week 3 (predose [Hour 0] and at 4 hours postdose), and at Week 12 and Week 24 visit days (predose [Hour 0]). The resulting data will be used to assess exposure, and exposure-safety and exposure-efficacy relationships.

JAK2 Mutation Status - JAK2V617F mutation burden will be assessed by a central laboratory in all patients at screening, then at Week 12, and every 12 weeks thereafter in patients who have the mutation.

Statistical Methods

The study has two primary endpoints: the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by MRI or CT scan, and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

The primary hypotheses of the study are to compare the pacritinib arms QD and BID (pooled) versus BAT arm for the two primary endpoints. The study will be claimed to be successful when both endpoints reach statistical significance ($p \leq 0.05$) individually.

The secondary hypotheses are to compare QD vs BAT and BID vs BAT, separately at a significance level of 0.025, on spleen reduction and TSS reduction, the two primary endpoints.

The Fisher Exact test will be used to evaluate both endpoints. Patients who meet the criteria for disease progression or drop out of the study before Week 24 will be considered non-responders.

A total of 300 patients is planned to be randomized (1:1:1) in the study. This sample size provides at least 95% power on the primary hypotheses (QD+BID vs BAT) for both endpoints individually (at an α-level of 0.05, 2-sided), and at least 93% power for each secondary hypothesis (QD vs. BAT; BID vs. BAT) independently (at an α-level of 0.025, 2-sided).

No interim analysis is planned.

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
Patients who continue an active BAT despite splenic progression will continue to be followed per this Study Assessments Calendar, except for discontinuation of Spleen Volume by MRI or CT. Patients who are on a "no treatment" BAT option after splenic progression will only be followed per the *Survival-only Follow-up* column in this calendar.
Patients who continue pacritinib despite splenic progression will continue to follow this Study Assessments Calendar until discontinuation of pacritinib, when they will move to the *Survival-Only Follow-up* column in this calendar.
Patients who discontinue pacritinib, but have not progressed will continue to follow this Study Assessments Calendar until progression occurs, and then will follow the *Survival-Only Follow-up* column in this calendar. Note: patients who have stopped taking pacritinib must complete a termination visit within 7 days of stopping the drug.
Patients who undergo splenic irradiation, splenectomy, or who initiate any non-protocol-directed anti-myelofibrosis treatment will subsequently be followed per the *Survival-Only Follow-up* follow-up column in this calendar.

Week	**Consent and Platelet Eligibility**	**Screen**[2]	**Symptom Assessment & Screening MRI Visit**	**Randomization** (patient need not be present)	**Start of Wk 1 (BL)**[3]	**Wk 1**[4]	**Start of Wk 2**[5]	**Start of Wk 3**	**End of Wk 4**	**End of Wk 8**	**End of Wk 12**[6]	**End of Wk 16**	**End of Wk 20**	**End of Wk 24**	**End of Wk 36 & q12w**	**Term**[7]	**30 d Post-Term**	**Survival-only** (Off Treatment) Follow-up
Day	-35 to -7	-14 to -5	-10 to -4	-3 to 1	1	4	8	15	28	56	84	112	140	168	252			q 6 mo
Window (+/- d):						1	3	3	3	3	7	7	7	7	7	7	3	30
Informed consent[25]	x	x																
Platelet count[1]	x			x														
Medical history		x																
Vital signs[8]		x			x		x	x	x	x	x	x	x	x	x	x		
Physical exam, including spleen measurement[9]		x			x		x	x	x	x	x	x	x	x	x	x		
GI assessment[4]		x			x	x		x										
12-lead ECG[10]		x			x		x	x										
ECOG performance status		x			x		x	x	x	x	x	x	x	x	x	x		
Hematology[11]		x		x	x			x	x	x	x	x	x	x	x	x		
Chemistry[12]		x			x			x	x	x	x	x	x	x	x	x		
Serum pregnancy test[24]		x									x			x	x			
Spleen volume by MRI or CT[13]			x								x			x	x	x		
Daily patient-reported symptoms: MPN-SAF TSS 2.0 Begin recording after receiving eDiary[14]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Daily pain medication log[15]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Table--1
PERSIST-2 Study Assessments Calendar

Special Cases: Modifications to Study Assessments Calendar

Patients crossing over from BAT to pacritinib based on above criteria for crossover will follow this Study Assessments Calendar, starting from *Start of Wk 1*, except that no PK or PD assessments will be performed.
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Week	**Con-sent and Platelet Eligibil-ity**	**Screen**[2]	**Symptom Assessment & Screening MRI Visit**	**Random-ization** (patient need not be present)	**Start of Wk 1 (BL)**[3]	**Wk 1**[4]	**Start of Wk 2**[5]	**Start of Wk 3**	**End of Wk 4**	**End of Wk 8**	**End of Wk 12**[6]	**End of Wk 16**	**End of Wk 20**	**End of Wk 24**	**End of Wk 36 & q12w**	**Term**[7]	**30 d Post-Term**	**Survival-only** (Off Treatment) Follow-up
Patient global impression assessment[16]					x					x		x		x	x	x		
Quality of life assessments; EORTC-QLQ-C30 EQ-5D-5L					x					x		x		x	x	x		
Pharmacokinetic (PK) assessment[17]					x			x			x			x				
Pharmacodynamic(PD) assessment[18]					x			x			x			x				
JAK2 mutation burden[19]		x									x			x	x			
Bone marrow biopsy[22]		x												x				
Distribute pacritinib					x				x	x	x	x	x	x	x			
Begin pacritinib dosing					x													
Perform pacritinib accountability[23]					x		x	x	x	x	x	x	x	x	x	x		
Toxicity assessments/AEs[20]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications		x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Record BAT treatments					x	x	x	x	x	x	x	x	x	x	x	x		
Transfusion history (RBC and platelet)		x			x	x	x	x	x	x	x	x	x	x	x	x		
Leukemic Transformation		x			x			x	x	x	x	x	x	x	x	x		x
Survival Only Follow-up (phone)[21]																		x

Table--1
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Week	**Consent and Platelet Eligibility**	**Screen**[2]	**Symptom Assessment & Screening MRI Visit**	**Randomization** (patient need not be present)	**Start of Wk 1 (BL)**[3]	**Wk 1**[4]	**Start of Wk 2**[5]	**Start of Wk 3**	**End of Wk 4**	**End of Wk 8**	**End of Wk 12**[6]	**End of Wk 16**	**End of Wk 20**	**End of Wk 24**	**End of Wk 36 & q12w**	**Term**[7]	**30 d Post-Term**	**Survival-only** (Off Treatment) Follow-up

Abbreviations:
AEs = adverse events
BAT = best available therapy
BL=baseline
BUN = blood urea nitrogen
CBC = complete blood count
CRF = case report form
CT = computed tomography
d = day(s); ECG = electrocardiogram
ECOG = Eastern Cooperative Oncology Group
eCRF = electronic case report form
GI = gastrointestinal
LDH = lactate dehydrogenase
MRI = magnetic resonance imaging
PD = pharmacodynamic(s)
PET-MF = post-essential thrombocythemia myelofibrosis
PK = pharmacokinetic(s)
PMF = primary myelofibrosis
PPV-MF = post-polycythemia vera myelofibrosis
RBC = red blood cell(s)
Term=study treatment termination visit
Wk = Week

1 Eligibility platelet count may be obtained at any time between Days -35 and -7 prior to randomization. Platelet count obtained during the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value should be used for platelet rebound stratification determination. If more than one such nadir count is obtained prior to randomization, the count obtained closest to randomization will be used for stratification. If patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion performed before randomization.
2 Screening procedures must be completed between Days -14 and -5, before treatment initiation. Clinical laboratory tests collected at screening must be performed at least 7 days after any prior therapy for PMF, PPV-MF, or PET-MF.
3 Day 1 assessments are required to be performed prior to initiation of study treatment. The baseline visit should also be conducted for patients on BAT who have documented disease progression and are planning to cross over to pacritinib if they meet the criteria for continuation or crossover. For these patients, the termination and baseline visits may be combined (all termination procedures plus locally obtained 12-lead ECG and pharmacodynamic assessment). Patients who cross over to pacritinib after Week 24 must complete an MRI within 30 days of starting pacritinib. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any change in frequency or consistency of bowel movements after starting study treatment.
4 The site will contact all patients by telephone on Day 4 ± 1 day to assess the need for modifying supportive treatment of any GI side effects. Patients will also be assessed at the beginning of Week 3 and throughout the study for GI safety.
5 The study visits at Weeks 2, 3, 4, and 8 have a scheduling window of ± 3 d; however, all procedures other than MRI or CT should be performed on the same day's visit.
6 The study visits at Weeks 12 and beyond have a scheduling window of ± 7 d; however, all procedures other than MRI or CT should be performed on the same day's visit.
7 The treatment termination visit is scheduled within 7 d after completing or terminating each study treatment arm. A final visit to assess events is scheduled 30 ± 3 d after the last study treatment day. If termination takes place at a regularly scheduled visit, these procedures may be performed at that time. Patients on BAT who have documented progression of disease and are planning to cross over to pacritinib must complete all baseline procedures except PK and PD procedures (all termination procedures plus local 12-lead ECG and central pharmacodynamic assessment) and record this information on the crossover Week 1 visit CRF. The spleen size at the end of BAT will serve as the new baseline for the patient. For patients on BAT who cross over to pacritinib after Week 24, spleen imaging must be performed within 30 days prior to starting pacritinib, and the spleen size at that time will serve as the new baseline.
8 Vital signs include blood pressure, pulse, respiratory rate, temperature, and body weight.
9 Height should be measured only on Day 1. Measurement of spleen by physical examination will be performed during screening, at baseline, and at each visit until study termination.
10 For patients assigned to pacritinib or those who have crossed over to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours post dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2 and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study. QTc interval prolongation identified on automated ECG calculations that is ≥grade 1 should be manually recalculated using the same method for any given patient. The manual recalculation should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.
11 Hematology: CBC, differential count, and platelet count. The most recent hematology evaluation obtained prior to randomization must be used to stratify the patient by baseline DIPSS risk category. Screening hematology assessments used to identify strata for randomization may be performed by local laboratories, but screening samples will also be sent for central laboratory evaluation.
12 Eligibility may be based on local laboratory values. Central blood chemistry values will include: ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect) creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid.
13 Spleen volume by MRI or CT will be reviewed centrally by an independent radiology facility. The screening MRI or CT must be performed prior to randomization between Days -10 to -4. Imaging should be performed without

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contrast agents. MRI or CT will be performed at the end of Week 12 ± 7 d and every 12 weeks thereafter, and at the termination of treatment. For each patient, the same imaging modality should be used throughout the study. Unscheduled imaging studies may be performed at the physician's discretion, if he/she considers disease-related symptoms to be worsening. Splenic progression will be followed for patients who discontinue treatment, but have not progressed. Patients with progressive disease documented prior to Week 24 who opt to continue on study treatment will not undergo Week 24 imaging if the date of progression is at or later than Week 20. For patients who cross over after Week 24, an MRI must be performed within 30 days prior to the start of pacritinib treatment.

14 Daily patient-reported disease-related symptoms assessed after receiving an eDiary and throughout treatment. Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment and daily through Week 48 of the study or until patient discontinues study treatment, whichever occurs first.

15 Patients will complete the pain medication log daily as long as the patient is completing the MPN-SAF TSS 2.0.

16 Patient global impression assessment and Quality of Life Assessments will be done every 8 weeks through Week 24, and then every 12 weeks thereafter until patient discontinues study treatment.

17 Five PK samples from patients in the pacritinib arm(s) will be collected from approximately 70 patients at a prespecified subset of clinical sites. Blood samples will be collected postdose (Hour 4) on Day 1, Week 1, predose (Hour 0) and postdose (Hour 4) on Day 1, Week 3 and predose (Hour 0) on the visit day of Weeks 12 and 24. Two PK samples will be collected from approximately 130 patients taking pacritinib at the remaining sites predose (Hour 0) on the visit day of Week 12 and Week 24.

18 PD assessment for patients in the pacritinib arm will be collected from patients at a prespecified subset of of clinical sites. Blood samples will be collected predose (Hour 0) and postdose (Hour 4) on Day 1 of Weeks 1 and 3 and predose (Hour 0) on the visit day of Weeks 12 and 24.

19 Samples for central analysis of *JAK2* mutation burden will be collected at screening, Week 12, and every 12 weeks thereafter in patients who have the mutation.

20 Toxicity assessments/AEs: Patients will be evaluated from the time of signing the Informed Consent Form through 30 d after the last study treatment. However, each SAE assessed as related to study treatment or study procedures will be collected through the patient's last day of study participation the event will be followed until it is resolved, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever occurs first.

21 Survival-only follow-up for each patient will continue for 3 years after Week 24 or past termination of study treatment, whichever occurs first.

22 Bone marrow biopsy must be obtained within 24 weeks prior to randomization and may be obtained any time before Day -3. Bone marrow biopsy will also be performed at Week 24. Patients who discontinue study treatment prior to Week 24 do not need another bone marrow biopsy.

23 At time of dispensing, the lot number for capsules dispensed and the number of capsules in bottle(s) should be recorded. Instruct patient to bring bottle to every visit. When a patient returns one or more bottles, count the remaining capsules in all bottle(s).

24 All women of child-bearing potential must have a pregnancy test at screening. Additional pregnancy tests every 12 weeks while on study treatment may be mandated as a country-specific requirement.

25 Informed consent must be obtained before any study-specific washout. This may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and standard MF treatments), or 7 days (potent CYP 3A4 inhibitors). Patients not requiring washout may sign the Informed Consent Form at any time prior to screening procedures.

Abbreviations	
Abbreviation	**Full Term**
AE	adverse event
ALT	alanine aminotransferase (syn: see SGPT)
AML	acute myeloblastic leukemia (or acute myeloid leukemia)
ANC	absolute neutrophil count
ASCT	allogeneic stem cell transplantation
AST	aspartate aminotransferase (syn: see SGOT)
BAT	best available therapy
BID	twice daily
BL	baseline
BUN	blood urea nitrogen
CBC	complete blood count
CI	clinical improvement
CMH	Cochran-Mantel-Haenszel
CR	complete remission or complete response
CRF(s)	case report form(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
d	day, days
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESA	erythropoiesis-stimulating agent
ET	essential thrombocythemia
FDA	Food and Drug Administration
FLT3	fms-like receptor tyrosine kinase 3
GCP	Good Clinical Practice
GI	gastrointestinal
h	hour, hours
HIV	human immunodeficiency virus
IC_{50}	50% inhibitory concentration

Abbreviations	
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Us
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
IRF	independent radiology facility
ITT	intent-to-treat
IWG	International Working Group
JAK2	Janus kinase 2
L	liter(s)
LCM	lower costal margin
LDH	lactate dehydrogenase
LFS	leukemia-free survival
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent(s)
mo	month(s)
MPD	myeloproliferative disease
MPN-SAF TSS 2.0	Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0
MRI	magnetic resonance imaging
ms	millisecond(s)
MTD	maximum tolerated dose
NCI	National Cancer Institute
nM	nanomolar
NYHA	New York Heart Association
OS	overall survival
^{32}P	phosphorus-32
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os, oral(ly)
PMF	primary myelofibrosis

Abbreviations	
PPV-MF	post-polycythemia vera myelofibrosis
PV	polycythemia vera
QD	daily
QTc	corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
ROC	receiver operating characteristic curve
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic-oxaloacetic transaminase (syn: see AST)
SGPT	serum glutamic pyruvic transaminase (syn: see ALT)
STAT	signal transducers and activators of transcription
T_{max}	time of maximum concentration
ULN	upper limit of normal
uMPD	unclassifiable myeloproliferative disease
wk	week, weeks

1 Background Information

1.1 JAK2 in Hematologic Malignancies

The Janus kinases (JAK) are a family of cytoplasmic tyrosine kinases consisting of JAK1, JAK2, JAK3, and TYK2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones, and growth factors. Their intracellular substrates include the signal transducer and activator of transcription (STAT) family of proteins. The JAK/STAT pathways, through the proper actions of the ligands, regulate important physiological processes, such as the immune response to viruses, hematopoiesis, lactation, and lipid homeostasis. However, dysfunctional signaling caused by a myriad of factors results in pathological conditions, such as allergies, asthma, rheumatoid arthritis, severe combined immune deficiency, and hematological malignancies. In particular, mutations in the *JAK2* gene have been associated with myeloproliferative disorders (MPDs), including polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF).

The incidence of the *JAK2V617F* mutation, as determined by allele-specific polymerase chain reaction in granulocytes from patients with MPDs, occurs in 35% to 50% of patients with primary MF (PMF), 32% to 57% of patients with ET, and 74% to 97% of patients with PV. This mutation, however, can also be found on rare occasions in patients with other chronic myeloid diseases, including myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative diseases (MDS/MPD), and unclassifiable MPD (uMPD). There is strong evidence that the *JAK2* mutation (and corresponding continuously active JAK2 tyrosine kinases) significantly contributes to the existence and progression of the disease. Its inhibition thus presents a suitable target for drug development. Even in patients without *JAK2* mutation, the JAK/STAT pathway may be deregulated, and these patients may also benefit from JAK2 inhibitor therapy.

1.2 Myelofibrosis

1.2.1 Clinical Presentation and Disease-related Symptoms

Myelofibrosis may present as either a primary myeloproliferative disorder or follow a diagnosis of PV or ET. Regardless of the original diagnosis, PMF, PPV-MF, and PET-MF have a common pathophysiological profile, characterized by elevated numbers of CD34-positive cells in the marrow in the early phase of the disease, followed in the later phases by marrow fibrosis, with decreasing numbers of CD34 cells in the marrow and a corresponding increase in splenic and liver engorgement by CD34 cells.

PMF, PPV-MF and PET-MF usually present with a white blood cell (WBC) count < 30,000/mm^3, prominent teardrops on peripheral smear, normocellular or hypocellular marrow with moderate to marked fibrosis, an absence of the Philadelphia chromosome or the BCR-ABL translocation, and frequent positivity for the *JAK2* mutation (Campbell et al 2006). In addition to the clonal proliferation of a multipotent hematopoietic progenitor cell, an event common to all chronic MPDs, these disorders are characterized by colonization of extramedullary sites, such as the spleen or liver (Barosi 1999, Tefferi 2000).

About 70% of patients with MF are symptomatic at presentation. The main physical findings are splenomegaly and hepatomegaly. Other symptoms include those secondary to a hypercatabolic state (fever, weight loss, and night sweats) and peripheral blood abnormalities (fatigue and dyspnea resulting from anemia and bleeding, and petechiae resulting from thrombocytopenia and/or abnormal platelet function). Gout and renal stones secondary to hyperuricemia are also common [4] (Ahmed et al, 2006). Other clinical manifestations of the disease include thromboembolic episodes, hemorrhage, splenic pain, early satiety, anemia, and bone pain.

PMF, PPV-MF, and PET-MF have similar types and distributions of bone marrow cytogenetic abnormalities (Tefferi, Mesa et al 2001), and they are known to harbor a common mutant allele, *JAK2V617F* (James et al 2005).

Transformation from PV to PPV-MF significantly worsens survival. *JAK2* mutations are almost always present in patients with PV and PPV-MF. Common clinical and laboratory findings in PPV-MF include a hyperproliferative bone marrow, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) Grade 2 to 3 marrow fibrosis, anemia, splenomegaly, and constitutional symptoms (Passamonti et al 2008).

Diagnostic tools for PMF, PPV-MF, and PET-MF include complete blood count (CBC), bone marrow aspiration and biopsy, cytogenetic analysis, peripheral blood smear analysis for teardrop-shaped RBCs, the number and kinds of WBCs, platelet count, and the presence of blast cells.

1.2.2 Current Strategies for Treating PMF, PPV-MF, and PET-MF

Currently, as no therapeutic strategy has been efficacious at reducing overall mortality, medical therapy for PMF, PPV-MF, and PET-MF is administered with supportive intent. Treatment is aimed at improving quality of life through palliation of symptoms and control of peripheral blood counts (Arana-Yi et al 2006). Therapeutic interventions usually are used only in symptomatic patients with MF, since asymptomatic patients demonstrate prolonged survival (Barosi 1999, Dupriez et al 1996).

At present, allogeneic stem cell transplantation (ASCT) is the only available method for altering the natural history of PMF, PPV-MF, or PET-MF (Passamonti et al 2008, Rondelli et al 2005). ASCT can completely reverse the fibrosis in bone marrow (Ni et al 2005) and restore normal hematopoiesis. However, while ASCT is potentially curative for patients with PMF, PPV-MF, and PET-MF, this form of treatment is largely limited to young patients with negligible comorbidities (Arana-Yi et al 2006). The International Working Group – Myelofibrosis Research and Treatment considers it "…reasonable to recommend ASCT for high- or intermediate-risk 2 patients" (Cervantes et al 2009). Thus far, no therapy has proven effective in prolonging overall survival (OS) in PMF, PPV-MF, or PET-MF (Arana-Yi et al 2006).

Current treatment approaches are aimed at mitigating specific disease symptoms, such as anemia. Transfusion therapy is the core strategy for treatment of disease-related anemia, and it is also used to manage thrombocytopenia. Long-term RBC transfusion therapy should be accompanied by oral iron chelation therapy to avoid long-term consequences of iron overload. Disease-associated anemia occasionally responds to erythropoietin, hydroxyurea, cladribine, thalidomide, lenalidomide, or interferon treatment (Ahmed et al 2006). These and other agents have been used to correct cytopenias, halt the progression of splenomegaly, or reduce the size of a site of extramedullary hematopoiesis in patients with PMF, PPV-MF, and PET-MF.

Danazol, a synthetic attenuated anabolic steroid with androgenic activity, has been used to treat anemia in PMF, PPV-MF, and PET-MF. Erythropoietin has been administered to patients with these diseases for palliation of constitutional symptoms and anemia (Arana-Yi et al 2006). The use of interferon-α can result in hematologic responses, including reduction in spleen size, but many patients do not tolerate this medication (Sacchi 1995, Gilbert 1998). Antiangiogenic and immunomodulatory drugs, such as thalidomide and lenalidomide, have shown activity in patients with MF (Gilbert 1998, Barosi et al 2002, Marchetti et al 2004, Tefferi, Cortes et al 2006, Mesa et al 2004, Strupp et al 2004), but they are not routinely used for the indications proposed in this study of pacritinib.

Other antiangiogenic agents, such as vatalanib and sorafenib, have been studied in PMF, PPV-MF, and PET-MF, but the data are not promising. Etanercept has been evaluated, but it was not superior to the combination of thalidomide and prednisone (Arana-Yi et al 2006).

The use of signal transduction inhibitors, such as imatinib, have resulted in an increase in the number of clonogenic megakaryocytic progenitors in bone marrow, suggesting they may be an effective treatment for thrombocytopenia in patients with MF (le Bousse-Kerdiles et al 2005).

For patients with PMF, PPV-MF, or PET-MF who have painful splenomegaly and no other treatment options, splenectomy may be performed. The decision to perform splenectomy involves weighing the benefits (long-term improvement in symptomatic splenomegaly, anemia, portal hypertension, and severe thrombocytopenia in 30% to 70% of patients) versus the risks (10% postoperative mortality, and 30% postoperative morbidity caused by infection, bleeding, or thrombosis; additionally, some investigators have reported accelerated progression to blast crisis).

1.2.3 Targeted Therapy for Myeloproliferative Disease

In 2011, JAK 1/2 inhibitor ruxolitinib received approval in the United States for the treatment of patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF based on the COMFORT I and II randomized controlled trials showing that treatment with ruxolitinib decreased spleen size and symptom score (Verstovsek et al 2012; Harrison et al 2012). Entry criteria for both studies was limited to patients with platelet counts >100,000/μL. The median platelet counts at entry for the two studies were 262,000/μL and 244,000/μL, respectively.

Ruxolitinib causes significant dose-related thrombocytopenia, and the dose must be adjusted in patients with platelet counts < 200,000/μL. In patients taking ruxolitinib who develop a platelet count < 50,000/μL, withholding all dosing is recommended until the platelet count recovers to 50,000/μL. In clinical trials, patients taking ruxolitinib who had pretreatment platelet counts between 100,000/μL and 200,000/μL had a higher frequency of grade 3 or 4 thrombocytopenia (16.7%) than patients with higher initial platelet counts (7.2%).

The incidence of thrombocytopenia (all grades) during randomized treatment in COMFORT I was 69.7% in the ruxolitinib arm compared with 30.5% in the placebo arm. The dose of ruxolitinib was adjusted downward for patients with platelet counts <100,000/μL and withheld for those with platelet counts <50,000/μL. In COMFORT II, protocol-specified dose modifications for thrombocytopenia were more frequent in the ruxolitinib arm than the best available therapy arm (41% vs. 1%).

Median time to recovery of platelet counts to above 50,000/μL was 14 days in patients requiring interruption of treatment due to thrombocytopenia (Jakafi label).

1.3 Pacritinib

Pacritinib is a novel JAK2/FLT3 inhibitor that has demonstrated promising antitumor activity in two mouse models of human malignancies. Preclinical toxicology studies have identified a safe starting dose for clinical trials. The potential indications that may be targeted include: (i) PV, ET, and MF, all of which are MPDs with a high frequency of a *JAK2V617F* mutation; (ii) certain leukemias and lymphomas where other forms of JAK aberrations have been reported; and (iii) acute myeloid leukemia (AML), in which FLT3 inhibitors have shown preliminary clinical promise.

1.3.1 Pharmacology

Pacritinib is a potent, selective inhibitor of JAK2 and FLT3 kinase activities (IC_{50} = 23 nM and 22 nM, respectively), as well as JAK2V617F mutant kinase activity (IC_{50} = 19 nM). Pacritinib is also a potent inhibitor of cellular proliferation in human leukemia and lymphoma cell lines selected for their dependence on the target kinases (cellular IC_{50} ranges from 0.03 to 0.24 μM). Consistent with these activities, exposure to pacritinib resulted in the reduction of phospho-JAK2, phospho-STAT3, or phospho-STAT5 in the relevant cell lines.

The therapeutic effects of pacritinib were assessed in an orthotopic model of MPD induced with Ba/F3-JAK2V617F cells. Pacritinib treatment at 150 mg/kg po bid significantly ameliorated symptoms, with 60% normalization of spleen weight and 92% normalization of liver weight. It was also very well tolerated.

1.3.2 Pharmacokinetics in Animals

PK following single intravenous or oral administration of pacritinib was evaluated in mice, rats, and dogs. Following oral administration, pacritinib showed rapid absorption in mice (T_{max} from 0.5 to 1.3 hours) and moderately fast absorption in rats and dogs (T_{max} ~ 4 hours). The oral terminal half-lives were 2.2, 5.7 and 4.4 h in mice, rats, and dogs respectively. As measured by liver blood flow, the systemic clearance of pacritinib from plasma was high in mice (8 L/h/kg) and dogs (1.6 L/h/kg) and moderate in rats (1.6 L/h/kg). The i.v. terminal half-lives were 5.6, 6, and 4.6 hours in mice, rats, and dogs, respectively. The oral bioavailability of pacritinib was 39% in mice, 10% in rats, and 24% in dogs.

1.3.3 Preclinical Toxicology

The adverse effects of pacritinib were evaluated in 30-day repeated oral dose toxicity studies with 14-day recovery in both mice and dogs, and in 26- and 39-week chronic toxicity studies in mice and dogs, respectively. Key findings included dose-dependent leukopenia accompanied by neutropenia (dog) and neutrophilia (mice) that partially reversed during recovery. Mice also showed dose-dependent but reversible thrombocytosis and anemia. In the chronic toxicity studies, low-magnitude decreases in neutrophils and red blood cell parameters were observed. No treatment-related hepatic changes were observed with the exception of increased AST (to +109%, male dogs) and increased triglycerides (to +57%, male and female dogs).

In the 30-day study in dogs, animals receiving mid and high doses of pacritinib experienced vomiting and diarrhea that increased in severity despite treatment with antiemetic and antidiarrheal medication. Similarly, in the 39-week study in dogs, an increased incidence of nausea and vomiting was observed at doses of 20 mg/kg/day and higher. Periods of low food consumption in individual animals receiving 40 and 50 mg/kg/day were accompanied by rapid weight loss (which was controlled and reversed with subcutaneous fluid and supplemental food) and were considered treatment related and adverse.

Based on these studies, the no observed adverse effect level was determined to be 100 mg/kg bid in mice and 10 mg/kg bid in dogs.

1.3.4 Summary of Clinical Pharmacology and Phase I Studies with Healthy Volunteers with Pacritinib

To date, CTI has completed two PK studies for pacritinib in healthy volunteers, including a food-effect study (SB1518-2010-006) characterizing the effects of a high calorie, high fat meal on the bioavailability and PK of pacritinib and a study assessing inter- and intra-individual variability of oral pacritinib in

healthy volunteers under fasted conditions at 100 mg, 200 mg and 400 mg doses (SB1518-2010-004). In addition, the single and multiple dose population PK of pacritinib has been characterized following multiple dose administration of pacritinib in two trials (SB1518-2007-001 and SB1518-2008-003) in patients with advanced myeloid malignancies.

After administration of single doses of pacritinib in a randomized, three-treatment, three-period crossover study in healthy volunteers under fasting conditions in study SB1518-2010-004, peak plasma concentrations were reached at a median T_{max} ranging from 4.5 h to 5.5 hours across the 100-400 mg dose range. While between-subject variability was relatively high (28-45%), the within-subject variability was low (13-15%), highlighting the consistent systemic exposure for pacritinib in individual subjects. The mean elimination half-life was approximately 34 hours and was not dependent on dose. The systemic exposure of pacritinib is healthy volunteers was comparable to that in patients. After oral administration of single 200-mg doses (2×100 mg capsules) of pacritinib under fed and fasted conditions in study SB1518-2010-006, the 90% confidence intervals for the geometric mean ratios (fed to fasted) for C_{max}, AUC_{0-t}, and AUC_{inf} were between 80% and 125%, demonstrating lack of an effect of food on absorption. Given this data, pacritinib can be orally administered without regard to timing of meals.

Pooled analyses of PK assessments from the two completed clinical trials in patients at pacritinib dose levels up to 600 mg QD showed slow absorption (T_{max} 4-6 hrs) and dose-related increases in systemic exposure up to 400 mg QD. Beyond the 400 mg QD dose level, there was minimal increase in exposure with doses up to 600 mg QD suggesting involvement of a saturable process in oral absorption of pacritinib. In addition, the results demonstrated a prolonged elimination half-life (mean Day 1 $t_{1/2}$ = 47 hrs), supporting a QD regimen of pacritinib in clinical development. Comparison of systemic exposure of pacritinib on Days 1 and 15 showed a 1.5- to 2-fold increase in systemic exposure at steady-state.

Pacritinib is not a PgP substrate at clinical exposure levels. While in vitro metabolism studies suggest that pacritinib is a potential substrate for CYP3A4 isozyme, the results of a mouse mass balance ADME study demonstrate that pacritinib is overwhelmingly eliminated by biliary excretion with minimal involvement of metabolism or renal excretion in the systemic clearance of pacritinib. Overall, the preclinical in vitro and in vivo data suggest limited liability of pacritinib in metabolic and PgP-related drug interactions.

At a pacritinib 100 mg QD regimen, mean steady-state plasma levels of pacritinib exceeded the in vitro IC_{50} values for inhibition of targeted kinases (JAK2/FLT3) and inhibition of whole cell proliferation (BaF3-JAK2 and MV4-11 cells). Pacritinib potently inhibited the proliferation of only a few tumor cell lines at submicromolar concentrations, consistent with its target selectivity. The most sensitive cell lines were either JAK2-dependent or mutant FLT3-dependent, including murine 32D (IC_{50} = 160 nM), human Karpas 1106P (IC_{50} = 240 nM), and mutant FLT3-dependent MV4-11 cells (IC_{50} = 32 nM). In a study using ex vivo expanded erythroid progenitors (EPs) treated with pacritinib, phos-STAT5 levels were inhibited in a dose-dependent manner (IC_{50} < 200 nM) and reduced the viability of expanded EPs from both normal volunteers with JAK2wt (IC_{50} = 260 nM) and PV patients with JAK2V617F (IC_{50} = 230 nM), with no significant differences observed between arms. Moreover, pacritinib treatment had no effect on the JAK2V617F allele frequency in EPs from PV patients, indicating similar drug sensitivity for EPs from the same patient, regardless of the presence of JAK2 mutation. A study to assess the effects of pacritinib on intracellular JAK2 signaling showed that phos-STAT3 was reduced in a dose-dependent manner in both Karpas 1106P and 32D cells.

1.3.5 Overview of Clinical Studies of Pacritinib in Patients with Myelofibrosis

Patients with MF have been studied in two clinical trials of pacritinib. Both phase 1/2 trials included dose-finding PK portions and safety and efficacy portions. SB1518-2007-001 enrolled patients with advanced myeloid malignancies, and SB1518-2008-003 enrolled patients with chronic idiopathic MF.

1.3.6 SB1518-2007-001: Phase 1/2 Study in Patients with Advanced Myeloid Malignancies

1.3.6.1 Phase 1

During the phase 1 portion of SB1518-2007-001, cohorts of 3 to 6 patients with advanced myeloid malignancies were enrolled into one of a series of escalating doses of pacritinib, ranging from 100 to 600 mg/day. Treatment was administered orally once a day for 28 d (defined as one cycle). Preliminary data were presented in 2009 (Verstovsek et al 2009).

Dose-limiting toxicities (DLTs) included grade 3 QTc prolongation in 1 patient with AML taking 150 mg and grade 3 diarrhea in 1 patient at 300 mg. At the 600-mg dose level, 1 patient reported grade 3 GI toxicity and 1 patient reported grade 2 blurred vision, dizziness, and unsteady gait. No DLTs were reported at 400 mg or 500 mg. Thus, the 500 mg dose level was determined to be the maximum tolerated dose (MTD).

Diarrhea and general GI toxicities, the most common toxicities that affected dosing, often resulted in dose interruption and dose reduction. On the basis of the safety and efficacy observations during long-term dosing, 400 mg/day was chosen as the recommended dose for the phase 2 study. The most commonly reported treatment-emergent events (> 20%) were diarrhea, nausea, vomiting, constipation, dyspnea, fatigue, and peripheral edema. Most events were mild to moderate in severity. Grade 3 or greater anemia and thrombocytopenia were each reported in 16% of patients and were the only events of grade 3 or higher severity that occurred in more than 10% of patients. Sixteen of the 43 patients (37%) had grade 3 (25,000 – 50,000/μL) or grade 4 (< 25,000/μL) thrombocytopenia at baseline.

Of the 36 patients with MF enrolled in the phase 1 portion, 25 had baseline splenomegaly ≥ 5 cm below the left costal margin. Eighteen of these 25 patients had at least 25% reduction in spleen size; these 18 patients included 6 patients whose spleens became nonpalpable.

PK analysis showed that pacritinib was rapidly absorbed, with T_{max} ranging from 3 to 5 hours. The estimated terminal half-life was 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations, measured by inhibition of STAT3 and STAT5 phosphorylation, were achieved at the starting dose of 100 mg/day.

1.3.6.2 Phase 2

The primary objective of this portion of the study was to assess spleen response rate as measured by the change in spleen volume between baseline, Day 1 of Cycle 4, and Day 1 of Cycle 7. Response was defined as a decrease of at least 35% in MRI-determined spleen volume any time between baseline and Week 24. Secondary objectives included spleen response by physical examination, duration of spleen response, safety, and tolerability.

Thirty-one patients were enrolled and received at least one dose of study drug (Table--2). Of these 31 patients, 13 had a history of either PV (11 patients) or ET (2 patients). Twenty-seven patients had received prior treatment for MF, and all had baseline splenomegaly that measured at least 5 cm below the LCM.

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
Age (yr)	
N	31
Mean (SD)	65.4 (8.62)
Median	67
25 - 75 percentile	60 - 72
Range	47 - 83
Gender	
N	31
Female	9 (29%)
Male	22 (71%)
Race	
N	31
American Indian or Alaska Native	0
Asian	0
Black or African American	1 (3%)
Native Hawaiian or Other Pacific Islander	0
White	30 (97%)
Other	0
Time Since Last Cancer Treatment (mo)	
N	31
Mean (SD)	121.1 (241.40)
Median	2
25 - 75 percentile	1 - 30
Range	1 - 606
ECOG Performance Status	
N	31
0	6 (19%)
1	17 (55%)
2	8 (26%)
>2	0
JAK 2 Mutation	

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
N	31
No	6 (19%)
Yes	25 (81%)
Type of JAK 2 Mutation	
N	25
V617F	25 (100%)
Other	0
FLT 3 Mutation	
N	23
No	23 (100%)
Yes	0
Baseline Hemoglobin (g/dL)	
N	31
Mean (SD)	9.845 (2.6000)
Median	9.000
25 - 75 percentile	8.10 - 11.80
Range	3.70 - 14.40
Baseline Platelet Count (10^3/µL)	
N	31
Mean (SD)	172.61 (130.924)
Median	126.00
25 - 75 percentile	62.0 - 260.0
Range	28.0 - 494.0
Baseline Platelet Count Category N(%)	
N	31
<50,000/µL	4 (12.9)
50,000 – 100,000/µL	9 (29.0)
≥100,000/µL	18 (58.1)
Baseline WBC (10^3/µL)	
N	31
Mean (SD)	12.180 (9.2365)
Median	8.910

Table--2 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2007-001	
Demographic/Baseline Characteristics	**Phase II (N=31)**
25 - 75 percentile	4.40 - 18.00
Range	1.50 - 38.20
Baseline Absolute Neutrophil Count (10^3/µL)	
N	31
Mean (SD)	8.86 (6.989)
Median	6.98
25 - 75 percentile	3.0 - 13.3
Range	0.9 - 29.4

Source: Table 2 (t02_demog 2012-02-29), Table 14 (t14_hema 2012-02-29), Table 1 (t_base_platelet_ph2_myel).
Abbreviations:
µL = microliter(s) ECOG = Eastern Cooperative Oncology Group FLT3 = fms-like receptor tyrosine kinase 3
g/dL = gram(s) per deciliter JAK2 = Janus kinase 2 N = number
SD = standard deviation WBC = white blood cell(s) yr = year(s).

Reasons for study drug discontinuation were lack of response (8 patients), disease progression (4 patients), withdrawal of consent (3 patients), adverse event (2 patients), and death (2 patients).

The most common treatment emergent adverse events (AEs) were diarrhea (90%), fatigue (58%), nausea (52%), and vomiting (35%). Most of these AEs were mild to moderate in severity (Table--3). Grade 3 AEs reported by more than one patient were anaemia (10%), thrombocytopenia (6%), cardiac failure congestive (10%), diarrhea (16%), abdominal pain (10%), fatigue (13%), pneumonia (6%), hypokalaemia (6%), and bone pain (13%). Grade 4 AEs were anemia (6%), thrombocytopenia (3%), pancytopenia (3%) fatigue (3%), hyperuricemia (6%), failure to thrive (3%), hyperglycaemia (3%), pain in extremity (3%), and muscular weakness (3%). Two serious adverse events (SAEs) were thought to be possibly related to treatment: grade 3 diarrhea in 1 patient and grade 3 dehydration in another. Both resolved without sequelae. No treatment-related deaths occurred and no SAE was reported in more than one patient.

Table--3 Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518-2007-001						
SOC/Preferred Term	**Phase II (N = 31)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Subjects with any Event	2 (6%)	7 (23%)	12 (39%)	6 (19%)	4 (13%)	31 (100%)
Blood and Lymphatic System Disorders	0	0	6 (19%)	3 (10%)	0	9 (29%)
Anaemia	0	1 (3%)	3 (10%)	2 (6%)	0	6 (19%)
Thrombocytopenia	0	0	2 (6%)	1 (3%)	0	3 (10%)
Cardiac Disorders						
Cardiac failure congestive	0	0	3 (10%)	0	0	3 (10%)
Gastrointestinal Disorders	9 (29%)	9 (29%)	13 (42%)	0	0	31 (100%)
Diarrhoea	14 (45%)	9 (29%)	5 (16%)	0	0	28 (90%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518-2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nausea	9 (29%)	6 (19%)	1 (3%)	0	0	16 (52%)
Vomiting	7 (23%)	3 (10%)	1 (3%)	0	0	11 (35%)
Abdominal pain	3 (10%)	3 (10%)	3 (10%)	0	0	9 (29%)
Constipation	5 (16%)	0	0	0	0	5 (16%)
Abdominal pain upper	2 (6%)	0	1 (3%)	0	0	3 (10%)
Ascites	0	2 (6%)	1 (3%)	0	0	3 (10%)
General Disorders and Administration Site Conditions	6 (19%)	13 (42%)	5 (16%)	1 (3%)	0	25 (81%)
Fatigue	2 (6%)	11 (35%)	4 (13%)	1 (3%)	0	18 (58%)
Oedema peripheral	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Asthenia	4 (13%)	1 (3%)	0	0	0	5 (16%)
Pyrexia	4 (13%)	0	0	0	0	4 (13%)
Chills	2 (6%)	1 (3%)	0	0	0	3 (10%)
Infections and Infestations	1 (3%)	4 (13%)	7 (23%)	0	1 (3%)	13 (42%)
Upper respiratory tract infection	2 (6%)	1 (3%)	0	0	0	3 (10%)
Urinary tract infection	0	2 (6%)	1 (3%)	0	0	3 (10%)
Investigations	5 (16%)	4 (13%)	1 (3%)	0	0	10 (32%)
Cardiac murmur	0	4 (13%)	0	0	0	4 (13%)
Weight decreased	4 (13%)	0	0	0	0	4 (13%)
Metabolism and Nutrition Disorders	5 (16%)	2 (6%)	3 (10%)	2 (6%)	1 (3%)	13 (42%)
Hyperuricaemia	2 (6%)	0	0	2 (6%)	0	4 (13%)
Hyperkalaemia	2 (6%)	1 (3%)	0	0	0	3 (10%)
Hypoalbuminaemia	1 (3%)	2 (6%)	0	0	0	3 (10%)
Hypokalaemia	1 (3%)	0	2 (6%)	0	0	3 (10%)
Musculoskeletal and Connective Tissue Disorders	7 (23%)	5 (16%)	4 (13%)	2 (6%)	0	18 (58%)
Bone pain	1 (3%)	1 (3%)	4 (13%)	0	0	6 (19%)
Pain in extremity	3 (10%)	2 (6%)	0	1 (3%)	0	6 (19%)
Back pain	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Muscle spasms	3 (10%)	0	0	0	0	3 (10%)
Nervous System Disorders	5 (16%)	2 (6%)	1 (3%)	0	0	8 (26%)
Neuropathy peripheral	1 (3%)	1 (3%)	1 (3%)	0	0	3 (10%)
Psychiatric Disorders	6 (19%)	5 (16%)	1 (3%)	0	0	12 (39%)

Table--3
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518-2007-001

SOC/Preferred Term	Phase II (N = 31)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Insomnia	7 (23%)	2 (6%)	0	0	0	9 (29%)
Respiratory, Thoracic and Mediastinal Disorders	9 (29%)	1 (3%)	5 (16%)	0	0	15 (48%)
Dyspnoea	4 (13%)	0	1 (3%)	0	0	5 (16%)
Cough	3 (10%)	0	0	0	0	3 (10%)
Dyspnoea exertional	3 (10%)	0	0	0	0	3 (10%)
Skin and Subcutaneous Disorders	10 (32%)	10 (32%)	2 (6%)	0	0	22 (71%)
Pruritus	4 (13%)	4 (13%)	1 (3%)	0	0	9 (29%)
Night sweats	4 (13%)	3 (10%)	0	0	0	7 (23%)
Rash	2 (6%)	1 (3%)	1 (3%)	0	0	4 (13%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations:
N = number SOC = system organ class.

Grade 4 thrombocytopenia was reported in 1 patient (923), a 59-year-old male with a prior diagnosis of PV. His baseline platelet count was 30,000/µL (grade 3) and his on-study nadir was 22,000/µL (grade 4). Associated splenic volume change was -20%.

Grade 3 thrombocytopenia was reported in 2 patients (907 and 916). Patient 907, a 76-year-old male with a prior diagnosis of PV, had a baseline platelet count of 59,000/ µL (grade 2) and an on-study nadir of 41,000/µL (grade 3). Associated splenic volume change was -26%. Patient 916, a 71-year-old male, had a baseline platelet count of 58,000/ µL (grade 2) and an on-study nadir of 54,000/µL (grade 2). Associated splenic volume change was -35%.

Among the 3 patients reporting grade 3 anemia, 2 had grade 2 anemia and one had grade 4 anemia at baseline. Both of the 2 patients reporting grade 4 anemia had grade 3 anemia at baseline.

Myelosuppression has been uncommon, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with normal platelet counts and those with baseline thrombocytopenia have tolerated pacritinib and responded equally well.

By MRI assessments, 17 patients (55%) experienced a spleen volume decrease of ≥ 25% from baseline through Week 24, and 5 patients (16%) experienced a spleen volume decrease of ≥ 35% from baseline through Week 24. According to organ measurement by physical examination, 12 patients (39%) experienced a spleen size decrease of ≥ 50% from baseline through Week 24 (data derived from T5.2-A_spleen_ALL.2012-02-29 using ITT denominator of 31). Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

A patient-reported outcome related to MF symptoms was assessed in this study using the myelofibrosis symptom assessment form (MFSAF) form (Mesa RA et al 2009). The study did not include a control arm, so it is not possible to evaluate the actual effect of pacritinib treatment on disease symptoms. However, on Day 1 of Cycle 7, patients who had a baseline score of ≥ 4 showed improvement in all

symptoms most relevant to MF; a mean score change of ≥ 2 was experienced in abdominal pain, bone pain, early satiety, inactivity, night sweats, pruritus, and fatigue.

1.3.7 SB1518-2008-003: Phase 1/2 Study in Patients with Chronic Idiopathic Myelofibrosis

1.3.7.1 Phase 1

During the phase 1 portion of SB1518-2008-003, cohorts of 3 to 6 patients with MF were enrolled into one of a series of escalating doses of pacritinib ranging from 100 to 600 mg/day. DLTs were observed in 2 of 4 patients at the 600 mg dose level: 1 experienced grade 3 diarrhea and 1 experienced grade 3 nausea, fatigue, and dehydration. The safety findings in this study were similar to those in SB1518-2007-001. The MTD based on first cycle data was determined to be 500 mg/day, and the recommended dose for phase 2 study, based on multicycle safety and efficacy data, was 400 mg/day.

The most commonly reported treatment-emergent AEs (> 20%) were diarrhea, nausea, vomiting, fatigue, constipation, abdominal pain, dizziness, ALT increased, anorexia, cough, pain in extremity, abdominal distension, peripheral edema, bone pain, headache, and rash. Most AEs were mild to moderate in severity. The only AEs of grade 3 or greater severity that occurred in more than 10% of patients were anemia, diarrhea, thrombocytopenia, and fatigue, each of which occurred in 15% of patients.

PK analysis showed a T_{max} of 3 to 7 hours and a terminal half-life of 1 to 2 days. Steady-state plasma levels were achieved by Day 15, and pharmacologically active concentrations were achieved at the starting dose of 100 mg on Day 1. No drug accumulation occurred upon repeated dosing over several cycles.

1.3.7.2 Phase 2

The objectives of the phase 2 portion of this study included spleen response rate, duration of spleen response, safety, and tolerability. Spleen response rate was defined as the proportion of patients achieving an MRI-determined reduction in spleen volume of 35% or more between baseline and Week 24.

Data are available for 34 patients in this trial (Table--4). Twenty-nine patients were previously treated for MF, and all enrolled patients had baseline splenomegaly that measured at least 5 cm below the LCM. Seven patients discontinued the study for the following reasons: AE (1 patient each for hyperbilirubinemia, allergic reaction, thrombocytopenia, and subdural hematoma), disease progression (1 patient), lack of response (1 patient), and withdrawal of consent (1 patient).

Table--4
Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2008-003

Demographic/Baseline Characteristics	MRI Phase II (N=34)
Age (yr)	
N	34
Mean (SD)	66.6 (10.44)
Median	69
25 - 75 percentile	60 - 72
Range	44 - 84
Gender	

Table--4 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2008-003	
Demographic/Baseline Characteristics	**MRI Phase II (N=34)**
N	34
Female	9 (26%)
Male	25 (74%)
Ethnicity	
N	34
Hispanic or Latino	2 (6%)
Not Hispanic or Latino	32 (94%)
Race	
N	34
American Indian or Alaska Native	0
Asian	1 (3%)
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	33 (97%)
Other	0
ECOG Performance Status	
N	32
0	9 (28%)
1	21 (66%)
2	2 (6%)
>2	0
Number of Prior Systemic Therapies	
N	34
Mean (SD)	1.9 (1.60)
Median	1
25 - 75 percentile	1 - 2
Range	0 - 6
Initial Stage of Disease	
N	34
MF0	1 (3%)
MF1	1 (3%)
MF2	7 (21%)
MF3	9 (26%)
Unknown or N/A	16 (47%)
Baseline Hemoglobin (g/dL)	

Table--4 Demographic and Baseline Characteristics and Laboratory Values of Patients in Phase 2 of SB1518-2008-003	
Demographic/Baseline Characteristics	**MRI Phase II (N=34)**
N	33
Mean (SD)	10.142 (1.8755)
Median	10.200
25 - 75 percentile	8.90 - 11.40
Range	5.50 - 14.10
Baseline Platelet Count (10^3/µL)	
N	33
Mean (SD)	167.39 (168.857)
Median	119.00
25 - 75 percentile	53.0 - 214.0
Range	15.0 - 859.0
Baseline Platelet Count Category	
<50,000/µL	7 (21.2)
50,000 – 100,000/µL	8 (24.2)
≥100,000/µL	18 (54.9)
Baseline WBC (10^3/µL)	
N	33
Mean (SD)	18.204 (19.5116)
Median	10.800
25 - 75 percentile	6.10 - 22.45
Range	1.14 - 89.60
Baseline Absolute Neutrophil Count (10^3/µL)	
N	34
Mean (SD)	12.21 (11.963)
Median	7.92
25 - 75 percentile	4.0 - 20.1
Range	0.3 - 56.4

Source: Table 2 (t02_demog 27FEB2012), Table 3 (t03_disease 27FEB2012), Table 14 (t14_hema 27FEB2012), Table 1 (t_base_platelet_ph2_myel).

Abbreviations:
µL = microliter(s); ECOG = Eastern Cooperative Oncology Group; g/dL = gram(s) per deciliter; MRI = magnetic resonance imaging; N = number; SD = standard deviation; WBC = white blood cells; yr = year(s).

Most AEs were mild to moderate in severity (Table--5). The most frequently occurring treatment emergent AEs were diarrhea (79%), nausea (41%), anemia (38%), fatigue (35%), abdominal pain (26%), pruritus (24%), and thrombocytopenia (24%). Grade 3 AEs reported by more than one patient were anemia (18%), thrombocytopenia (15%), fatigue (15%), diarrhea (9%), abdominal pain (6%), GI hemorrhage (6%), pneumonia (6%), AST increased (6%), QT prolongation (6%), dehydration (6%), and

iron overload (6%). Grade 4 AEs were anemia (9%), thrombocytopenia (6%), hyponatremia (6%), atrial fibrillation (6%), neutropenia (3%), leukopenia (3%), fatigue (3%), cellulitis (3%), septic shock (3%), blood uric acid increased (3%), hyperuricemia (3%), and renal cell cancer (3%). Grade 5 AEs were septic shock (3%), sepsis (3%), and subdural hematoma (3%). The only death considered related to treatment was the subdural hematoma. The only SAE reported in more than one patient was septic shock (2 patients, 6%). Ten SAEs reported in 6 patients were thought to be related to treatment; each SAE was reported in a single patient: grade 3 febrile neutropenia, grade 3 hyperbilirubinemia, grade 3 dehydration, grade 4 thrombocytopenia, grade 4 myocardial infarction, grade 4 septic shock, grade 4 hyperuricemia, grade 4 hyponatremia, and grade 5 subdural hematoma.

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518-2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Subjects with any Event	3 (9%)	3 (9%)	15 (44%)	9 (26%)	3 (9%)	33 (97%)
Blood and Lymphatic System Disorders	2 (6%)	5 (15%)	9 (26%)	5 (15%)	0	21 (62%)
Anaemia	0	4 (12%)	6 (18%)	3 (9%)	0	13 (38%)
Thrombocytopenia	1 (3%)	0	5 (15%)	2 (6%)	0	8 (24%)
Gastrointestinal Disorders	17 (50%)	9 (26%)	5 (15%)	0	0	31 (91%)
Diarrhoea	15 (44%)	9 (26%)	3 (9%)	0	0	27 (79%)
Nausea	13 (38%)	1 (3%)	0	0	0	14 (41%)
Vomiting	8 (24%)	3 (9%)	0	0	0	11 (32%)
Abdominal pain	5 (15%)	2 (6%)	2 (6%)	0	0	9 (26%)
Flatulence	6 (18%)	0	0	0	0	6 (18%)
Constipation	3 (9%)	1 (3%)	0	0	0	4 (12%)
General Disorders and Administration Site Conditions	10 (29%)	5 (15%)	5 (15%)	1 (3%)	0	21 (62%)
Fatigue	3 (9%)	3 (9%)	5 (15%)	1 (3%)	0	12 (35%)
Asthenia	2 (6%)	1 (3%)	1 (3%)	0	0	4 (12%)
Pyrexia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Investigations	9 (26%)	2 (6%)	4 (12%)	1 (3%)	0	16 (47%)
Aspartate aminotransferase increased	3 (9%)	0	2 (6%)	0	0	5 (15%)
Metabolism and Nutrition Disorders	6 (18%)	5 (15%)	7 (21%)	2 (6%)	0	20 (59%)
Dehydration	1 (3%)	3 (9%)	2 (6%)	0	0	6 (18%)
Anorexia	2 (6%)	3 (9%)	0	0	0	5 (15%)
Hyperuricaemia	3 (9%)	0	1 (3%)	1 (3%)	0	5 (15%)
Hypomagnesaemia	3 (9%)	1 (3%)	0	0	0	4 (12%)
Musculoskeletal and Connective Tissue Disorders	12 (35%)	3 (9%)	0	0	0	15 (44%)
Musculoskeletal pain	2 (6%)	2 (6%)	0	0	0	4 (12%)

Table--5
Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients in Phase 2 of SB1518-2008-003

SOC/Preferred Term	Phase II (N = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Nervous System Disorders	10 (29%)	1 (3%)	1 (3%)	0	0	12 (35%)
Dizziness	5 (15%)	1 (3%)	0	0	0	6 (18%)
Dysgeusia	4 (12%)	0	0	0	0	4 (12%)
Headache	3 (9%)	0	1 (3%)	0	0	4 (12%)
Psychiatric Disorders	4 (12%)	2 (6%)	0	0	0	6 (18%)
Insomnia	4 (12%)	0	0	0	0	4 (12%)
Respiratory, Thoracic and Mediastinal Disorders	5 (15%)	8 (24%)	4 (12%)	0	0	17 (50%)
Dyspnoea	1 (3%)	3 (9%)	0	0	0	4 (12%)
Skin and Subcutaneous Disorders	15 (44%)	4 (12%)	1 (3%)	0	0	20 (59%)
Pruritus	6 (18%)	1 (3%)	1 (3%)	0	0	8 (24%)
Alopecia	4 (12%)	0	0	0	0	4 (12%)

Source: Table 8.2 (t8.2_aegrade_10_ALL.2012-02-29).
Abbreviations:
N = number SOC = system organ class.

Among the patients reporting grade 3 anemia, all had grade 2 or grade 3 anemia at baseline. Among the 3 patients reporting grade 4 anemia, 1 had grade 3 anemia, 1 had grade 1 anemia, and 1 had no lab value at baseline.

Myelosuppression has been relatively infrequent, and treatment-related hematologic toxicity does not appear to be clinically significant. Patients with severe baseline hematologic abnormalities, including those with platelet counts <150,000/µL, appear to tolerate pacritinib as well as patients with normal and lesser degrees of abnormal hematopoiesis.

By MRI assessments, 12 patients (35%) experienced a decrease in spleen volume of at least 25% from baseline through Week 24, and 8 patients (24%) experienced a decrease in spleen volume of at least 35% from baseline through Week 24 (data derived from Table 5.2-A [t05.2-A_spleen_ALL.27FEB2012 using ITT denominator of 34]). According to organ measurement by physical examination, 14 patients (41%) experienced a decrease in spleen size of at least 50% from baseline through Week 24. Reduction of splenomegaly was observed in patients with thrombocytopenia as well as in patients with normal platelet counts.

Patients completed the MFSAF (Mesa RA et al 2009) at baseline and throughout the trial. Intra- and inter-patient symptom severity varied widely at baseline. On Day 1 of Cycle 4, patients who had a baseline score of ≥4 showed improvement in some symptoms, with mean decreases of ≥2 in early satiety, abdominal pain, night sweats, and pruritus.

1.3.8 Phase 1 and 2 Experience with Pacritinib in Myelofibrosis: Summary and Conclusions

- Fifty-six patients with MF have been treated with escalating doses of pacritinib in the phase 1 portions of studies SB1518-2007-001 and SB1518-2008-003. An additional 65 patients have been treated in the phase 2 portions of these studies in Australia and the US.
- A total of 36 patients with starting platelet counts ≤150,000/μL have been treated, with an apparent response rate similar to those with higher platelet counts and no consistent treatment-related platelet suppression.
- Pacritinib did not appear to increase anemia or RBC transfusion requirements.
- Pacritinib has a favorable safety profile and is generally well tolerated in patients with MF, including those with PMF, PPV-MF, and PET-MF. Side effects are predominantly GI and are readily managed with symptomatic treatment and/or study drug interruption or dose reduction. AEs associated with myelosuppression are uncommon, and pacritinib is well tolerated and active in patients with cytopenias-particularly thrombocytopenia.
- Median baseline platelet counts in patients treated with pacritinib in phase 2 studies were 126,000/μL and 119,000/μL, approximately half of those in the ruxolitinib studies (262,000/μL and 244,000/μL).
- The overall incidence of all grades of thrombocytopenia reported as adverse events in efficacy and safety trials with pacritinib was 17%. Twelve percent of patients experienced a 2-grade or greater shift in platelet counts from baseline to worst platelet count, and 5% experienced a 2-grade or greater shift in platelet counts from baseline to end of study (Table--6).
- In comparison, the incidence of all grades of thrombocytopenia was 69% in the COMFORT I trial, and the incidence of thrombocytopenia requiring dose adjustment was 41% in the COMFORT II trial.

Table--6
Shift from Baseline Platelet Count by CTC Grade in Phase 2 of SB1518-2007-001 and SB1518-2008-003

	Baseline Platelet Count CTC Grade (N = 65)				
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nadir Platelet Count CTC Grade (N = 64)					
0	16 (25.0%)	0	0	0	0
1	11 (17.2%)	3 (4.7%)	0	0	0
2	0	4 (6.3%)	5 (7.8%)	0	0
3	1 (1.6%)	5 (7.8%)	6 (9.4%)	4 (6.3%)	0
4	1 (1.6%)	0	1 (1.6%)	5 (7.8%)	2 (3.1%)
End of Study Platelet Count CTC Grade (N = 64)					
0	20 (31.3%)	4 (6.3%)	0	0	0
1	7 (10.9%)	2 (3.1%)	2 (3.1%)	0	0
2	0	5 (7.8%)	6 (9.4%)	1 (1.6%)	0
3	1 (1.6%)	1 (1.6%)	4 (6.3%)	6 (9.4%)	1 (1.6%)
4	1 (1.6%)	0	0	2 (3.1%)	1 (1.6%)

Source: (t_platelet_shift_from_base_ph2_myel).
Abbreviations:
CTCAE = Common Terminology Criteria for Adverse Events N = number

- A notable proportion of the 65 patients with MF who were treated with pacritinib experienced a reduction in splenomegaly on both MRI and physical examination assessments. Among 49 patients with post-baseline follow-up evaluations, 29 (59%) had a 25% or greater reduction in MRI-assessed spleen volume and 13 (27%) had a 35% or greater reduction in MRI-assessed spleen volume.

Twenty-six (41%) of 63 evaluable patients had at least a 50% reduction in physical examination-assessed spleen size as a best response. Patients with thrombocytopenia showed similar treatment effects.

- Clinical experience through phase 2 has demonstrated the safety and activity of pacritinib in patients with MF and warrants phase 3 trials to confirm the efficacy and safety of this drug in this patient population.

1.3.9 PERSIST-1: Phase 3 Study of Pacritinib versus Best Available Therapy in Patients with PMF, PPV-MF, or PET-MF

This ongoing phase 3 study will compare the efficacy of pacritinib with that of BAT in patients with PMF, PPV-MF, or PET-MF. The primary objective is to assess the proportion of patients in each arm achieving a ≥35% reduction in spleen volume from baseline to Week 24. The secondary objective is to assess the proportion of patients in each arm with ≥50% reduction from baseline to Week 24 on the MPN-SAF TSS 2.0.

A total of 351 patients at approximately 100 centers in the US, Europe, Russia, and Oceania will be randomized in a 2:1 allocation to pacritinib or BAT. BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, with the exclusion of JAK2 inhibitors. BAT also includes watchful waiting (no treatment). Spleen volume will be measured at baseline and every 12 weeks thereafter. Patients previously treated with JAK2 inhibitors are excluded. There are no exclusion criteria based on platelet count.

2 Rationale for Study

Two phase 2 studies of pacritinib have been conducted in patients with MF. Data from these trials show that pacritinib can be safely administered to patients with MF, including those who also have thrombocytopenia. Pacritinib treatment led to clinically meaningful reduction in spleen size and volume in a substantial proportion of patients with MF in the phase 2 studies. Pacritinib treatment improved disease-associated symptoms. These effects were observed in patients with thrombocytopenia, including those with platelet counts < 100,000 /μL, as well as in those with normal platelet counts. These findings warrant phase 3 investigation to confirm the efficacy and safety of pacritinib, both in patients with normal and low platelet counts. For the subgroup of patients with low platelet counts, the currently approved JAK inhibitor requires significant dose reduction and is less effective than in patients with normal platelet counts. Pacritinib may fill a significant unmet need in patients with low platelet counts and also provide effective treatment for nonthrombocytopenic patients with MF.

2.1 Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arm(s) of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

2.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.
2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in the TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.3 Exploratory Objectives

The exploratory objectives are the evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of RBC transfusion independence (Appendix 1a)
9. Achievement of reduced RBC transfusion dependence (Appendix 1a)
10. Clinical improvement in hemoglobin level (Appendix 2)
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence (Appendix 1b)
13. Clinical improvement in platelet count (Appendix 2)
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4)

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamics (PD) objectives are to assess exposure and exposure response relationships on the safety and efficacy of pacritinib.

3 Study Design

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two-dose schedules of pacritinib in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to one of three treatment arms:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia) and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF.

Patients may not receive splenic irradiation or a splenectomy while receiving study treatment.

Spleen volume will be measured by MRI or CT scan at baseline and every 12 weeks thereafter, and at other time points as clinically indicated. MRI is the preferred modality. Imaging should be performed without contrast agents. The analysis of the primary outcome will take place when all randomized patients have completed the Week 24 MRI or CT evaluation, exhibited disease progression, or discontinued study treatment, whichever occurs first. An independent radiology facility (IRF), blind to treatment assignments, will measure spleen volumes.

Patients will also be followed for safety, OS, PFS, LFS, frequency of RBC and platelet transfusions, and other exploratory endpoints. Bone marrow slides obtained at or prior to baseline, as required for study eligibility, and those obtained at Week 24 may be evaluated by a central pathology laboratory, in addition to local pathology review.

An Independent Data Monitoring Committee (IDMC) will monitor the safety of pacritinib. No interim efficacy analysis is planned.

For patients who are no longer taking pacritinib or those in the BAT arm who are no longer receiving study treatment, follow-up for survival and leukemic progression will continue until 3 years past Week 24 or past termination of all study treatment, whichever occurs first. The maximum duration of trial participation for an individual patient will be 3.5 years. The estimated duration of the entire trial is 4.5 years.

3.1 Progression of Disease

Patients may experience one or more of the following: splenic progression, splenic irradiation, splenectomy, or leukemic transformation. All of these events represent progression of disease and must be reported. A patient who has experienced one event will continue to be followed for other events, as described below. For a patient who is randomized to BAT and subsequently crosses over to pacritinib, 2 splenic progression events may be experienced, and both should be reported.

Progression of disease is defined as one or more of the following:

- Splenic progression, defined as in increase in splenic volume of ≥25% from baseline, based on centrally read MRI or CT scan

- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
  - Bone marrow blast count ≥20%

Patients with progression of disease will continue to be followed for other events, and all of these events should be reported.

Although the date of the first event is considered the date of progression of disease, subsequent events must also be reported.

3.2 Criteria for Treatment Continuation After Progression of Disease

To continue assigned or crossover study treatment after progression of disease, a patient must meet all of the following criteria:

- Progression of disease is declared based only on an increase in splenic volume of ≥25% from baseline on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation
- Patient continues to receive clinical benefit from study treatment and is not experiencing excessive drug toxicity; investigator must describe clinical benefit in the CRF.

3.3 Criteria for Crossover from BAT to Pacritinib Treatment

To cross over from BAT to pacritinib, a patient must meet all of the following criteria:

- Patient has completed at least 24 weeks on BAT, or has progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of ≥25% from baseline, on centrally read MRI or CT scan
- Patient has not undergone splenic irradiation or splenectomy
- Patient does not meet criteria for leukemic transformation

Each patient is to receive pacritinib or BAT until progression of disease or the occurrence of unacceptable toxicity, or until the patient no longer derives benefit from treatment (Appendix 11).

Patients on BAT may cross over to pacritinib at any time after splenic progression if leukemic transformation, splenectomy, or splenic irradiation have not occurred, or after completing 24 weeks of treatment with or without progression. Patients may continue on active (drug) study treatment after disease progression, as detailed below.

Patients on BAT who have splenic progression but do not wish to cross over to pacritinib will be followed for safety, survival, and leukemic transformation, but not splenic progression as long as they continue the BAT treatment they were taking at the time of progression. Note that patients whose BAT treatment consists of no treatment (no drugs) at the time of splenic progression will be followed for leukemic transformation and survival.

Patients crossing over from BAT to pacritinib will follow the same visit schedule (eg, baseline, Weeks 1, 2, and 4) as patients who are randomized to pacritinib, except that no PK or PD assessments will be performed. At the time of crossover from BAT to pacritinib, the patient must discontinue all BAT therapies, including erythropoietic agents. There may be up to 1 week between BAT discontinuation and the start of crossover pacritinib treatment. BAT washout is not needed prior to starting pacritinib treatment. If a patient crosses over from BAT to pacritinib after Week 24, an MRI or CT must be completed within 30 days prior to the start of pacritinib treatment. This will define the crossover baseline spleen volume, and patients will be subsequently followed for a second, post-crossover event of splenic progression.

Patients who cross over from BAT to pacritinib will continue to be followed for splenic and leukemic progression, even if splenic progression was already documented on BAT.

4 Patient Selection and Withdrawal

4.1 Target Population

4.1.1 Inclusion Criteria

1. Intermediate-1 or -2 or high risk (Passamonti et al. 2010; Appendix 5) PMF, PPV-MF, or PET-MF (Tefferi and Vardiman 2008; Barosi et al. 2008; Appendix 6)
2. Thrombocytopenia (platelet count ≤100,000/μL) at any time after signing informed consent
3. Informed consent may be signed up to 35 days prior to randomization
4. Palpable splenomegaly ≥5 cm below the LCM in midclavicular line by physical examination
5. Total Symptom Score (TSS) ≥13 on the MPN-SAF-TSS 2.0, not including the inactivity question (Appendix 7)
6. Age ≥18 years old
7. ECOG performance status 0 to 3 (Appendix 8)
8. Peripheral blast count <10%
9. Absolute neutrophil count (ANC) >500/μL
10. Patients who are platelet or RBC transfusion-dependent are eligible
11. Adequate liver and renal function, defined by liver transaminases (AST/SGOT and ALT/SGPT) ≤3 × ULN (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4 x ULN, and creatinine ≤2.5 mg/dL
12. At least 6 months from prior splenic irradiation
13. At least 12 months from prior ^{32}P therapy
14. At least 1 week since prior treatment (most recent dose) with a potent cytochrome P450 3A4 (CYP3A4) inhibitor (Appendix 9)
15. At least 2 weeks since receiving any treatment for PMF, PPV-MF, or PET-MF
16. If fertile, males and females must agree to use effective birth control methods during the study. Women of childbearing potential must use highly effective methods (defined as those resulting in a failure rate of <1% per year when used consistently and correctly) for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release). Males must use a condom for the duration of the study and for 90 days after the last dose of study treatment. When abstinence is used as a method of birth control, only true abstinence is acceptable, when this is in line

with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

17. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
18. Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument
19. Able to understand and willing to sign the informed consent form.

4.1.2 Exclusion Criteria

1. Any gastrointestinal (GI) or metabolic condition that could interfere with absorption of oral medication
2. Life expectancy less than 6 months
3. Prior treatment with more than 2 JAK2 inhibitors or pacritinib
4. There is no maximum cumulative prior JAK2 inhibitor treatment (approved or investigational)
5. Completed allogeneic stem cell transplantation (ASCT) or are eligible for and willing to complete ASCT
6. History of splenectomy or planning to undergo splenectomy
7. Uncontrolled intercurrent illness, including but not limited to ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
8. Active bleeding requiring hospitalization during the screening period
9. Other malignancy within the last 3 years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated nonmetastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
10. Inflammatory or chronic functional bowel disorder, such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
11. Clinically symptomatic and uncontrolled cardiovascular disease
12. History of any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure
13. New York Heart Association Class III or IV congestive heart failure (Appendix 10)
14. Patients with National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) grade 2 cardiac arrhythmias may be considered for inclusion with the approval of the medical monitor if the arrhythmias are stable, asymptomatic and unlikely to affect patient safety. Patients will be excluded if they have ongoing cardiac dysrhythmias of CTCAE grade ≥3, corrected QT interval (QTc) prolongation >450 ms, or other factors that increase the risk for QT prolongation (eg, heart failure, hypokalemia [defined as serum potassium < 3.0 mEq/L that is persistent and refractory to correction], or family history of long QT interval syndrome).
15. Erythropoietic agent within 28 days prior to randomization
16. Thrombopoietic agent within 14 days prior to randomization
17. Known seropositivity for human immunodeficiency virus (HIV)
18. Known active hepatitis A, B, or C virus infection
19. Women who are pregnant or lactating

4.2 Criteria for Withdrawal of Patients

4.2.1 Withdrawal from Study Treatment

Patients may discontinue or be withdrawn from treatment at any time. All reasonable efforts should be made to retain patients who discontinue treatment in the study and to conduct all follow-up assessments required by the protocol, including MRI or CT scanning and follow-up for progressive disease, leukemic transformation, and survival. Reasons for discontinuing treatment may include but are not limited to the following:

- Documented disease progression, defined as:
  - Splenic progression, defined as an increase in splenic volume of ≥25% from baseline based on centrally read MRI or CT scan
  - Splenic irradiation
  - Splenectomy
  - Leukemic transformation, defined as one or more of the following:
    - Increase in peripheral blood blast percentage to ≥20%, sustained for ≥8 weeks
    - Bone marrow blast count ≥20%
- Unrelated intercurrent illness that, in the judgment of the principal investigator, will affect assessments of clinical status to a significant degree
- Pregnancy
- Patient's decision
- Patient noncompliance with study drug
- Clinical need for concomitant therapy that is not permitted in the study
- Decision on the part of the investigator or CTI BioPharma Corp.'s medical monitor that it is in the patient's best interest to withdraw from study treatment
- Death

4.2.2 Withdrawal from Study Procedures

Patients will be withdrawn from study procedures for the following reasons:

- Withdrawal of consent for study procedures
- Decision on the part of the investigator or Cell Therapeutics' medical monitor that it is in the patient's best interest to withdraw from study procedures

For patients who discontinue treatment and study procedures, all reasonable efforts should be made to maintain the patient in the study and continue follow-up for OS and LFS.

4.2.3 Withdrawal from the Study

Patients will be withdrawn from the study, including follow-up, for the following reasons:

- Withdrawal of consent
- Lost to follow-up
- Death

- Sponsor decision to terminate the study

5 Method of Treatment Assignment and Blinding

Eligible patients will be centrally randomized in a 1:1:1 allocation to receive either pacritinib dosed QD, pacritinib dosed BID, or BAT using a central interactive web response system or interactive voice response system.

Randomization will be stratified by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤100,000/μL versus >100,000/μL). To be included in the >100,000/μL group, patients meet both of the following criteria: 1) rebound platelet count >100,000/μL and 2) >50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The first qualifying platelet value after informed consent and the most recent platelet count obtained prior to randomization will be the basis for determining platelet rebound stratification. For patients who receive any platelet transfusions, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization. If necessary due to ROW enrollment and regulatory strategies, the ROW stratum may be divided into 2 or more strata as appropriate.

A patient's treatment assignment will be known to the investigator, site personnel, the patient, clinical monitors, and pharmacovigilance personnel. The sponsor will remain blinded until the database lock for primary analysis. Independent radiographic assessors will remain blinded throughout the study.

6 Study Treatment

6.1 Study Drug Administration

Patients taking pacritinib will be supplied with 100 mg capsules of the drug. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib once a day, at the same time of day, orally, with or without food. Patients assigned to BID dosing will take 200 mg (2 capsules) of pacritinib twice each day at the same times of day, orally, with or without food (Table--7).

Patients receiving BAT will be treated on a schedule commensurate with the therapy chosen by the investigator.

Table--7
Study Treatment Schedule

Treatment	Dose/Regimen
Pacritinib (QD)	Pacritinib 400 mg (4 capsules) once a day orally, at the same time of day, with or without food.
Pacritinib (BID)	Pacritinib 200 mg (2 capsules) twice each day orally, at the same time of day, with or without food
Best Available Therapy (BAT)	Physician's choice of treatment for PMF, PPV-MF, or PET-MF

6.2 Study Drug Description and Storage

Pacritinib for oral administration is supplied in capsules containing 100 mg (as the free base) in red cap/gray body size 0 opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000.

Each capsule contains 146 mg of pacritinib citrate which is equivalent to 100 mg pacritinib free base.

Pacritinib capsules should not be opened or crushed. Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water.

Pacritinib capsules should be stored at controlled room temperature 20º to 25ºC or 68º to 77º F, with excursions allowed from 15° to 30ºC or 59° to 86ºF. All pacritinib supplies must be kept in a restricted-access area.

BAT may include any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

6.3 Dose, Route, and Mode of Administration

Patients in the pacritinib arms will be supplied with 100-mg capsules of pacritinib. If assigned to the QD dosing arm, patients will take 400 mg (4 capsules) of pacritinib orally, once a day, at the same time of day, with or without food. If assigned to the BID dosing arm, patients will take 200 mg (2 capsules) of pacritinib twice each day orally, at the same times of day, with or without food. On days when PK and/or PD samples are to be obtained, pacritinib will be administered in the clinic.

6.4 Compliance with Treatment

At every study visit, patients in the pacritinib arm and those who have crossed over to pacritinib arm will return bottles in which pacritinib is supplied with all remaining untaken pacritinib capsules.

6.5 Pacritinib Treatment Adjustments

6.5.1 Treatment Interruption

Safety parameters including AEs, hematology, and serum chemistry will be monitored according to the protocol. Pacritinib treatment may be withheld for up to 2 weeks due to drug-related toxicities. A longer recovery period may be allowed based on the toxicity, but must be agreed upon between the investigator and medical monitor.

After treatment interruption, patients may resume the pacritinib treatment at the same dose level or at a reduced dose level. No dose re-escalation is allowed.

6.5.2 Pacritinib Dose Management Guidelines for QTc Interval Prolongation

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 by CTCAE Version 4.0 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and

method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in this section. Dose management for QTc interval prolongation is summarized in Table--8.

For grade 3 QTc prolongation, hold treatment until toxicity resolves to grade ≤1. If, within 7 days, toxicity resolves to grade ≤1, restart pacritinib at 200 mg/day. When restarted, pacritinib dosing will be 200 mg QD for the 400 mg QD arm and 100 mg BID for the 200 mg BID arm. No dose re-escalation is allowed.

After restart of pacritinib, QTc monitoring should follow this schedule with EKGs obtained on:

- Restart Day 1 at 4 hours (± 1 hour) after ingestion of the first reduced dose
- Restart Day 7 (± 2 days) 4 hours after dosing (± 1 hour)
- Restart Day 14 (± 2 days) 4 hours after dosing (± 1 hour)
- Restart Day 28 (± 2 days) at any time relative to dosing
- Restart Day 56 (± 7 days) at any time relative to dosing

If grade 3 toxicity does not resolve to grade ≤1 within 7 days, discontinue all treatment with pacritinib. If grade 3 toxicity recurs despite dose reduction to 200 mg/day, discontinue all treatment with pacritinib.

For grade 4 QTc prolongation, discontinue all treatment with pacritinib.

Table--8
Treatment Toxicity and Dose Management: QTc Interval Prolongation

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3 (first occurrence)	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 within 7 days, treatment may be resumed at 200 mg daily (for QD dosing arm patients) or 100 mg twice daily (for BID dosing arm patients). In patients who resume pacritinib treatment, follow-up EKGs should be obtained to monitor QTc intervals at the following time points after resumption of pacritinib treatment: ▪ Restart Day 1 at 4 hours (± 1 hour) after ingestion of the first reduced dose ▪ Restart Day 7 (± 2 days) 4 hours (± 1 hour) after dosing ▪ Restart Day 14 (± 2 days) 4 hours (± 1 hour) after dosing ▪ Restart Day 28 (± 2 days) at any time relative to dosing ▪ Restart Day 56 (± 7 days) at any time relative to dosing ▪ Toxicity that does not resolve to grade ≤ 1 within 7 days requires treatment discontinuation.
3 (second occurrence)	▪ Discontinue treatment.
4	▪ Discontinue treatment.

6.5.3 Pacritinib Dose Management Guidelines for Pacritinib-Related Nonhematologic Toxicities other than QTc Prolongation

A maximum of 2 dose reductions is allowed. The first dose reduction will be a 100 mg reduction from the original dose. For patients taking 400 mg QD, the dose will be reduced to 300 mg QD. For patients taking 200 mg BID, the dose will be reduced to 200 mg Q AM and 100 mg Q PM.

The second dose reduction will be another 100 mg reduction. For patients taking 300 mg QD, the dose will be reduced to 200 mg/day. For patients taking 200 mg Q AM and 100 mg Q PM, the dose will be reduced to 100 mg BID.

Once the dose is reduced, no re-escalation is allowed.

Dose management for nonhematologic toxicities is summarized in Table--9.

The lowest dose of pacritinib used in the study will be 200 mg/day. If toxicity persists despite dose reduction to 200 mg/day, the patient should be discontinued from treatment.

Table--9
Treatment Toxicity and Dose Management: Pacritinib-Related Nonhematologic Toxicities

CTCAE Toxicity Grade	Management/ Action
1 or 2	No change.
3	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed at the same level or the next lower dose, at the discretion of the investigator after discussion with the sponsor. ▪ Toxicity that does not resolve to grade ≤ 1 or to the baseline grade within 7 days requires dose reduction to the next lower dose level.
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed, but dose will be reduced by one dose level from the level at which the toxicity was observed. ▪ If grade 4 toxicity occurs at the lowest dose of 200 mg/day, the patient should be discontinued from the study.

6.5.4 Dose Management Guidelines for Hematologic Toxicities

Myelosuppression is an expected event in patients with MF. However, myelosuppression with associated complications such as fever, infection, or bleeding or myelosuppression that worsens during treatment (based on local laboratory values) must be reported as an AE.

Patients with myelosuppression may receive supportive care including transient use of granulocyte-colony stimulating factor for the treatment of febrile neutropenia and transfusion as clinically indicated. Patients receiving pacritinib are not allowed to receive hematopoietic growth factors such as erythropoietin for the treatment of anemia.

Patients with clinically significant worsening of myelosuppression (as judged by the investigator and based on local laboratory values) for more than 7 days or myelosuppression associated with infection or bleeding should have pacritinib dosing interrupted. Pacritinib may be restarted at a reduced dose once the

toxicity has resolved to grade ≤ 2 or to the baseline grade and the complications of myelosuppression such as infection or hemorrhage have resolved.

6.6 Concomitant and Excluded Therapies

BAT will include any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved inhibitors of Janus kinases, and may include any treatment received before study entry. BAT also includes watchful waiting (no treatment).

Patients taking pacritinib, including those randomized to pacritinib and those who have crossed over from BAT to pacritinib, may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF during the study.

Patients should receive full supportive care, including transfusions of blood and blood products, antidiarrheal and antiemetic agents (see below), and antibiotics when appropriate.

All concomitant medications and blood products administered during the patient's participation in the study must be recorded in the source documents and electronic case report forms (eCRFs).

Patients may not receive other investigational agents during the study.

Patients may not receive treatment with any potent CYP3A4 inhibitors for 1 week prior to administration of pacritinib and during treatment with pacritinib. Some BAT therapies also have CYP3A4 interactions and/or other drug-drug interactions. Prescribing instructions should always be consulted to ensure adherence to administration guidelines for each prescribed BAT. See Appendix 9 for a list of common potent CYP3A4 inhibitors.

6.6.1 Management of Gastrointestinal Toxicity

The need for managing GI effects of pacritinib, particularly diarrhea, should be anticipated. A careful baseline evaluation of bowel habits (frequency and consistency of bowel movements) should be obtained at baseline for all patients.

The site will contact all patients by telephone during the first week (on Day 3, 4, or 5 of initial treatment, and on Day 3, 4, or 5 after crossover to pacritinib) and at the beginning of Week 3 (of initial treatment or after crossover to pacritinib) to evaluate GI toxicity and assess the need for modifying the treatment of GI side effects. At the baseline visit, all patients will be provided with a prescription (and instructions to fill that prescription) for loperamide (Imodium) or a similarly effective antidiarrheal drug. Patients will be instructed to start taking the prescribed loperamide or other antidiarrheal drug per package and physician instructions as soon as they notice any changes in frequency or consistency of bowel movements after starting study treatment.

Early intervention for diarrhea should be initiated for patients with increases of one grade or more in diarrhea (Appendix 12). At the investigator's discretion, prophylactic use of anti-diarrheals may be initiated for patients or populations in whom it is judged necessary to enhance patient safety. Standard supportive care measures to control symptoms of GI toxicity such as diarrhea, constipation, and nausea should be provided.

6.7 BAT Treatment Adjustments

Patients on the BAT arm who are being treated with ruxolitinib must be dosed according to the instructions in the current labeling recommendations.

7 Study Assessments

7.1 Criteria for Evaluation

7.1.1 Efficacy

7.1.1.1 Spleen Volume

Spleen volume measurement by MRI or CT scan will be performed at screening and every 12 weeks thereafter, or at other time points if spleen size progression is suspected by other assessments (eg, physical examination). Unscheduled imaging studies can be performed at physician discretion if he/she considers disease related symptoms to be worsening. All images generated as part of unscheduled evaluations must be submitted by the investigator for central review. MRI is the preferred modality; CT scan will be used for patients who cannot undergo MRI, or for whom MRI is not available. Imaging should be performed without contrast agent. For each patient, the same imaging modality should be used throughout the study. Two independent radiologists, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. In the case of significant disagreement between the first two radiologists, a third independent radiologist, also blinded to all patient and site identifiers and treatment assignments, will adjudicate to establish the spleen volume measurement. A spleen response is defined as a reduction in spleen volume of ≥35% at any time.

7.1.1.2 Spleen Size Assessment by Physical Examination

Spleen size, assessed by physical examination as the distance below the LCM at the midclavicular line, will be performed with each scheduled physical examination.

7.1.1.3 Disease-Related Signs and Symptoms

Patients will complete the MPN-SAF TSS 2.0 (Appendix 7) daily for 7 to 10 consecutive days prior to starting treatment and then daily through Week 48 of the study or until the patient discontinues study treatment, whichever occurs first.

The pain medication log will be completed daily by patients, as long as they continue to complete the daily MPN-SAF TSS 2.0. The patient global impression assessment will be completed by patients every 8 weeks through Week 24 and then every 12 weeks until the patient discontinues study treatment.

7.1.1.4 Survival

Patients will be followed for survival and for transformation to AML (as assessed by the investigator, investigator-obtained records, or if these are not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

7.1.1.5 Quality of Life

The EQ-5D-5L and EORTC-QLQ-C30 version 3.0 will be completed at baseline, Week 8, Week 16, Week 24, and then every 12 weeks as long as the patient remains on study treatment. Patients will discontinue quality of life assessments at study treatment termination.

7.1.1.6 Other Assessments

Patients will also be followed for leukemic transformation, frequency of RBC and platelet transfusions, and other exploratory endpoints.

Bone marrow slides obtained at or prior to baseline as required for study eligibility and those obtained at Week 24 may be evaluated by central pathology, in addition to local pathology review.

Bone marrow biopsy evaluation (aspirate and core) obtained per protocol will be performed per local standards of care. Bone marrow biopsy sample should be evaluated for myeloblast percentage. In addition, routine and specific evaluations for myelofibrosis should be done, including (but not limited to), the following assessments: cell count and differential, megakaryocyte proliferation and atypia, reticulin and collagen staining and staging, bone marrow cellularity, granulocytic proliferation, decreased erythropoiesis, and cytogenetic analysis (including *JAK2V617F*).

7.1.2 Safety

7.1.2.1 AEs

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported. SAEs that occur after study completion and are considered by the investigator to be related to pacritinib should be reported to the Sponsor.

7.1.2.2 Hematology

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Hematology parameters (CBC with differential and platelet count) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local standards of care. Similarly, unscheduled CBC with differential and platelet count may be performed locally and/or centrally whenever clinically indicated.

7.1.2.3 Blood Chemistry

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Blood chemistry parameters (ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin [total, direct, and indirect], creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid) will be evaluated by a central laboratory at screening, baseline, beginning of Week 3, completion of Weeks 4, 8, 12, 16, 20, and 24, and every 12 weeks thereafter, and at termination of study treatment. Investigators may use either local laboratory or central laboratory results to monitor safety and document AEs as per the local

standards of care. Similarly, unscheduled chemistries may be performed locally and/or centrally whenever clinically indicated

7.1.2.4 ECG Assessment

All patients will have a single 12-lead ECG at screening. Screening ECGs should be performed at least 1 week after the end of prior therapy. For patients assigned to pacritinib on either dose schedule, or patients who have crossed over from BAT to pacritinib, a single 12-lead ECG will be performed at screening, within 1 hour prior to dosing, at 4 hours after in-clinic dosing on Day 1 of Weeks 1, 2, and 3, and as clinically indicated. For patients assigned to BAT, a single 12-lead ECG will be performed at screening, at baseline, on Day 1 of Weeks 1, 2, and 3 (without regard to timing of BAT dosing), and as clinically indicated. Local ECG readings will be used throughout the study.

QTc interval prolongation identified on automated ECG calculations that is ≥ grade 1 should be manually recalculated. The QTc calculation method is chosen by the investigator, but the same method should be used during the study for a given patient. The manual recalculation result and method should be entered on the eCRF and used to guide clinical decisions, including toxicity management as detailed in section 6.5.2.

7.1.3 Pharmacokinetics

PK samples (five) for assessment of systemic exposure will be collected from approximately 70 patients taking pacritinib at a prespecified subset of sites at the following time points:

- Day 1 of Week 1: at 4 hours postdose
- Day 1 of Week 3: predose (Hour 0) and at 4 hours postdose
- Week 12 and Week 24: predose (Hour 0)

PK samples (two) for assessment of systemic exposure will be collected from approximately 130 patients taking pacritinib at the remaining sites at the following time points:

- Week 12 and Week 24: predose (Hour 0)

On the day prior to PK blood sampling, the patient must record the time of dosing and report it the following day. On the day of PK blood sampling, patients must not take the daily dose of pacritinib prior to the clinic visit.

Results will be used to evaluate the relationship between drug exposure and safety and efficacy.

PK samples will not be collected from patients crossing over from BAT to pacritinib.

7.1.4 Pharmacodynamics

PD samples for assessment of pSTAT3 levels, an established PD marker for JAK-STAT signaling pathway inhibition, will be collected from patients taking pacritinib at a prespecified subset of sites, the same approximate 70 patient, five-sample PK cohort as described above in Section 7.1.3, at the following time points:

- Day 1 of Week 1 and Week 3: predose (Hour 0) and at 4 hours postdose

- Week 12 and Week 24: predose (Hour 0)

PD samples will not be collected from patients crossing over from BAT to pacritinib.

7.1.5 *JAK2* Mutation Burden

JAK2V617F mutation burden will be assessed by a central laboratory in all patients at screening, at Week 12, and every 12 weeks thereafter and at termination of study treatment in patients who have the mutation at screening.

7.2 Informed Consent and Washout of Prior Therapies, 35 to 7 Days Before Beginning Study Treatment

Informed consent must be obtained before any study-specific washout. The informed consent process should be documented in the patient's medical chart. Informed consent should be obtained between 35 and 7 days prior to the start of treatment. Washout may require 4 weeks (erythropoietic agents), 2 weeks (thrombopoietic agents and MF treatments), or 7 days (potent CYP3A4 inhibitors). Patients not requiring washout may sign informed consent at any time prior to screening procedures. The informed consent process should be documented in the patient's medical chart. Eligibility platelet count may be obtained at any time within this window.

7.3 Screening Procedures, 5 to 14 Days Before Beginning Study Treatment

Informed consent must be obtained before study procedures and screening evaluations are performed unless those evaluations are performed as part of standard of care. Patients who do not meet eligibility criteria at screening may be rescreened at a later date.

The screening evaluations listed below are to be carried out **between 14 and 5 days prior to the start of treatment**. Laboratory assessments and ECGs should be performed at least 1 week after the end of prior therapy, except eligibility platelet count which may be obtained between 35 and 7 days before beginning study treatment.

- Medical history
- *JAK2V617F* mutation status (for baseline pharmacodynamic assessment; in addition, collect medical and disease history of mutation status if documentation is available)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including height, clinical signs and symptoms, and spleen measurement
- GI assessment
- 12-lead ECG
- ECOG performance status
- Hematology: CBC with differential and platelet count
- BM biopsy within 24 weeks of randomization (may be obtained any time before Day -3)
- Serum chemistry, including ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin (total, direct, and indirect), creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid
- Serum pregnancy test for women of childbearing potential
- AEs

- Concomitant medications
- Transfusion history
- Assess for leukemic transformation

7.4 Symptom Assessment and Screening MRI Visit, 4 to 10 Days Before Beginning Study Treatment

- Patient-reported symptoms on MPN-SAF TSS 2.0 must be completed daily for 7 to 10 consecutive days prior to starting treatment
- Pain medication log will begin when MPN-SAF TSS 2.0 symptom reporting begins
- MRI or CT scan (without contrast) for measurement of spleen volume

7.4.1 Randomization, Up to 3 Days Before Beginning Study Treatment

Randomization: Patient must first sign informed consent, then complete all screening procedures, and meet all eligibility criteria. Note that screening procedures include at least two platelet counts to determine 1) the first qualifying platelet value after informed consent and 2) the platelet rebound count for stratification.

Platelet count obtained during the the randomization period (Days -3 to 1) will be used in determination of platelet rebound stratification. In the case of patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to the transfusion and this value be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for the platelet rebound stratification determination. Should patients receive frequent platelet transfusions and counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion obtained before randomization.

7.4.2 Beginning of Week 1, Study Day 1

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples patients in the pacritinib arm at PK sites: Hour 4 (postdose)
- PD samples for patients in the pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)

- Dispense prescription for antidiarrheal drug and instruct patient to fill it and to begin taking it at onset of gastrointestinal symptoms
- Dispense pacritinib or begin treatment with BAT
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.3 Week 1, Study Day 4 (± 1 d)

- The site (either the investigator or a surrogate) is to contact the patient by telephone to assess the need for modifying the treatment of any GI side effects.
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.4 Beginning of Week 2, Study Day 8 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (within 1 hour prior to dosing for patients on pacritinib and at any time for patients on BAT)
- 12-lead ECG 4 hours after dosing (patients on pacritinib only)
- ECOG performance status
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history

7.4.5 Beginning of Week 3, Study Day 15 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- GI assessment

- 12-lead ECG (1 only for BAT patients; 2 for pacritinib patients; predose and at 4 hours postdose)
- ECOG performance status
- PK samples for patients in pacritinib arm at PK sites: Hour 0 (predose) and Hour 4 (postdose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose) and Hour 4 (postdose)
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.6 End of Week 4, Study Day 28 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.7 End of Week 8, Study Day 56 (± 3 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log

- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.8 End of Week 12, Study Day 84 (± 3 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.9 End of Week 16, Study Day 112 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry

- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.10 End of Week 20, Study Day 140 (± 7 d)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.11 End of Week 24, Study Day 168 (± 7 d)

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Bone marrow biopsy
- Serum chemistry
- MRI or CT without contrast to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)

- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- PK samples for patients on pacritinib arm at PK sites: Hour 0 (predose)
- PD samples for patients in pacritinib arm at PD sites: Hour 0 (predose)
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.12 End of Week 36, Study Day 252 (± 7 d), and Every 12 Weeks Thereafter

- *JAK2V617F* mutation status (patients with mutation at screening)
- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue patient-reported symptoms on MPN-SAF TSS 2.0
- Continue pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Dispense pacritinib
- Pacritinib accountability
- Serum pregnancy test, if mandated as a country-specific requirement
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.13 Termination of Study Treatment (up to 7 days after completion of all study drug treatment)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiration rate, body temperature, and body weight
- Physical examination, including spleen measurement
- ECOG performance status
- Hematology
- Serum chemistry
- MRI or CT scan (without contrast) to assess spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Patient-reported symptoms on MPN-SAF TSS 2.0
- Pain medication log
- Patient global impression assessment
- EORTC-QLQ-C30 version 3
- EQ-5D-5L
- Pacritinib accountability
- AEs
- Concomitant medications
- Record all BAT treatments
- Transfusion history
- Assess for leukemic transformation

7.4.14 Post-Termination (30 ± 3 days after study treatment termination)

- AEs: Last time point for collection and follow-up of nonserious AEs and SAEs deemed not related to study treatment or procedures. Please refer to Follow-up section for more details.
- Concomitant medications

7.4.15 Follow-up

SAEs assessed as related to study treatment or study procedures will be collected from the time of signing informed consent through the patient's last day of study participation, and followed until the event resolves, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever comes first. SAEs assessed as unrelated to study drug or study procedures and non-serious AEs will be collected from the time of signing informed consent through the last day of study participation and followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.

Patients will be followed for survival and for transformation to AML (as assessed by investigator, investigator-obtained records, or if not available, by patient-provided history) until 3 years after the **first** of the following time points:

- Week 24 visit
- Date of last treatment with initially assigned study drug

8 Pharmacokinetic Analysis and *JAK2* Mutation Burden

8.1 Blood Sample Collection, Handling, and Shipping

Blood samples for PK and *JAK2* mutation burden analyses should be collected in appropriate blood collection tubes as defined in the study manuals. On the days when blood samples for PK analysis are collected, patients should be instructed not to take pacritinib at home. The time/date when the prior dose was administered must be recorded on the appropriate CRF page. At minimum, tubes are to be labeled with the patient number, study number, and specimen identification number.

The sponsor will provide the investigator with a manual containing details for the preparation of blood samples to be collected. Shipment and analysis instructions will be provided to the investigator in a separate manual.

8.2 Pharmacokinetic, Pharmacodynamic, and *JAK2* Mutation Burden Assessments

Blood samples for PK and PD analyses will be collected predose and postdose on the specified study days for patients in the pacritinib arm per the two prespecified subsets of the clinical sites.

Blood samples will be collected for central analysis of *JAK2V617F* mutation burden in all patients at screening, and then only in mutation-positive patients at subsequent time points.

9 Assessment of Safety

9.1 Adverse Events

9.1.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Examples of AEs include, but are not limited to:

- Any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, medical diagnosis, or concomitant disease temporally associated with the use of the study drug, whether considered related to study drug or not
- Abnormalities observed during the study that meet any of the criteria below
  - Any laboratory or other test result that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring
  - Requires discontinuation, dose reduction, or delay of study drug
  - Requires that the patient receive specific corrective or supportive therapy
  - Clinically significant changes noted during physical examinations, ECGs, imaging studies, biopsies, and other safety assessments, whether or not these procedures were required by the protocol

Progressive disease is not an AE, unless it is the primary cause of death. If the primary cause of death is progressive disease, the primary AE term should be reported as “progressive myelofibrosis.” Signs and symptoms associated with disease progression may be recorded as secondary AE terms.

9.1.2 Reporting Adverse Events

All baseline conditions and AEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation.

For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported; AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of the patient, or may be detected through a clinically meaningful procedure. To prevent bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

The following information should be captured for all AEs: date of onset and resolution, severity per Common Terminology Criteria for Adverse Events (CTCAE), seriousness, the investigator's assessment of relationship to study drug, event outcome, and action taken with study medication due to the reported event. If concomitant treatment is given for the AE, this information should be captured on the appropriate eCRF. If the AE is an abnormal local laboratory value or test result, this information should also be captured on the appropriate eCRF.

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF and symptoms of the illness or disorder should not be reported as separate AEs with the exception of progressive disease, as discussed above. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting investigator (eg, "anemia" versus "low hemoglobin value").

If an AE results in early termination of the patient's study treatment period, "AE" should be selected as the reason for discontinuation on the eCRF. However, if the AE that resulted in early termination was a sign or symptom of progressive disease, "progressive myelofibrosis" should be selected as the reason for discontinuation on the eCRF.

Special Considerations

- Elective procedures or routinely scheduled treatments are not AEs. However, any untoward medical event occurring during a prescheduled elective procedure or routinely scheduled treatment should be documented as an AE.
- Baseline conditions are not AEs; however, worsening of a baseline condition following study drug administration is an AE.
- Death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. However, sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

If progressive disease is the primary cause of death, the term "progressive myelofibrosis" should be reported as the AE term. All AEs ongoing at the time of death that are not the primary cause of death will remain not resolved on the eCRFs.

9.1.3 Criteria for Assessing Adverse Events

9.1.3.1 Severity

The term "severe" is a measure of intensity; a severe event is not necessarily serious.

The National Cancer Institute (NCI) CTCAE version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities identified as AEs. A copy of these criteria is provided in the study manual, however minor version updates (ie, 4.01, 4.02 and above) may be used at the discretion of the sponsor.

9.1.3.2 Relationship

The relationship of an AE to the study treatment(s) will be assessed using the guidelines described below. If an AE is deemed related to study treatment(s) (eg, for BAT) but the investigator cannot attribute the relationship solely to a single treatment, the investigator should indicate that the AE is related to all possible agents. Any AE for which there is no assessed causal relationship shall be assessed by the sponsor as related, and will require immediate follow up with the site to determine the investigator's assessment.

Definite

There is a reasonable causal relationship between the study treatment and the event, and the event occurred within a plausible time relationship to treatment administration, and the event cannot be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge.

Probable

There is reasonable causal relationship between the event and the study treatment, the event occurred within a plausible time relationship to treatment administration, and the event is unlikely to be attributed to the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event follows a clinically reasonable response on withdrawal of study treatment.

Possible

There is a reasonable causal relationship between the event and study treatment, the event occurred within a plausible time relationship to study treatment administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. Dechallenge information is lacking or unclear.

Unlikely

There is a temporal relationship of the event to study treatment but not a reasonable causal relationship, or there is no temporal relationship to study treatment administration or the condition under study, concurrent disease, other drugs or chemicals, or other circumstances provide a plausible explanation for the event.

Unrelated

There is no temporal relationship between the event and study treatment administration (study treatment given too early or late or study drug not administered). There is no reasonable causal relationship between the event and the study treatment. The condition under study, concurrent disease, other drugs or chemicals, or other circumstances provides a plausible explanation for the event.

9.1.3.3 Outcome

AEs will be characterized according to the outcomes described in Table--10

Table--10
Outcomes of Adverse Events

Outcome	Description
Recovered/Resolved	One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated
Recovered/Resolved with Sequelae	One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury
Recovering/Resolving	One of the possible results of an adverse event outcome that indicates the event is improving
Not Recovered/Not Resolved	One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated
Fatal	The termination of life as a result of an adverse event
Unknown	Not known, not observed, not recorded, or refused

9.1.3.4 Action Taken with Study Drug

Action taken with the study drug in relation to the AE will be characterized as follows:

- Dose increased
- Dose not changed
- Dose reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

9.1.4 Serious Adverse Events

9.1.4.1 Definition of a Serious Adverse Event

An SAE is an AE that, at any dose, suggests a significant hazard or side effect, regardless of its relationship to the study drug. An AE is serious if it meets any of the criteria below:

1 Results in death
2 Is life-threatening: in the view of the investigator, the event placed the patient at immediate risk of death. This does not include an AE that, had it occurred in a more severe form, might have caused death.

3 Requires inpatient hospitalization or prolongation of an existing hospitalization (see Exceptions below)

4 Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

5 Is a congenital anomaly/birth defect

6 Is an important medical event that is not fatal, life threatening, or requiring hospitalization, but may be considered serious if, based on appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above (1 - 5)

7 Cancer/overdose: All cases of new cancers, with the exception of disease progression/transformation to acute myeloid leukemia, and drug overdose (defined as accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. Determination of seriousness will be reached in consultation with the Safety Physician, CTI Global Pharmacovigilance US Headquarters or designee.

9.1.4.2 Exceptions

Hospitalizations not reported as SAEs include admissions for:

1 Planned, nonlife-threatening medical/surgical procedures

2 Routine health assessments requiring admission for health status documentation (eg, routine gastroscopy, colonoscopy, etc)

3 Other life circumstances that have no bearing on health status and require no medical/surgical intervention (eg, lack of housing, family circumstances, etc.)

4 Administration of study medication

9.1.4.3 Reporting Serious Adverse Events to the Sponsor

AEs and SAEs will be collected during the clinical trial from the time the subject signs the informed consent through the subject's last day of study participation. All SAEs, irrespective of causal relationship, must be recorded on a paper SAE Report Form and reported to the Sponsor within 24 hours of becoming aware of the event via either Fax or e-mail.

Fax (US Only): 1-508-416-2654 Fax (outside the US): +44 870 7107157 Email: safety@aptivsolutions.com

Special Considerations:

- SAEs considered to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the investigator or Sponsor shall be followed until the event resolves, stabilizes or the patient is lost to follow up.
- SAEs assessed as unrelated to study drug or study procedures shall be followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.
- For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported.
- All SAEs for randomized patients must have a corresponding AE recorded on the eCRF with an exact match to the event term or description.

- An SAE form should be completed for any event for which doubt exists regarding its seriousness.
- If an ongoing SAE changes in intensity, relationship to study drug, or as new information becomes available and/or known for the event, a follow-up SAE Report form should be completed and sent to the Sponsor within 24 hours of the change in SAE assessment.
- Any SAE that occurs after study completion and is considered by the investigator to be related to pacritinib should be reported to the sponsor.

A narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted by revising the SAE Report Form as soon as the information becomes available.

Source documents should be submitted only in English. If source documents are not in English, the investigator must summarize the source documents and provide a complete English narrative that includes a description of the event as it evolved the results of all diagnostic procedures performed and treatments administered, and the outcome of the event.

9.1.4.4 Reporting Serious Adverse Events to the Regulatory Agencies, Institutional Review Boards and/or Ethics Committees

The Sponsor will evaluate reported SAEs for expedited reporting as assessed against the most current approved version of the Investigator Brochure for pacritinib SAEs, or against the local Summary of Product Characteristics (SPC) for BAT SAEs. If a brand name for a BAT product is unknown or unavailable, the SPC of the local market leader will be used to assess the suspect product(s) for regulatory reporting purposes. Until an AE is identified in the Reference Safety Information of the IB or SPC, it is considered unexpected, regardless of whether the AE has been submitted previously as an expedited report.

Expedited reporting will be performed by the Sponsor in accordance with local regulation.

Upon receiving an expedited report, the investigator must review and retain the notice with the Investigator Brochure and shall be responsible for submitting expedited reports to their IRB/EC in accordance with institutional guidelines. Regardless of institutional guidelines, investigators shall submit expedited reports to their IRB/EC in the event that the sponsor identifies an expedited report to represent a new and/or unforeseen risk.

In support of required progress reports, the Sponsor will provide the investigator and/or Ethics Committee with a summary of all SAEs reported for the study at predefined intervals (e.g. quarterly) and/or upon request.

Pregnancy

Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment and/or within one month of ending treatment even if the subject is withdrawn from study, this must be reported to the Sponsor immediately on the Pregnancy Reporting Form. The investigator must obtain written authorization (medical records release) from a female partner of a male subject prior to obtaining follow-up.

The investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcome. All pregnancy outcomes will be recorded on the Pregnancy Report Form.

Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will also be recorded in the AE eCRF and on the SAE Report Form. The associated SAE Report Form should be sent to the Sponsor per the procedure and timelines described within Section 9.1.4.3, Reporting Serious Adverse Events to the Sponsor.

Overdose

Overdose is defined as any deviation from the defined or prescribed use of study drug as applicable for the drug and trial design. Occurrences of overdose should be reported to the sponsor on an SAE Report Form. Reports of overdose will be evaluated on a case by case basis. Additional instructions for reporting overdose information will be provided by the Sponsor in the study binder.

Deaths

All deaths that occur during the study must be recorded on the appropriate eCRF. As described in Section 9.1.2 and 9.1.3.1, death alone is not considered an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. Progressive disease is not an AE, except when it is a cause of death. When progressive MF is a cause of death, it should be reported as an AE and SAE as per above.

Sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

9.2 Laboratory Evaluation

All scheduled clinical laboratory test values collected as part of the study will be evaluated by a central laboratory.

The investigator may use local or central laboratory evaluations (as dictated by local standards of care) to facilitate real-time decisions about study treatment administration, eligibility, and dose modifications and for evaluation of signs and symptoms. If any AE is identified, or clinical intervention results from local laboratory tests, the test result and local laboratory normal ranges for that test will be reported on the appropriate eCRF.

Treatment decisions (such as dose delays) and adverse events may be based on either local or central laboratory results.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central lab or independent review panel for study purposes, treatment decisions must be made by the investigator based on his or her clinical assessment of the patient and his or her interpretation of local labs, radiology assessments, and other tests.

9.3 Vital Signs and Physical Examination

Vital signs will be obtained at each study visit. Physical examinations are performed at screening, baseline, every 12 weeks thereafter, and at study termination.

9.4 ECOG Performance Status

ECOG performance status will be assessed at each visit (Appendix 8).

9.5 Safety Surveillance

An IDMC will meet periodically throughout the study (eg, every 6 months), or as described within the IDMC Charter, to review accumulating safety data from the entire clinical trial.

10 Data Management

The CTI Clinical Data Management Department or its designee will prepare guidelines for data entry and data handling, which will include procedures for data verification and electronic edit checks. The complete data management process will be described in the Data Management Plan.

10.1 Data Collection

An electronic data capture (EDC) system will be used for this study. Designated site personnel will enter subject data required by the protocol into eCRFs based on source documents. Personnel will not receive access to the EDC system until they have completed all training requirements. The EDC system will provide an automatic audit trail of all changes made to the clinical database.

10.2 Data Entry and Quality Control

Data items will be entered directly from source documents by designated site personnel using single data entry. Concomitant medications entered into the database will be encoded using the World Health Organization (WHO) Drug Reference Dictionary. AEs, coexisting disease, and other data items will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in a database system maintained by the central vendor. If clinical intervention is performed on the basis of any local laboratory test result, the test result and local laboratory normal ranges will be entered into the EDC system.

CTI staff or designees will review the data on a periodic basis to ensure validity, accuracy and completeness. Data suspected to be discrepant or incomplete will be questioned using data queries. Data queries resulting from these reviews will be sent to the study sites via the EDC system. The staff at the study sites will respond to the queries in the EDC system and these responses will be reviewed by CTI staff or designee. Only data that do not unblind the Sponsor will be reviewed by the Sponsor.

11 Statistical Analysis Plan

Statistical analysis of the study data will be the responsibility of CTI Biostatistics Department or its designee. This section describes the statistical methodology used in the primary analysis of the co-primary endpoints. Analysis of the exploratory endpoints and other supportive, sensitivity, or subgroup analyses will be specified in a separate statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of the clinical database.

11.1 Endpoints

11.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of the study are:

- the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT and,
- the proportion of patients with a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

11.1.2 Exploratory Endpoints

The exploratory endpoints are:

1 Overall survival (OS)
2 Progression-free survival (PFS)
3 Leukemia-free survival (LFS)
4 Time to achievement of ≥35% reduction in spleen volume from baseline by MRI or CT
5 Duration of maintenance of ≥35% reduction from baseline in spleen volume
6 Best response in spleen volume by MRI or CT
7 Duration of treatment
8 Achievement of red blood cell (RBC) transfusion independence (Appendix 1a)
9 Achievement of reduced RBC transfusion dependence (Appendix 1a)
10 Clinical improvement in hemoglobin level (Appendix 2)
11 Frequency of RBC transfusions
12 Achievement of platelet transfusion independence (Appendix 1b)
13 Clinical improvement in platelet count (Appendix 2)
14 Frequency of platelet transfusions
15 Change in *JAK2V617F* allele burden
16 Quality of life, as measured by the EQ-5D-5L (Appendix 3) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0 (Appendix 4).

Details for the definition and analysis of the exploratory endpoints are provided in the Statistical Analysis Plan.

11.2 Hypotheses

11.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in:

- a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and
- a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0

than treatment with BAT.

11.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

11.3 Analysis Populations

11.3.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. This population will be used for the primary analysis of the efficacy endpoints.

11.3.2 Evaluable Population

The evaluable population for each endpoint is defined as all randomized patients who have an evaluable baseline and follow-up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for the supportive analyses of the efficacy endpoints.

11.3.3 Per-Protocol Population

The per-protocol (PP) population is defined as all randomized patients who receive any study treatment, have a baseline assessment, complete relevant follow-up assessments, and have no major protocol violations. Patients in this population will be analyzed according to the treatment actually received. The PP population will be used for the supportive analyses of the primary efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

11.3.4 Safety Population

The safety population is defined as all randomized patients who receive any dose of study treatment. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received.

11.3.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK, plasma

PD markers or STAT3 phosphorylation analysis. The study pharmacokineticist will review data listings of patient dosing and sample records to identify patients with appropriate samples for the analysis.

11.4 Efficacy Analysis

Efficacy analyses including all hypothesis testing will be performed after the last patient completes the Week 24 assessments or experiences progressive disease, whichever comes first. Analysis of long-term safety and efficacy will be performed as supportive analyses as specified in the Statistical Analysis Plan.

11.4.1 Reduction in Spleen Volume

The primary analysis of the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT will be based on the IRF assessments. The analysis will be performed using the ITT population. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be presented by the 3 treatment arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression or drop out of the study before Week 24 will be considered to have not achieved the ≥35% reduction. The numbers and percentages for each reason for not achieving the ≥ 35% reduction will be presented by treatment arm. The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the appropriate confidence intervals based on the Agresti-Caffo method will be provided.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by geographic region (US, Canada, Europe, and rest of the world [ROW]), risk category (intermediate-1 versus intermediate-2 versus high-risk) and by rebound platelet count (≤ 100,000/μL versus > 100,000/μL). The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata.

The primary analysis will be repeated using other post-baseline reduction in spleen volume (Week 12, Week 36, and Week 48). The mean or median reduction in spleen volume over time will be evaluated. More details will be provided in the SAP.

11.4.2 Improvement in Total Symptom Score

All the analyses outlined in Section 11.4.1 will be repeated using the proportion of patients with a ≥ 50% reduction from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

The TSS endpoint is obtained as follows:

- The daily TSS is the sum of the individual symptom scores for tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side. Daily TSS is set to missing if one of these individual symptom scores is missing.
- The baseline TSS is the mean of the daily TSS over the 7 consecutive days immediately prior to randomization. Baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to randomization.
- The Week 24 TSS is the mean of the daily TSS over the 28 consecutive days prior to the Week 24 visit. The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to the Week 24 visit. Patients with a missing Week 24 TSS, including those

who meet the criteria for disease progression or drop out of the study before Week 24, will be considered to have not achieved the ≥ 50% reduction.

- The percent reduction in TSS from baseline to Week 24 is then computed by:

$$\text{TSS \% Reduction} = \left(\frac{\text{Week 24 TSS} - \text{Baseline TSS}}{\text{Baseline TSS}}\right) * 100$$

A sensitivity analysis will be conducted using the average of the 7 daily TSS prior to the Week 24 visit as the Week 24 TSS. The details of the analysis will be described in the SAP.

In addition, exploratory analyses of the correlation of Week 24 TSS with Week 24 spleen size, STAT3 phosphorylation, and patient global impression assessment will be performed. Details are provided in the SAP.

11.4.3 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1 The primary hypothesis will be tested at $\alpha = 0.05$ (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on:
   a. the difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24, and
   b. the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24

   individually.

   The study reaches its primary objective (claimed to be successful) when both endpoints reach statistical significance ($\alpha = 0.05$, 2-sided).

2 If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in a) the QD arm versus the BAT arm and b) the BID arm versus the BAT arm at the 2-sided 0.025 α-level.
   a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be tested at a 2-sided $\alpha = 0.025$.
   b. If the p-value is less than α, the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24 will be tested at a 2-sided $\alpha = 0.025$.

11.5 Safety Analysis

The assessment of safety will be based mainly on the frequency of AEs and the number of laboratory values that fall outside of predetermined ranges.

Treatment-emergent AEs will be coded using MedDRA version 16.0 and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients with an event. The following subsets of treatment-emergent AEs will also be summarized by treatment arm: AEs related to study treatment, CTCAE grade 3 or 4 AEs, AEs leading to treatment discontinuation, deaths, and SAEs. Ongoing AEs in patients who cross over to pacritinib will be assessed at the time of the crossover, and the CTCAE grade at the time of crossover will be considered the new baseline.

Clinical laboratory data will be summarized with descriptive statistics by treatment and timepoint. Each patient's data will be classified by the CTCAE grade, where possible, and be summarized in shift tables comparing the worst post-baseline visit to baseline.

11.6 Determination of Sample Size

A sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. Based on previous studies, it is assumed that the proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24 is 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. It is also assumed that the proportion of patients achieving a ≥ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm.

For primary hypotheses (pooled QD/BID vs BAT), a sample size of 300 patients provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for the secondary hypothyses testing independently; i.e., comparing QD pacritinib arm with the BAT arm and comparing the endpoint in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is ≥ 93% power to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

11.7 Interim Analyses

No interim analyses are planned for this study.

12 Pharmacokinetic and Pharmacodynamic Analyses

The PK parameters will be summarized with descriptive statistics. The relationship between exposure and the efficacy and safety of pacritinib will be evaluated. Population PK analysis will be performed.

13 Independent Data Monitoring Committee

An IDMC will be chartered to monitor and evaluate the safety of all patients in this trial. The IDMC will periodically review summaries of trial data, including all safety data, identifying any clinically relevant trends, and making recommendations as to whether the study should continue. The IDMC Charter will include operational and logistical procedures for the IDMC.

14 Study Administration and Investigator Obligations

For studies conducted outside the United States under a US IND, the principal investigator must comply with US FDA IND regulations and with those of relevant national and local health authorities.

14.1 Study Drug Accountability

CTI BioPharm Corp. will provide pacritinib. The recipient will acknowledge receipt of the drug by returning the appropriate shipping receipt form according to the study-specific pharmacy manual. Damaged supplies will be replaced.

Accurate records of all pacritinib dispensed from and returned to the study site should be recorded by using the Drug Inventory Log (refer to study-specific pharmacy manual).

Pacritinib will be disposed of at the study site according to institutional standard operating procedures after study monitors have completed the drug inventory reconciliation. The method of destruction must be documented. A copy of the destruction certification along with the inventory of destroyed clinical material will be provided to CTI BioPharma Corp.

14.2 Informed Consent

CTI BioPharma Corp. will provide a sample ICF to each site. CTI BioPharma Corp. or its designee must review any proposed deviations from the sample ICF. Patients must be re-consented to the most current version of the ICF during their participation in the study. The investigator must provide the final local IRB/REB/IEC approved informed consent form to CTI BioPharma Corp. for regulatory purposes.

The patient or the patient's legally authorized representative must sign the ICF before his or her participation in the study. The source record for each patient shall document that informed consent was obtained prior to participation in the study. A copy of each signed ICF or Addendum to an existing ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed consent forms must remain in each patient's study file and must be available for verification by the study monitor at any time.

14.3 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, CTI BioPharma Corp., its designees and the IRB/IEC/REB for each study site, if appropriate.

14.4 Case Report Forms

CTI BioPharma Corp. will provide eCRFs, which should be completed in accordance with instructions from CTI BioPharma Corp.

14.5 Study Monitoring

Representatives of CTI BioPharma Corp. or their designee must be allowed to visit all study site locations at appropriate intervals to assure compliance with Good Clinical Practice (GCP), satisfactory enrollment

rate, data recording, and protocol adherence. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The investigator agrees to cooperate with the monitor to ensure any problems detected in the course of these monitoring visits are resolved. In addition to these visits, CTI BioPharma Corp. will routinely monitor each site by phone to keep abreast of patient status and to answer questions.

In order for the investigator to participate in this trial, the trial monitor must have direct access to source data for data verification. This will be done by comparing data from the eCRFs with data from the patient's clinic or hospital records (permission will be sought from the patient as part of the consent process).

In addition, CTI BioPharma Corp. internal auditors and government inspectors may evaluate the study. They must be allowed access to eCRFs, source documents, and other study files. CTI BioPharma Corp. audit reports will be kept confidential.

The investigator should promptly notify CTI BioPharma Corp. of an audit scheduled by any regulatory authority, and promptly forward copies of audit reports.

14.6 Record Retention

US FDA regulations (21CFR§312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that the principal investigator retain records and documents pertaining to the conduct of the study and distribution of investigational drug, including eCRFs, consent forms, laboratory test results, radiographic assessments, and medication inventory records for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. CTI BioPharma Corp. will notify the principal investigator of these events.

No records should be disposed of without the written approval of CTI BioPharma Corp.

15 Ethics

15.1 Good Clinical Practice

The investigator and sponsor will ensure that this study is conducted in full compliance with Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines, US FDA regulations 21 CFR Parts 50, 56, and 312, and with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient.

15.2 Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC)

The appropriate IRB, REB, or IEC must approve in writing the protocol and ICF for this study in accordance with the laws and regulation of the country in which the research is conducted prior to any patient being registered in this study.

Before the investigational drug will be shipped to the investigator, the investigator must provide CTI BioPharma Corp. with a copy of the IRB or REB or IEC approval letter stating that the study protocol and informed consent form have been reviewed and approved. Original US FDA Form 1572 (for all studies

conducted under US IND regulations) signed by the principal investigator, and a copy of the CV for the principal investigator, and a copy of an IRB/REB/IEC approved informed consent form are also required.

The investigator must also report all serious and medically significant AEs to the IRB/REB/IEC according to the local regulation.

Appendix 13 lists the responsibilities of the investigator.

16 Termination of Study

CTI BioPharma Corp. will retain the right to terminate the study and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory enrollment with regard to quality or quantity
- Deviations from GCP
- Deviation from protocol requirements, without prior approval from CTI BioPharma Corp.
- Inaccurate and/or incomplete data recording on a recurrent basis
- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

In terminating the study, CTI BioPharma Corp. and the investigator will assure adequate consideration to the protection of the patients' interest.

17 Study Amendments

Changes in any portion of this protocol must be documented in the form of an amendment from CTI BioPharma Corp. and must be approved by the site's IRB/REB/IEC before the amendment can be implemented at the site. The IRB/REB/IEC chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions.

18 Use of Information and Publication

CTI BioPharma Corp. recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The Clinical Study Agreement will describe the details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial.

19 References

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Appendix 1a - Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	$\geq$ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al, 2011	

Appendix 1b – Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

Appendix 2 - International Working Group Consensus Criteria for Treatment Response in Myelofibrosis with Myeloid Metaplasia

Clinical Improvement	
Hemoglobin	A minimum 20g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100g/L) for 8 weeks or more
Platelet count	A minimum 100% increase in platelet count and an absolute platelet count of at least 50,000/μL (applicable only for patients with baseline platelet count below 50,000/μL) for 8 weeks or more
Tefferi et al 2006	

Appendix 3 - EQ-5D-5L Health Questionnaire

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

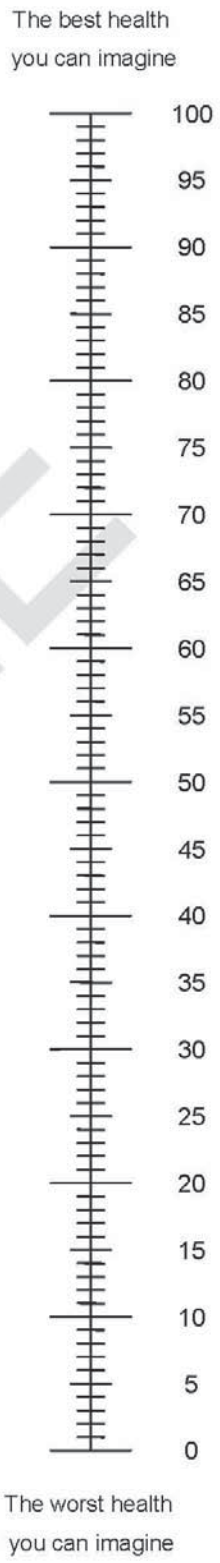
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



3

Appendix 4 - EORTC QLQ-C30 Version 3

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

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

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5 - Dynamic International Prognostic Scoring System in Primary Myelofibrosis (Passamonti et al, 2010)

Prognostic Variable	Value		
	0	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, x 10^9/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

Risk Category	
Low	0
Intermediate-1	1-2
Intermediate-2	3-4
High	5-6

Appendix 6 - Diagnostic Criteria for Primary Myelofibrosis, Post-Polycythemia Myelofibrosis and Post-Essential Thrombocythemia Myelofibrosis

	Major Criteria	Minor/Additional Criteria
Primary myelofibrosis (PMF) Diagnosis requires meeting all 3 major criteria and at least 2 minor criteria[1]	1. Megakaryocyte proliferation and atypia[3] accompanied by either reticulin and/or collagen fibrosis **or** 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) 2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm 3. Demonstration of JAK2V617F or other clonal marker **or** No evidence of reactive marrow fibrosis	1. Leukoerythroblastosis 2. Increased serum LDH 3. Anemia 4. Palpable splenomegaly
Post-polycythemia vera myelofibrosis (PPV-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5cm (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 degrees C)
Post-essential thrombocythemia myelofibrosis (PET-MF) Diagnosis requires meeting both major criteria and at least 2 additional criteria[2]	1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1] 2. Bone marrow fibrosis grade 2-3 (on 0-3 scale)[4] or grade 3-4 (on 0-4 scale)[5]	1. Anemia[6] and a ≥2 mg ml^{-1} 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

	Major Criteria	Minor/Additional Criteria
		margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5 degrees C)

Abbreviations:
WHO - World Health Organization
MDS - myelodysplastic syndrome
CML - chronic myelogenous leukemia
LDH - lactate dehydrogenase

[1] Tefferi A, Vardiman, JW 2008
[2] Barosi G, Mesa RA, Thiele J, et al. 2008
[3] Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering
[4] Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain) (see WHO criteria)
[5] Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis (see WHO criteria)
[6] Below the reference range for appropriate age, sex, gender and altitude considerations

Appendix 7 – Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (Version 2.0)

Symptom	0 to 10 Ranking
Select the one number that describes the worst severity you have experienced with each of the following in the past 24 hours:	
Tiredness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Pain under ribs on the left side	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix 8 - Eastern Cooperative Oncology Group Performance Status Scale Grade Description (Oken et al 1982)

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 9 - Selected Potent Inhibitors of CYP3A4

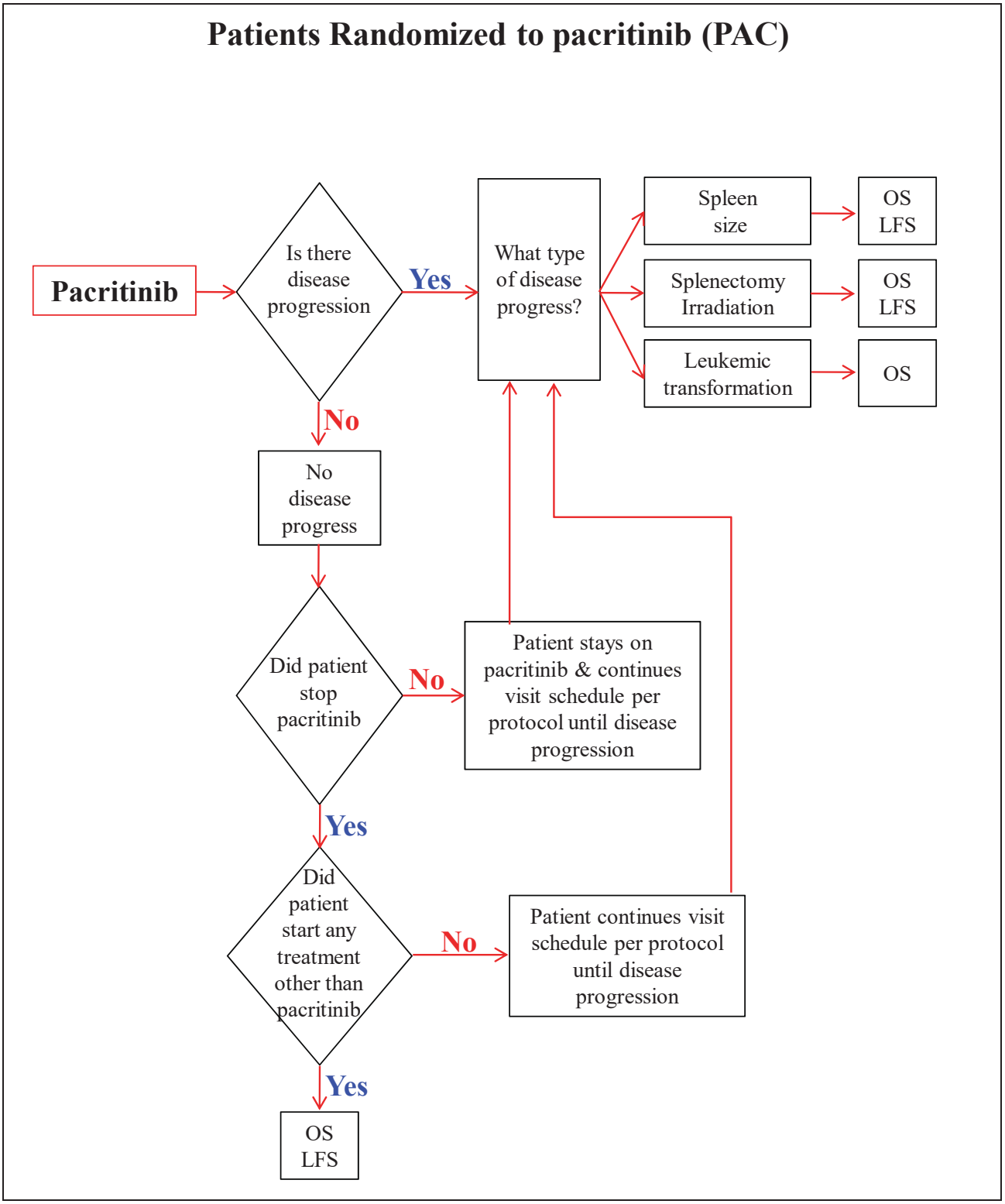
boceprevir	nefazodone
ciprofloxacin	nelfinavir
clarithromycin	norfloxacin
conivaptan	posaconazole
erythromycin	quinidine
fluconazole	ritonavir
grapefruit	saquinavir
grapefruit juice	Seville oranges
indinavir	star fruit
itraconazole	telaprevir
ketoconazole	telithromycin
lopinavir	troleandomycin
mibefradil	voriconazole
This list is not comprehensive. When considering using an agent that could be a potential CYP3A4 inhibitor/inducer, please discuss this with the medical monitor. Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://wwwpharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.	

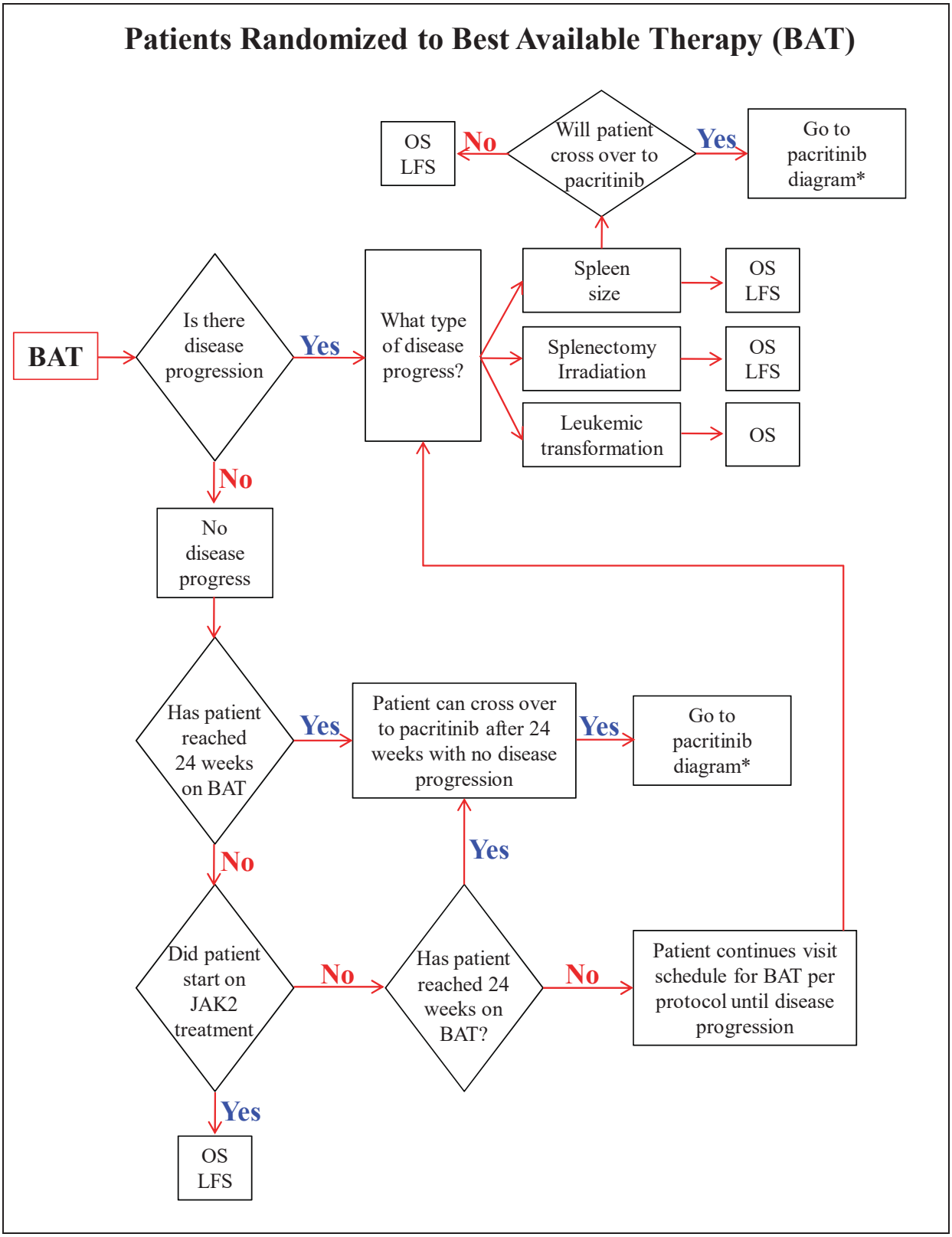
Appendix 10 - The Stages of Heart Failure, New York Heart Association (NYHA) Classification

To determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
Source: Dolgin et al.	

Appendix 11 – Study Flowchart




Patients Randomized to Best Available Therapy (BAT)
BAT
Is there disease progression
Yes
No
What type of disease progress?
Spleen size
Splenectomy Irradiation
Leukemic transformation
OS LFS
OS LFS
OS
Will patient cross over to pacritinib
No
Yes
OS LFS
Go to pacritinib diagram*
No disease progress
Has patient reached 24 weeks on BAT
Yes
No
Patient can cross over to pacritinib after 24 weeks with no disease progression
Yes
Go to pacritinib diagram*
Yes
Did patient start on JAK2 treatment
No
Has patient reached 24 weeks on BAT?
No
Patient continues visit schedule for BAT per protocol until disease progression
Yes
OS LFS

Appendix 12 - Common Terminology Criteria for Adverse Events: Diarrhea (Version 4.03)

Definition: A Disorder Characterized by Frequent and Watery Bowel Movements.	
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Appendix 13 - Responsibilities of the Investigator

For a complete list of investigator responsibilities refer to the ICH guideline for GCP, Section 4.0; *Investigator*. The responsibility of the investigator includes but is not limited to the following criteria:

1. To provide the qualifications of the investigator(s) by Curriculum Vitae and/or other documentation to the sponsor or regulatory authorities upon request.
2. To be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator Brochure, in the product information, and in other information sources provided by the sponsor.
3. To comply with GCP and applicable regulatory requirements.
4. To permit monitoring and auditing by the sponsor, access to all relevant trial documents, and inspection by appropriate regulatory authorities.
5. To maintain a list of qualified persons to whom the investigator has delegated significant trial-related duties.
6. To be able to demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.
7. To have sufficient time to properly conduct and complete the trial within the agreed trial period.
8. To have available adequate facilities and qualified staff to conduct the trial properly and safely for the foreseen duration of the trial, and to ensure that other trials do not divert essential patients or facilities away from the trial.
9. To ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
10. To ensure that adequate medical care is provided to a patient for any adverse experiences, related to the trial, during and following his/her participation in a trial.
11. To inform a patient when medical care is needed for inter-current illness of which the investigator becomes aware.
12. To inform (if possible) the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.
13. To secure written and dated IRB/IEC/REB approval prior to initiating a trial for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements), and any other written information to be provided to patients.
14. To provide the IRB/IEC/REB with all trial-relevant documents for review.
15. To conduct the trial in compliance with the protocol as approved by the IRB/IEC/REB and agreed to by the sponsor and applicable regulatory authorities.
16. To sign the protocol (with the sponsor), or an alternative contract, to confirm their agreement on conducting the trial.
17. To not implement any deviation from, or changes of, the protocol without agreement by the sponsor and approval from the IRB/IEC/REB of an amendment, except where necessary to eliminate an immediate risk to trial patients, or when the changes involve only logistical or administrative aspects of the trial, and to document and explain any such deviations. If a deviation or change in the protocol was implemented by the investigator to eliminate an immediate hazard(s) to patients without prior IRB/IEC approval/favorable opinion; the deviation (and reason for) or proposed change must be submitted as soon as possible:
    - To the IRB/IEC/REB for review and approval/favorable opinion;
    - To the sponsor for agreement and, if required;

- To the regulatory authority(ies).

18. To assume full responsibility for investigational products at the trial site (whether through personal supervision or through assignment of these duties to a qualified health care professional). This includes responsibility for usage, accountability (including all necessary documentation), storage and handling, instruction and supervision of any personnel authorized in the usage of the investigational product, and disposition of supplies upon completion of the trial.
19. To follow all randomization procedures and protect the integrity of the blind (if used). In the event of premature unblinding in a blinded trial, the investigator is to promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse experience) of the investigational products.
20. To ensure that the confidentiality of all information about patients and information supplied by the sponsor is respected by all persons involved in the trial.
21. In regards to data collection and management:
    - To collect and record data properly and ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports;
    - To ensure that data reported on the eCRFs, which are derived from source documents, are consistent with the source documents, and that all discrepancies are explained;
    - To follow the sponsor's guidance in making changes or corrections to eCRFs;
    - To maintain the essential trial documents as required by the applicable regulatory requirements, until notification by the sponsor.
22. To provide all requested reports or notification of changes affecting the conduct of the trial, and/or increasing the risk to patients to the sponsor, IRB/IEC, investigative institution, or applicable regulatory agency.
23. To report all deaths, serious adverse experiences, adverse experiences and laboratory abnormalities to the sponsor according to the procedures specified in the protocol.
24. To promptly inform the trial patients in the event that the trial is terminated prematurely or suspended for any reason, and to provide appropriate therapy and follow-up procedures. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator is to inform the institution, where required by the applicable regulatory requirements, and the investigator/institution is to promptly inform the sponsor and the IRB/IEC, and provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
25. To promptly notify the sponsor and investigative institution (with detailed written explanation) of any change or retraction of IRB/IEC approval, where applicable.
26. To provide, upon completion of the trial, all required reports and/or summaries to the sponsor, the IRB/IEC and applicable regulatory authorities.

Study PAC326 (PERSIST-2)

Statistical Analysis Plan

Version: 1.0
May 19, 2016

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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1 Scope

This document describes the statistical analyses and data presentations to be performed for protocol PAC326, "A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis".

This statistical analysis plan (SAP) provides a detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of pacritinib in the scope of the study. It provides additional details concerning the statistical analyses that were originally outlined in the protocol. This SAP will be finalized and signed prior to the unblinding of the clinical database. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post hoc in the clinical study report.

Due to the United States Food and Drug Administration (FDA) full clinical hold on February 8, 2016 when all patients were required to discontinue pacritinib, the following modifications have to be made to the originally planned analyses specified in the protocol:

- All analyses of all efficacy and safety endpoints will take place after the last patient completes the 30-day Post Treatment Termination assessments instead of the Week 24 assessments.
- Many patients were not given the opportunity to reach Week 24 for outcome assessment with the implementation the clinical hold. The Full Analysis Set (FAS) will be used to evaluate the study objectives instead of the intent-to-treat (ITT) population. The FAS includes all randomized patients who had an opportunity to reach Week 24 for outcome assessments. Details are outlined in section 5.2.
- There will be no long term follow up for efficacy and safety. Therefore, there are limitations to the evaluation of all time to event endpoints (overall survival, progression-free survival, duration of response, etc.; sections 7.3 to 7.7) and endpoints evaluated over time due to the limitation of follow up.

2 Study Objectives and Hypotheses

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arms of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the

proportion of patients achieving a ≥ 50% reduction in the Total Symptom Score (TSS) from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

2.1.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.
2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.1.3 Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥ 35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of red blood cell (RBC) transfusion independence
9. Achievement of reduced RBC transfusion dependence
10. Clinical improvement in hemoglobin level
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence
13. Clinical improvement in platelet count
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life, as measured by the EQ-5D-5L and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0.

2.1.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on PD effect (i.e., pSTAT3 inhibition) and the safety and efficacy of pacritinib.

2.2 Hypotheses

The hypothesis tests described below are based on the full analysis set (section 5.2).

2.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in

1 a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and
2 a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0

than treatment with BAT.

2.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

3 Summary of Study Design

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two dose schedules of pacritinib, in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes “no treatment” and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF. Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter using the same imaging modality, through 48 weeks post randomization or until progression of disease or withdrawal from study treatment. TSS as measured by MPN-SAF TSS 2.0 will be recorded daily through 48 weeks post treatment initiation or until end of study treatment, whichever occurs first.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints for 3 years after their Week 24 visit or the end date of treatment with the initially assigned study drug, whichever comes first.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

4 Randomization and Blinding

Randomization will be stratified by geographic region (US vs. Canada vs. Europe vs. rest of the world [ROW]), the risk category (intermediate-1 vs. intermediate-2 vs. high risk per Passamonti et al. 2010) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). To be included in the > 100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count > 100,000/μL and 2) > 50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The most recent platelet count obtained prior to randomization on Days -3 to 1 during the screening period will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization.

Although this is an open label study, the double-blind procedure was followed in-house (see the PERSIST-2 Study Blinding Plan). The clinical database will be unblinded after data review has been completed, protocol violations have been identified, the data have been declared clean, and this SAP has been signed off.

5 Analysis Populations and Approaches to Analysis

5.1 Full Analysis Set

The full analysis set (FAS) is defined as all randomized patients who had an opportunity to reach Week 24 for outcome assessments. As the clinical hold occurred on February 8, 2016, patients randomized on or after to September 7, 2015 would not have had this opportunity. Therefore, the FAS population will include patients randomized prior to

September 7, 2015. Patients in this population will be analyzed according to the arm to which they were assigned at randomization. This population will be used for the analyses of the efficacy endpoints as well as for the analyses of demographics, baseline characteristics, and medical history.

5.2 Evaluable Population

The evaluable population for each endpoint is defined as all patients in the FAS who have evaluable baseline and follow up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for the supportive analyses of the efficacy endpoints.

5.3 Per-protocol Population

The per-protocol (PP) population is defined as all patients in the FAS who receive any study treatment and have no major protocol violations. The major protocol violations that will exclude patients from the PP population are defined as follows:

- Did not meet one of the following inclusion criteria:
  - Inclusion 1: Intermediate-1 or -2 or High risk PMF, PPV-MF, or PET-MF
  - Inclusion 4: Palpable splenomegaly ≥ 5 cm below the LCM by physical examination
  - Inclusion 5: TSS ≥ 13 on the MPN-SAF TSS 2.0, not including the inactivity question
  - Inclusion 8: Peripheral blast count < 10%
  - Inclusion 12: At least 6 months from prior splenic irradiation
  - Inclusion 13: At least 12 months from prior ^{32}P therapy
  - Inclusion 15: At least 2 weeks since any treatment for PMF, PPV-MF, or PET-MF
- Did not meet one of the following exclusion criteria:
  - Exclusion 3: Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
  - Exclusion 6: History of splenectomy or planning to undergo splenectomy
  - Exclusion 10: Inflammatory or chronic functional bowel disorder such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
  - Exclusion 15: Erythropoietic agent within 28 days prior to randomization
  - Exclusion 16: Thrombopoietic agent within 14 days prior to randomization
- Patients in the pacritinib arms taking any of the BAT treatment options for treatment of MF.
- Visits scheduled outside the analysis window specified for baseline and Week 24 for the relevant endpoint.

Patients in the PP population will be analyzed according to the treatment actually received and their correct strata if there is mis-stratification. The PP population will be

used for the supportive analyses of the efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

5.4 Safety Population

The safety population is defined as all randomized patients who receive at least one dose of study treatment, including patients on the BAT arm treated with watchful waiting. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received. This population will also be used for analyses of demographics, baseline characteristics, and medical history.

5.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK or STAT3 phosphorylation analysis.

6 Demographics, Baseline Characteristics, and Medical History

6.1 Demographics and Baseline Characteristics

Descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum) will be provided for those variables measured on a continuous scale. The frequency distribution (counts and percentages (n and %)) will be provided for those variables measured on a nominal scale.

The demographic and baseline characteristics will be analyzed with the following variables in the full analysis set and the safety population.

6.1.1 Demographic Variables

Age, age category (< 65 years vs. ≥ 65 years), gender, race, ethnicity, height, weight, body mass index, ECOG performance status, and geographic region.

6.1.2 Baseline Disease Characteristic Variables

Spleen length by physical exam, bone marrow biopsy (cellularity, reticulin and collagen fibrosis staging, and myeloblast percentage), JAK2V617F status, baseline platelet count and category (< 50,000/μL vs. ≥ 50,000/μL), rebound platelet category, baseline hemoglobin and category (< 100 g/L vs. ≥ 100 g/L), current MF diagnosis, time since current MF diagnosis, non-bone marrow diagnostic criteria at initial MF diagnosis, current DIPSS risk category, transfusion history (within 90 days prior to Informed Consent date), red blood cell (RBC) transfusion dependence, platelet transfusion dependence, prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), prior treatment with ruxolitinib (yes vs. no), duration of prior treatment with ruxolitinib (< 6 months vs. ≥ 6 months), and most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day).

6.2 Prior Therapy and Medical History

Prior therapy and medical history are any therapy or diseases that occurred or any medication taken prior to the first day of study drug dosing or prior to the randomization date if patients were never dosed. Prior therapy includes both prior MF and non-MF therapies. Both will be summarized for patients in the full analysis set and the safety population.

For prior MF therapy, number of prior radiation therapies, type of prior radiation therapy, number of prior systemic medical therapy regimens, type of prior systemic medical therapies, and transfusion history for each cellular blood product will be summarized by the frequency distribution (n and %).

Prior non-MF therapies will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term using WHO Drug Dictionary version 01, March 2013.

Medical history will be summarized by frequency distribution (n and %) of system organ class and preferred term by MedDRA dictionary version 16.0 for patients in the full analysis set and the safety population. A listing of medical history will also be generated.

7 Efficacy Analysis

The efficacy and exploratory endpoints are defined below. Additionally, the planned analyses for these endpoints are described.

7.1 Reduction in Spleen Volume

The primary efficacy endpoint of the study is the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT based on independent radiology facility (IRF) reads. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 35% reduction. To test the primary and secondary hypotheses, the treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. These analyses will be performed in the full analysis set. The same analyses will be performed based on the evaluable and PP (if necessary) populations as supportive analyses. A sensitivity analysis may be performed using all randomized patients and using Bayesian methods to estimate the probability of Week 24 response in patients who did not have an opportunity to reach Week 24 due to the FDA clinical hold.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count (≤ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.
The proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to other post-baseline time points will be summarized as well. In addition, using the evaluable population, descriptive statistics of the percent change in spleen volume from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

The post-baseline spleen scan data used for all analyses will be the scans collected at the nominal post-baseline visit or Termination scans collected within 2 weeks (+/- 14 days) of the nominal study day which are also within 7 days of treatment termination. For example, Termination scans collected within 2 weeks (+/- 14 days) of study day 168 (nominal week 24 study day) will be considered the Week 24 scans if also collected within 7 days of treatment termination. Baseline scans are the scans collected at the screening MRI visit.

7.2 Improvement in Total Symptom Score

The secondary efficacy endpoint of the study is the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

7.2.1 TSS Algorithm

- **The daily TSS** is the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side.
- **The baseline TSS** is the mean of the daily TSS over the 7 consecutive days prior to the start of treatment. Please note that in the protocol, baseline TSS was defined relative to randomization date with the assumption that treatment would start at randomization. Missing values during these days are handled as described below (section 7.2.2).
- **The Week 24 TSS** is the mean of the daily TSS obtained during the 28 consecutive days prior to the Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Patients with a missing baseline or Week 24 TSS, including those who meet the criteria for disease progression before Week 24 and those who drop out of the study before Week 24, or patients who cross

over to treatment with pacritinib prior to Week 24 will be considered to have not achieved the ≥ 50% reduction. Events occurring prior to Week 24 occurred prior to study day 154.

- **The percent reduction in TSS from baseline to Week 24** is computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 24 TSS - Baseline TSS}}{\text{Baseline TSS}}\right) * 100.$$

Other post-baseline TSS and percent reduction from baseline are similarly defined, except that the post-baseline visit date alone is used as a point of reference at timepoints at which spleen volume is not assessed but a study visit is scheduled and nominal study day alone is used as a point of reference at timepoints at which a study visit is not scheduled. Only post-baseline symptom scores reported within 1 day of treatment termination will be used for analysis.

7.2.2 Handling of Missing Values

- If any of the seven individual symptoms scores are missing, the TSS for that day will be considered as missing.
- The baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to the start of study treatment.
- The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Missing TSS at other post-baseline timepoints is similarly handled.

7.2.3 Primary Analyses

The primary analysis of the improvement in TSS will compare the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24. The numbers and percentages of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. The same analyses will be performed based on the evaluable and PP populations as supportive analyses.

7.2.4 Secondary Analyses

The treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count (≤ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact CMH test will be used to test if

treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.
The same analyses will be repeated with the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to other post-baseline time points. In addition, using the evaluable population, descriptive statistics of the percent change in TSS from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

7.2.5 Exploratory Analyses

The percent change from baseline over time in individual symptom scores as measured by the MPN-SAF TSS 2.0 will be evaluated and descriptive statistics of the percent change in individual symptom scores from baseline over time will be presented. The individual symptom scores for each timepoint will be computed as the mean of the daily individual symptom scores obtained during the 28 days prior to that spleen volume scan date. The individual symptom scores at each timepoint will be considered missing if fewer than 20 daily individual symptom scores are available out of the 28 consecutive days prior to that timepoint.

The moving average of TSS will be evaluated as well. The TSS score for a timepoint will be computed as the mean of the 7 daily TSS prior to that timepoint. If fewer than 4 daily TSS are available out of the 7 days, the moving average TSS will be considered missing for that timepoint. A plot of the proportion of patients with a ≥ 50% reduction in TSS from baseline to each timepoint through Week 48 or initial treatment termination, whichever is earlier, will be presented by treatment arm.

The correlation of Week 24 TSS with Week 24 spleen volume and patient global impression assessment (as anchors) will be computed and tested for a significant difference from zero.

7.3 Overall Survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause. OS analysis is planned after long term follow up, i.e., 3 years after the last patient's Week 24 visit or their end date of treatment with the initially assigned study drug, whichever comes first. If a patient is alive or the survival status is unknown by the time of this analysis, survival will be censored at the date the patient was last known to be alive, regardless of whether patients crossed over to a pacritinib regimen from BAT. Though on treatment follow up is limited due to early termination of treatment resulting from the FDA hold and though there is confounding by crossover of BAT patients to a pacritinib regimen, OS will be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median survival time and the corresponding 95% confidence interval, and overall survival curves will be presented by arm. In addition, reasons for censoring will be summarized by arm. The impact of crossover will be evaluated by rank-preserving structural failure time (RPSFT) analysis (Robins and Tsiatis, 1991) and by separating BAT patients who crossover from those who do not.

Additionally, the effect of prognostic factors for MF on OS will be explored using Cox proportional hazards models.

7.4 Progression Free Survival (PFS)

PFS is defined as the time from the start of treatment to the date of progressive disease or death due to any cause (whichever is first reported). PFS will be based on disease progression assessment by the investigator using the definition below. The progression date is the earliest time when any progression is observed. Progression of disease is defined as one or more of the following: splenic progression (defined as in increase in splenic volume of ≥ 25% from baseline based on MRI or CT scan), splenic irradiation, splenectomy, or leukemic transformation (defined as an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%). Patients will be censored at the last progressive disease assessment date if they are alive with no documented progression before analysis. Patients who cross over during the study will be censored at the last assessment date prior to crossing over. Table 1 below provides the rules for progressive disease events and censoring for the primary analysis.

Table--1
PFS Event and Censoring Rules

	Situation	**Date of Event or Censoring**
PFS Event	Progression documented	Earliest date when any progression is observed
	Death	Date of death if no progression
Censor	No post-baseline disease progression assessments	Day 1
	No progression	Date of last progressive disease assessment with evidence of no progression
	Crossover from BAT to Pacritinib	Last progressive disease assessment date prior to the crossover date
	Lost to follow-up	Date of last progressive disease assessment showing no progression

The same analysis methods used for OS (section 7.3) will be used for PFS. Time to progression (time from the start of treatment to the date of progressive disease) may also be evaluated as an exploratory analysis.

7.5 Leukemia Free Survival (LFS)

LFS is defined as the time from the start of treatment to the date of leukemic transformation or death due to any cause. Leukemic transformation is defined as the first date of an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%. Patients will be censored at the date of last assessment for leukemic transformation if they are alive with no documented transformation before analysis. Patients who cross over during the study will be censored at the last assessment date prior to crossing over. Table 2 provides the rules for LFS events and censoring for the analysis of LFS.

Table--2 LFS Event and Censoring Rules		
	Situation	**Date of Event or Censoring**
LFS Event	Leukemic transformation documented	Earliest date when transformation is observed
	Death	Date of death if no leukemic transformation
Censor	No post-baseline disease progression assessments	Day 1
	No leukemic transformation	Date of last assessment with evidence of no leukemic transformation
	Crossover from BAT to Pacritinib	Last assessment date prior to the crossover date
	Lost to follow-up	Date of last assessment showing no leukemic transformation

The same analysis methods used for OS (section 7.3) will be used for LFS.

7.6 Time to Achievement of a ≥ 35% Reduction from Baseline in Spleen Volume

Time to achievement of a ≥ 35% reduction from baseline in spleen volume will be calculated as the time from start of treatment to the date of the first scan with a ≥ 35% reduction from baseline in spleen volume, that is: date of first ≥ 35% reduction – start of treatment date + 1. Patients will be censored at the last radiological assessment date if they have not yet achieved the ≥ 35% reduction from baseline in spleen volume by the Termination visit. The same analysis methods used for OS (section 7.3) will be used for time to achievement of a ≥ 35% reduction from baseline in spleen volume.

7.7 Duration of Maintenance of a ≥ 35% Reduction from Baseline in Spleen Volume

Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume is only defined for responders. The duration will be calculated in the following three ways:

1. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume per IRF assessment to the date of first documented evidence of no longer meeting the ≥ 35% reduction from baseline criteria, that is: duration = Day of < 35% reduction from baseline - Day of first ≥ 35% reduction + 1,
2. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 35% reduction from baseline and ≥ 25% increase from nadir, and
3. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 10% reduction from baseline.

Patients will be censored at the last radiological assessment date if they are alive with no documented loss of response before analysis. The same analysis methods used for OS (section 7.3) will be used for duration of spleen response.

7.8 Best Response in Spleen Volume

Best response in spleen volume is based on the percent change in spleen volume from baseline to any time during the study on initial treatment. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline at any time on study on initial treatment will be presented by treatment arm.

7.9 Percent Change in Spleen Length

Although it is not a study objective, the percent change in spleen length below the left costal margin from baseline will be evaluated as well. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from baseline to Week 24 will be summarized by treatment arm. Patients with a missing Week 24 spleen length, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 50% reduction.
The percent change in spleen length from baseline to post baseline visits will be evaluated as well. Descriptive statistics will be provided by treatment arm. Additionally, the correlation of percent change from baseline in spleen volume and the percent change from baseline in spleen length below the left costal margin will be evaluated.

7.10 Endpoints Relating to RBC Transfusion

A patient is defined as RBC transfusion independent at any time point if that patient had no RBC transfusion in at least 3 months (90 days) preceding that time point as per Gale et al. 2011. The patient is RBC transfusion dependent if, in the 3 months (90 days) preceding, they were transfused with ≥ 2 RBC units per month on average. RBC transfusion independence/dependence is indeterminate if they were transfused with between 0 and 2 RBC units per month on average in that surveillance period (Gale et al. 2011). See Table 3 below. The frequency of RBC transfusion is defined by the number of units of RBC transfused per month over a specific period of time. The analyses planned for endpoints relating to RBC transfusions are defined below.

Table--3
Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	≥ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al. 2011	

7.10.1 Achievement of RBC Transfusion Independence

Achievement of RBC transfusion independence is defined in patients who were RBC transfusion-dependent at baseline, i.e., patients with a baseline RBC transfusion frequency (defined in section 7.10.3) of ≥ 2 units per month. For these patients, achievement of RBC transfusion independence at Week 24 is defined as having had no RBC transfusions in the 3 months (90 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of RBC transfusion independence.

7.10.2 Achievement of Reduced RBC Transfusion Dependence

Achievement of reduced RBC transfusion dependence is defined in patients who were not RBC transfusion independent at baseline, i.e., patients who were either RBC transfusion dependent or indeterminate at baseline. Reduction in RBC transfusion dependence is defined as having a ≥ 50% decrease in the average units of RBC transfusions per month over the 3 months (90 days) prior to their Week 24 visit date compared to baseline units of RBC transfusions per month. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of reduced RBC transfusion dependence.

7.10.3 Frequency of RBC Transfusions

Change from baseline in the frequency of RBC transfusions (units/month) will be summarized by arm over time through Week 24 using descriptive statistics in patients receiving at least one unit of RBC at baseline or while on study treatment. The frequency of RBC transfusions at baseline is defined as the number of units of RBC transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline RBC transfusion frequency is computed as the sum of the number of units of RBC transfusions in the 90 days prior to the informed consent date and the number of units of RBC transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ units\ from\ Transfusion\ History + \#\ units\ from\ IC\ to\ start\ of\ treatment)}{\left(90 + (treatment\ start\ date - IC\ date + 1)\right)\ days} \times 30\frac{days}{month}.$$

At post-baseline timepoints, the frequency of RBC transfusions is defined as the number of units of RBC transfusions per month in the three months (90 days) preceding the visit date. That is,

$$\frac{(\#\ units\ in\ the\ 90\ days\ preceding\ the\ visit\ date)}{90\ days} \times 30\frac{days}{month}.$$

7.11 Endpoints Relating to Platelet Transfusion

There are platelet count thresholds below which American Society of Hematology and American Society of Clinical Oncology guidelines (Schiffer et al and Slichter et al) recommend platelet transfusions, but standard definitions for platelet transfusion independence/dependence do not exist. We define platelet transfusion independence at any time point as having had no platelet transfusions in the month (30 days) preceding that time point. Otherwise, the patient is platelet transfusion dependent. See Table 4 below. The frequency of platelet transfusions is defined by the number of platelet transfusions over a specified period of time. Note that for the purposes of the analysis, platelet transfusion must be given to support platelet counts or to control non-surgical bleeding. Platelets given prophylactically for surgical procedures will not count towards platelet transfusion independence/dependence. The analyses planned for endpoints relating to platelet transfusions are defined below.

Table--4
Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

7.11.1 Achievement of Platelet Transfusion Independence

Achievement of platelet transfusion independence is defined in patients who were platelet transfusion-dependent at baseline, i.e., patients who had ≥1 platelet transfusion per month. For these patients, achievement of platelet transfusion independence is defined as having had no platelet transfusions in the month (30 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of platelet transfusion independence. Platelet transfusion independence/dependence will also be explored using other cut-offs and the continuous measure of the number of episodes of platelet transfusions.

7.11.2 Frequency of Platelet Transfusions

The change from baseline in the frequency of platelet transfusions (times/month) will be summarized by treatment arm every four weeks through their Week 24 visit date using descriptive statistics in patients receiving at least one platelet transfusion at baseline or while on study treatment. The frequency of platelet transfusions at baseline is defined as the number of platelet transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline platelet transfusion frequency is computed as the sum of the number of transfusions in the 90 days prior to the informed consent date and the number of transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ transfusions\ in\ Transfusion\ History + \#\ transfusions\ from\ IC\ to\ start\ of\ treatment)}{\left(90 + (treatment\ start\ date - IC\ date + 1)\right)\ days} \times 30\frac{days}{month}.$$

At post-baseline timepoints, frequency of platelet transfusions is defined as the number of platelet transfusions in the month (30 days) preceding the visit date.

7.12 Clinical Improvement in Hemoglobin Level

Clinical improvement in hemoglobin level is defined for the subgroup of patients with baseline hemoglobin level of less than 100 g/L. A clinical improvement in hemoglobin level is defined as having a minimum of 20 g/L increase in hemoglobin level at Week 24 or becoming transfusion independent for 8 weeks or more, i.e., no RBC transfusions in the 8 weeks prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (section 7.8) will be used for clinical improvement in hemoglobin level.

7.13 Clinical Improvement in Platelet Count

Clinical improvement in platelet count is defined for the subgroup of patients with baseline platelet count below 50,000/μL. A clinical improvement in platelet count is defined as a minimum 100% increase from baseline in platelet count at Week 24 and an absolute platelet count of ≥ 50,000/μL for 8 weeks or more prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (section 7.8) will be used for clinical improvement in platelet count.

7.14 Change in JAK2V617F Allele Burden

The percent change from baseline to post-baseline visits in the level of the JAK2V617F mutation, defined as the percent of cells positive for the V617F mutation, will be calculated for each patient and summarized by treatment arm.

7.15 QOL Based on EQ-5D-5L and EORTC QLQ-C30

There are 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as an overall health score recorded on the EQ-5D-5L (Rabin et al. 2011). Each dimension has 5 levels coded 1 through 5 indicating increasing problems or difficulty in that dimension. There should be only one response for each dimension and missing values be coded as 9. The 5 codes are combined (concatenated) to compute a unique health state for each patient. These health states will be converted to country-specific index values (using a bridge to EQ-5D-3L responses and established country-specific index values) to facilitate the computation of quality-adjusted life years (QALYs). The overall health score has a possible value ranging from 0 to 100 and represents the patient's impression of their health, where 0 represents the worst health and 100 represents the best health imagined. Missing overall health scores will be assigned 999. See Table 5.

Table--5 Levels of the EQ-5D-5L Instrument	
EQ-5D-5L Dimensions and Scale	**Levels**
Mobility	1 to 5
Self-care	1 to 5
Usual activities	1 to 5
Pain/discomfort	1 to 5
Anxiety/depression	1 to 5
Overall Health	0 to 100

The frequency distribution of the codes in each dimension will be presented by treatment arm at baseline and at each post-baseline visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24). The overall health score and the index values will be summarized by treatment arm at baseline. The change from baseline in the overall health score and the index values will be summarized by treatment arm at Weeks 8, 16, and 24.

The EORTC QLQ-C30 Version 3 (Fayers et al. 2001) has 30 questions (items) which are combined to form 15 scales for the global health status/quality of life, functional, and symptom assessment of cancer patients. There is 1 global health status/quality of life scale comprising 2 items, each having possible individual scores ranging from 1 to 7 and, hence, a range of 6. There are 5 multi-item functional scales assessing physical, role, emotional, cognitive, and social functioning. Nine symptom scales assess fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Individual scores for the functional and symptom scales range from 1 to 4, with a range of 3. See Table 6.

Table--6 Scales of the EORTC QLQ-C30 Instrument	
EORTC QLQ-C30 Scales	**Scores for Individual Items**
Global Health Status/Quality of Life (2 items)	1 to 7
Functional (15 items)	
Physical	1 to 4
Role	1 to 4
Emotional	1 to 4
Cognitive	1 to 4
Social Functioning	1 to 4
Symptom (13 items)	
Fatigue	1 to 4
Nausea and Vomiting	1 to 4

Table--6 Scales of the EORTC QLQ-C30 Instrument	
EORTC QLQ-C30 Scales	**Scores for Individual Items**
Pain	1 to 4
Dyspnoea	1 to 4
Insomnia	1 to 4
Appetite Loss	1 to 4
Constipation	1 to 4
Diarrhea	1 to 4
Financial Difficulties	1 to 4

The scores for each scale will be set to missing if the answers to more than half of the items in the scale are missing. A raw score for each scale is determined by the average of the individual scores in each scale. The total score for the global health status/quality of life scale and each symptom scale is computed by $\left(\frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each functional scale is computed by $\left(1 - \frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each scale will be summarized by treatment arm at baseline. The change from baseline of the total score in each scale will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.16 Global Impression Assessment

There is 1 domain in the global impression assessment instrument with possible scores ranging from 1 (very much improved) to 7 (very much worse). The scores for the global impression assessment will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.17 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1. The primary hypothesis will be tested at α = 0.05 (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on
    a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24, and
    b. The difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24

individually. The study reaches its primary objective (claims to be successful) when both endpoints reach statistical significance (α = 0.05, 2-sided)

2. If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in a) the QD arm versus the BAT arm and b) the BID arm versus the BAT arm at the 2-sided 0.025 α-level.
    a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be tested at the 2-sided α = 0.025 level.
3. If the p-value is less than α = 0.025, the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24 will be tested at the 2-sided α = 0.025 level.

7.18 Subgroup Analyses of Efficacy

Subgroup analyses are planned to evaluate any potential impact of demographics or baseline disease characteristics on the primary and secondary endpoints. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Depending on the sample size, other subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), JAK2617F mutation status at baseline (present vs. not present), prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day), RBC transfusion dependency at baseline (dependent vs. not dependent), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and baseline platelet count (< 50,000/μL vs. ≥ 50,000/μL). Additionally, BAT patients treated with ruxolitinib will be analyzed separately.

8 Exposure to Study Treatment

Exposure to initial study treatment will be evaluated by the duration of treatment, cumulative dose, actual dose intensity, and relative dose intensity in the safety population.

Duration of treatment (weeks): is defined as the duration from first day of initial study treatment to the last day of initial study treatment, i.e.,

$$\frac{(\text{Date of last dose of initial study treatment} - \text{date of first dose of initial study treatment} + 1)}{7},$$

Descriptive statistics will be provided for duration of treatment by treatment arm. Duration of treatment will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median duration of treatment and the corresponding 95% confidence interval, and estimated duration of treatment curves will be presented by arm.

Cumulative dose (mg): is defined as the sum of all doses of initial study treatment taken and descriptive statistics will be provided for the pacritinib arms only. The numbers and

percentages of patients with any dose modifications will be provided by treatment arm. Reasons for dose modifications will also be summarized.

Actual dose intensity (ADI, mg/day) = (total dose taken in mg) ÷ (duration of treatment in days) and descriptive statistics will be provided for the pacritinib arms only.

Relative dose intensity (RDI, %) = (ADI) ÷ (planned daily dose) * 100. The planned pacritinib dose is 400 mg/day and descriptive statistics will be provided for the pacritinib arms only.

Exposure to pacritinib after crossover will be analyzed separately (section 10).

Time to crossover will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median time to crossover and the corresponding 95% confidence interval, and estimated time to crossover curves will be presented for the BAT arm. Descriptive statistics for the time to crossover in weeks will be presented for patients who crossed over from BAT to pacritinib, with duration defined as (date of first dose of pacritinib after crossover – date of first dose of initial study treatment + 1)/7. The numbers and percentages of patients taking each BAT therapy will be presented. Additionally, the numbers and percentages of the first BAT therapy taken will be presented.

9 Safety Analysis

Safety analyses include treatment emergent adverse events, clinical labs, ECG, vital signs, performance status, and any abnormal findings observed during the performance of physical examinations by treatment received after randomization through the end of initially assigned study treatment + 30 days. The safety data after patients crossover from BAT to pacritinib will be analyzed separately (section 10).

9.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Analysis of AEs will be based on Treatment Emergent Adverse Events (TEAEs). A TEAE is defined as an adverse event (AE) occurring after the first dose of study treatment and within 30 days after the last study treatment date. In addition, an AE is also considered a TEAE if it is an AE starting more than 30 days after the last study treatment, but the investigator assessed the AE with a relationship to study drug of “Possible”, “Probable”, or “Definite” or if it is an AE with a missing start date but with an end date after the first study drug dose date. An AE occurring after the first dose of study drug that also occurred prior to the first dose of study drug is only considered a TEAE if the AE worsened in grade after the first dose of study drug. An AE occurring after crossover to a pacritinib regimen that also occurred prior to crossover is only considered a TEAE if the AE worsened in grade after crossover.

TEAEs will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE, having a TEAE in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. CTCAE (version 4.0) grades and relationship to study medication will be summarized as appropriate. For summaries by CTC grade or relatedness, only the highest CTC grade or degree of relatedness of each SOC and/or preferred term will be summarized. A patient having the same event more than once will be counted only once and by greatest severity or closest relationship.

In addition, serious TEAEs (SAEs), CTC grade 3 or 4 TEAEs, TEAEs leading to study medication discontinuation, interruption, or dose reduction, TEAEs with an outcome of death, related TEAEs (see section 9.1.3.2 of the protocol), and TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be summarized. A listing of all SAEs will be generated.

The preferred term of TEAEs of all grades and grade 3 or 4 TEAEs will also be presented for each treatment arm by decreasing frequency in the pooled pacritinib arms. These summaries will also be repeated for TEAEs of all grades and grade 3 or 4 TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first).

The numbers and percentages for the causes of all deaths will be presented by treatment arm. A listing of all deaths, both on and off treatment, will also be generated. On treatment deaths are defined as deaths that occur on treatment and within 30 days of treatment discontinuation.

9.1.1 TEAEs of Special Interest

The following TEAEs are considered to be of interest: Diarrhea, Nausea, Vomiting, Neutropenia (including neutrophils decreased), Thrombocytopenia (including platelets decreased), Anaemia (including hemoglobin decreased), Infections and Infestations (SOC), Cardiac AEs, Neurotoxicity, and Haemorrhages. The preferred terms included in Cardiac AEs of special interest are all terms in the Standardised MedDRA Queries (SMQs) of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events. The preferred terms included in the Haemorrhages AEs of special interest are all terms in the SMQ of Haemorrhages. See Appendix 15.1 on page 39 for the preferred terms for neurotoxicity events of special interest.

TEAEs of special interest will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE of special interest, having a TEAE of special interest in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. Cardiac and Haemorrhages TEAEs of special interest will also be summarized by SMQ. CTC grade 3 or 4 TEAEs of special interest and those starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be similarly summarized. Additionally, the incidence and prevalence of each TEAE of special interest with 8-week intervals from

baseline will be presented by treatment arm. Incidence and prevalence will also be presented for grade 3 or 4 TEAEs of special interest.

Times to onset and resolution of the first TEAE will also be analyzed for each TEAE of special interest. Time to onset of the first TEAE is defined as the time from start of study drug to the start date of the first occurrence of the TEAE, i.e., time in days is calculated as (start date of first occurrence of the TEAE) – (date of first dose of study treatment) + 1. Subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. Time to resolution of first TEAE is defined as the time from the start date of the first occurrence of the TEAE to its resolution (AE outcome being "recovered/resolved" in CRF). In the absence of resolution, subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. The same analysis methods used for OS (section 7.3) will be used for time to onset of first and time to resolution of these TEAEs of special interest.

9.2 Clinical Laboratory Measurements

Hematology and Chemistry laboratory measures are collected via central lab.

9.2.1 Hematology

The hematology measurements to be analyzed are: hemoglobin, platelet counts, white blood cell counts, neutrophil counts, lymphocyte counts, monocyte counts, and eosinophil counts. When there are non-missing results for both automated and manual hematology differentials, the manual results will be used for analysis if all the hematology results being analyzed are present.

The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each hematology measure. Descriptive statistics of change and percent change from baseline in hematology values will be presented by visit. Plots of the percent change in hemoglobin and platelet counts over time will be presented.

9.2.2 Chemistry

The following clinical chemistry measures will be analyzed: ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, indirect bilirubin, creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid levels. Summaries of the worst CTCAE grade will be presented for ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, creatinine, sodium, potassium, calcium, phosphate, magnesium, albumin, glucose, and cholesterol in either direction of abnormality (i.e., abnormally low or high). The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each chemistry measure. Descriptive statistics of change and percent change from baseline in clinical chemistry values will be presented by visit.

The derived visit window definitions for clinical hematology and chemistry are displayed in Table 7.

Table--7
Analysis Window Definitions for Clinical Chemistry and Hematology Results

Visit	**Nominal Day**	**Range**
Baseline	1 (first dose date)	[-14, 1]
Week 3	15	[2, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.3 Other Clinical Safety

9.3.1 Electrocardiogram (ECG)

The frequency distribution of abnormal ECG measurements on study (after the first study drug treatment through the last dose of study drug) will also be summarized. The proportion of subjects with the following QTc intervals will tabulated by visit (including worst and last on treatment values) and treatment arm:

- A measured value > 450 ms
- A measured value > 480 ms
- A measured value > 500 ms
- > 30 ms above baseline
- > 60 ms above baseline

9.3.2 Vital Sign Measurements

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) of change and percent change from baseline in vital sign measurements, including weight, will be presented by visit.

The frequency distribution of abnormal vital sign measurements (as noted by the investigator) on study (on or after the first day of treatment) will be displayed.

A table summarizing clinically notable blood pressure and weight measurements which are aligned with CTCAE cut-offs, where available, will be displayed. The proportion of subjects whose worst observed values while on study (on or after the first day of treatment) meet the following clinically notable criteria will be tabulated by treatment arm:

- Systolic Blood Pressure
  - < 85 mm Hg
  - ≥ 140 - < 160 mm Hg
  - ≥ 160 mm Hg
- Diastolic Blood Pressure
  - < 50 mm Hg
  - ≥ 90 - < 100 mm Hg
  - ≥ 100 mm Hg
- Weight gain from baseline
  - ≥ 5% - < 10% increase
  - ≥ 10% - < 20% increase
  - ≥ 20% increase
- Weight loss from baseline
  - ≥ 5% - < 10% decrease
  - ≥ 10% - < 20% decrease
  - ≥ 20% decrease

The derived visit window definitions for vital signs are displayed in Table 8.

Table--8
Analysis Window Definitions for Vital Signs Results

Visit	**Nominal Day**	**Range**
Baseline	1 (first dose date)	[-14, 1]
Week 2	8	[2, 11]
Week 3	15	[12, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]

Table--8 Analysis Window Definitions for Vital Signs Results		
Visit	**Nominal Day**	**Range**
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.4 Concomitant Medication

A medication will be considered a concomitant medication if it was taken by the patient at any time on study (on or after the first day of treatment and within 30 days after the last dose of study drug). The following will also be considered concomitant medications:

- Medications missing both start and stop dates.
- Medications having a start date prior to the last dose of study drug and missing the stop date.

Concomitant medications will be summarized by ATC class and preferred term.

9.5 Supplemental Procedures

Procedures received from the first day of treatment to the last day of treatment will be summarized by SOC class and preferred term.

9.6 Subgroup Analysis of Safety

Treatment-emergent adverse events, including all AEs, grade 3/4 AEs, and SAEs, and hematology toxicity will also be summarized by subgroups as appropriate. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Additionally subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), prior treatment with JAK2 inhibitors (yes vs. no), baseline platelet count (< 50,000/μL vs. ≥ 50,000), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and JAK2V617F mutation status at baseline (present vs. not present). Additionally, safety within the subgroup of BAT patients treated with ruxolitinib will be explored.

10 Analysis of Patients who Crossover from BAT to Pacritinib

Selected descriptive efficacy and safety summaries defined above will be repeated for crossover patients. Baseline for these summaries will be considered to be the last assessment prior to or at crossover. The following summaries will be presented for crossover patients.

- **Best response in spleen volume** is based on the percent change in spleen volume from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **The moving average of TSS** as defined in section 7.2.5 for BAT patients after crossover.
- **Best response in spleen length** is based on the percent change in spleen length from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **Exposure to study treatment** as outlined for the pacritinib arms in section 8.
- **Deaths**: the numbers and percentages for each cause of death after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **TEAEs** as outlined in section 9.1 that occur after crossover will be summarized by pacritinib regimen and in the pooled regimens.

Reasons for crossover from BAT to a pacritinib regimen will also be summarized. A listing of all patients who crossover from BAT to a pacritinib regimen will also be generated.

11 Pharmacokinetic and Pharmacodynamic Analysis

The study pharmacokineticist will review the individual concentration-time data prior to the conduct of PK analysis to ascertain the integrity of the concentration-time data set. Population PK/PD analysis will be conducted to characterize the exposure of pacritinib in MF patients following administration of 400 mg QD and 200 mg BID regimens. The PK and PD measures will be summarized with descriptive statistics by pacritinib treatment arm. In addition, the exposure-response relationship for pacritinib will be characterized on key safety (e.g., thrombocytopenia, myelosuppression, anemia, hemorrhage, GI, cardiac failure, and arrhythmia AEs) and the primary and secondary efficacy (i.e., reduction in spleen volume and reduction in TSS) endpoints. The correlation of Week 24 spleen volume and TSS with Week 24 STAT3 phosphorylation will be evaluated as well.

12 Power and Sample Size

It is assumed that the proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. These assumptions were made based on response rates seen

in the COMFORT-I and -II randomized controlled trials and the SB1518-2007-001 and SB1518-2008-003 Phase 2 trials. It is also assumed that the proportion of patients achieving a ≥ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm. These assumptions were made based on response rates seen in the COMFORT-I randomized controlled trial.

With these assumptions, the original sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. For the primary hypothesis (pooled QD/BID vs. BAT), this sample size provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is ≥ 93% to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

Due to the FDA clinical hold, the FAS is being used to evaluate the study objectives. It is estimated that a total of 220 patients meet the FAS definition. With the same assumptions above, this sample size provides 97% and >99% power to test the primary hypothesis (pooled QD/BID vs. BAT) of a treatment difference in spleen volume reduction and a treatment difference in TSS reduction, respectively, at an α-level (2-sided) of 0.05. This sample size also provides 86% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

13 Data Handling Rules

13.1 Definition of Baseline Value

The baseline value for safety analyses will be defined as the last assessment prior to the start of treatment, unless otherwise specified.

13.2 Partial Current MF Diagnosis Date

For patients who have a partial diagnosis date, the 15th of the month will be used if day is missing, and July 15th will be used if both the month and day are missing.

13.3 Partial or Missing AE Onset and Resolution Dates

For AE summaries, the missing day of onset of an adverse event will conservatively be set to:

- First day of the month that the AE occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the AE occurred.
- The 15th of the month and year if the AE month and year are before the month and year of the first treatment.

If the onset date of an adverse event is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 1st of the year if the AE year is before the year of the first study treatment.

If the day of resolution of an adverse event is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year, whichever is earlier. If the day of resolution of an adverse event is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented “as is” in listings.

13.4 Laboratory Results Reported as a Range

Laboratory results that are reported as less than or greater than a certain value (limit of quantification) or as a range of values will be imputed for analysis using the rules described below.

Myeloblast Percentages

- Myeloblast results in the hematology data reported as <X% will be imputed with the value (X-1)% for analysis.
- Myeloblast results in the hematology data reported as ≤X% will be imputed with the value X% for analysis.
- Myeloblast results in the hematology data reported as X-Y% will be imputed with the value Y% for analysis.

Other Laboratory Results

- Laboratory results reported as <X will be imputed with the value (X-1) for analysis. Results reported as <X.Y will be imputed by subtracting one from the

last significant digit (Y). Results reported as <0.1 will be imputed as 0 for analysis as long as the normal range extends to 0.

- Laboratory results reported as >X will be imputed with the value (X+1) for analysis. Results reported as >X.Y will be imputed by adding one to the last significant digit (Y).

14 References

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15 Appendix

15.1 Neurotoxicity Events of Special Interest

The neurotoxicity events of special interest include, but are not limited to, amnesia, blindness, burning sensation, carpal tunnel syndrome, cognitive disorder, confusional state, disturbance in attention, dizziness, dysgeusia, dyskinesia, dysphonia, dysstasia, gait disturbance, facial neuralgia, gait disturbance, headache, hemianopia, hyperaesthesia, hypoaesthesia, incontinence, lethargy, memory impairment, migraine, muscular weakness, myopathy, neck pain, neuralgia, neuropathy peripheral, paraesthesia, Parkinson's disease, peroneal nerve palsy, sensation of heaviness, status epilepticus, syncope, tinnitus, tremor, urinary incontinence, urinary retention, vertigo, vertigo positional, vestibular disorder, VIIth nerve paralysis, vision blurred, visual field defect, and visual impairment. Additional terms will be included as they are identified.

Study PAC326 (PERSIST-2)

Statistical Analysis Plan

Version: 1.1
July 8, 2016

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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Protocol Version Date: July 31, 2014

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Table of Contents

1 Scope

This document describes the statistical analyses and data presentations to be performed for protocol PAC326, "A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis".

This statistical analysis plan (SAP) provides a detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of pacritinib in the scope of the study. It provides additional details concerning the statistical analyses that were originally outlined in the protocol. This SAP will be finalized and signed prior to the unblinding of the clinical database. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post hoc in the clinical study report.

Due to the United States Food and Drug Administration (FDA) full clinical hold on February 8, 2016 when all patients were required to discontinue pacritinib, the following modifications have to be made to the originally planned analyses specified in the protocol:

- All analyses of all efficacy and safety endpoints will take place after the last patient completes the 30-day Post Treatment Termination assessments instead of the Week 24 assessments.
- Many patients were not given the opportunity to reach Week 24 for outcome assessment with the implementation the clinical hold. The Full Analysis Set (FAS) will be used to evaluate the study objectives instead of the intent-to-treat (ITT) population. The FAS includes all randomized patients who had an opportunity to reach Week 24 for outcome assessments. Details are outlined in section 5.1.
- There will be no long term follow up for efficacy and safety. Therefore, there are limitations to the evaluation of all time to event endpoints (overall survival, progression-free survival, duration of response, etc.; sections 7.3 to 7.7) and endpoints evaluated over time due to the limitation of follow up.

2 Study Objectives and Hypotheses

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the efficacy of two dose-schedule arms of pacritinib (pooled once-daily [QD] and twice-daily [BID] dosing arms) with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the

proportion of patients achieving a ≥ 50% reduction in the Total Symptom Score (TSS) from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

2.1.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.
2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.1.3 Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥ 35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of red blood cell (RBC) transfusion independence
9. Achievement of reduced RBC transfusion dependence
10. Clinical improvement in hemoglobin level
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence
13. Clinical improvement in platelet count
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life, as measured by the EQ-5D-5L and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0.

2.1.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on PD effect (i.e., pSTAT3 inhibition) and the safety and efficacy of pacritinib.

2.2 Hypotheses

The hypothesis tests described below are based on the full analysis set (section 5.1).

2.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in

1 a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and
2 a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0

than treatment with BAT.

2.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

3 Summary of Study Design

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two dose schedules of pacritinib, in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes “no treatment” and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF. Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter using the same imaging modality, through 48 weeks post randomization or until progression of disease or withdrawal from study treatment. TSS as measured by MPN-SAF TSS 2.0 will be recorded daily through 48 weeks post treatment initiation or until end of study treatment, whichever occurs first.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints for 3 years after their Week 24 visit or the end date of treatment with the initially assigned study drug, whichever comes first.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

4 Randomization and Blinding

Randomization will be stratified by geographic region (US vs. Canada vs. Europe vs. rest of the world [ROW]), the risk category (intermediate-1 vs. intermediate-2 vs. high risk per Passamonti et al. 2010) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). To be included in the > 100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count > 100,000/μL and 2) > 50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The most recent platelet count obtained prior to randomization on Days -3 to 1 during the screening period will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization.

Although this is an open label study, the double-blind procedure was followed in-house (see the PERSIST-2 Study Blinding Plan). The clinical database will be unblinded after data review has been completed, protocol violations have been identified, the data have been declared clean, and this SAP has been signed off.

5 Analysis Populations and Approaches to Analysis

5.1 Full Analysis Set

The full analysis set (FAS) is defined as all randomized patients who had an opportunity to reach Week 24 for outcome assessments. As the clinical hold occurred on February 8, 2016, patients randomized on or after to September 7, 2015 would not have had this opportunity. Therefore, the FAS population will include patients randomized prior to

September 7, 2015. Patients in this population will be analyzed according to the arm to which they were assigned at randomization. This population will be used for the analyses of the efficacy endpoints as well as for the analyses of demographics, baseline characteristics, and medical history.

5.2 Evaluable Population

The evaluable population for each endpoint is defined as all patients in the FAS who have evaluable baseline and follow up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for the supportive analyses of the efficacy endpoints.

5.3 Per-protocol Population

The per-protocol (PP) population is defined as all patients in the FAS who receive any study treatment and have no major protocol violations. The major protocol violations that will exclude patients from the PP population are defined as follows:

- Did not meet one of the following inclusion criteria:
  - Inclusion 1: Intermediate-1 or -2 or High risk PMF, PPV-MF, or PET-MF
  - Inclusion 4: Palpable splenomegaly ≥ 5 cm below the LCM by physical examination
  - Inclusion 5: TSS ≥ 13 on the MPN-SAF TSS 2.0, not including the inactivity question
  - Inclusion 8: Peripheral blast count < 10%
  - Inclusion 12: At least 6 months from prior splenic irradiation
  - Inclusion 13: At least 12 months from prior ^{32}P therapy
  - Inclusion 15: At least 2 weeks since any treatment for PMF, PPV-MF, or PET-MF
- Did not meet one of the following exclusion criteria:
  - Exclusion 3: Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
  - Exclusion 6: History of splenectomy or planning to undergo splenectomy
  - Exclusion 10: Inflammatory or chronic functional bowel disorder such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
  - Exclusion 15: Erythropoietic agent within 28 days prior to randomization
  - Exclusion 16: Thrombopoietic agent within 14 days prior to randomization
- Patients in the pacritinib arms taking any of the BAT treatment options for treatment of MF.
- Visits scheduled outside the analysis window specified for baseline and Week 24 for the relevant endpoint.

Patients in the PP population will be analyzed according to the treatment actually received and their correct strata if there is mis-stratification. The PP population will be

used for the supportive analyses of the efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

5.4 Safety Population

The safety population is defined as all randomized patients who receive at least one dose of study treatment, including patients on the BAT arm treated with watchful waiting. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received. This population will also be used for analyses of demographics, baseline characteristics, and medical history.

5.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK or STAT3 phosphorylation analysis.

6 Demographics, Baseline Characteristics, and Medical History

6.1 Demographics and Baseline Characteristics

Descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum) will be provided for those variables measured on a continuous scale. The frequency distribution (counts and percentages (n and %)) will be provided for those variables measured on a nominal scale.

The demographic and baseline characteristics will be analyzed with the following variables in the full analysis set and the safety population.

6.1.1 Demographic Variables

Age, age category (< 65 years vs. ≥ 65 years), gender, race, ethnicity, height, weight, body mass index, ECOG performance status, and geographic region.

6.1.2 Baseline Disease Characteristic Variables

Spleen length by physical exam, bone marrow biopsy (cellularity, reticulin and collagen fibrosis staging, and myeloblast percentage), JAK2V617F status, baseline platelet count and category (< 50,000/μL vs. ≥ 50,000/μL), rebound platelet category, baseline hemoglobin and category (< 100 g/L vs. ≥ 100 g/L), current MF diagnosis, time since current MF diagnosis, non-bone marrow diagnostic criteria at initial MF diagnosis, current DIPSS risk category, transfusion history (within 90 days prior to Informed Consent date), red blood cell (RBC) transfusion dependence, platelet transfusion dependence, prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), prior treatment with ruxolitinib (yes vs. no), duration of prior treatment with ruxolitinib (< 6 months vs. ≥ 6 months), and most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day).

6.2 Prior Therapy and Medical History

Prior therapy and medical history are any therapy or diseases that occurred or any medication taken prior to the first day of study drug dosing or prior to the randomization date if patients were never dosed. Prior therapy includes both prior MF and non-MF therapies. Both will be summarized for patients in the full analysis set and the safety population.

For prior MF therapy, number of prior radiation therapies, type of prior radiation therapy, number of prior systemic medical therapy regimens, type of prior systemic medical therapies, and transfusion history for each cellular blood product will be summarized by the frequency distribution (n and %).

Prior non-MF therapies will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term using WHO Drug Dictionary version 01, March 2013.

Medical history will be summarized by frequency distribution (n and %) of system organ class and preferred term by MedDRA dictionary version 16.0 for patients in the full analysis set and the safety population. A listing of medical history will also be generated.

7 Efficacy Analysis

The efficacy and exploratory endpoints are defined below. Additionally, the planned analyses for these endpoints are described.

7.1 Reduction in Spleen Volume

The primary efficacy endpoint of the study is the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT based on independent radiology facility (IRF) reads. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 35% reduction. To test the primary and secondary hypotheses, the treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. These analyses will be performed in the full analysis set. The same analyses will be performed based on the evaluable and PP (if necessary) populations as supportive analyses. A sensitivity analysis may be performed using all randomized patients and using Bayesian methods to estimate the probability of Week 24 response in patients who did not have an opportunity to reach Week 24 due to the FDA clinical hold.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count (≤ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.
The proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to other post-baseline time points will be summarized as well. In addition, using the evaluable population, descriptive statistics of the percent change in spleen volume from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

The post-baseline spleen scan data used for all analyses will be the scans collected at the nominal post-baseline visit or Termination scans collected within 2 weeks (+/- 14 days) of the nominal study day. For example, Termination scans collected within 2 weeks (+/- 14 days) of study day 168 (nominal week 24 study day) will be considered the Week 24 scans. Scans collected in BAT patients on or after crossover to pacritinib will be excluded from the primary analysis. Baseline scans are the scans collected at the screening MRI visit.

7.2 Improvement in Total Symptom Score

The secondary efficacy endpoint of the study is the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

7.2.1 TSS Algorithm

- **The daily TSS** is the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side.
- **The baseline TSS** is the mean of the daily TSS over the 7 consecutive days prior to the start of treatment. Please note that in the protocol, baseline TSS was defined relative to randomization date with the assumption that treatment would start at randomization. Missing values during these days are handled as described below (section 7.2.2).
- **The Week 24 TSS** is the mean of the daily TSS obtained during the 28 consecutive days prior to the Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Patients with a missing baseline or Week 24 TSS, including those who meet the criteria for disease progression before Week 24 and those who drop out of the study before Week 24, or patients who cross

over to treatment with pacritinib prior to Week 24 will be considered to have not achieved the ≥ 50% reduction. Events occurring prior to Week 24 occurred prior to study day 154.

- **The percent reduction in TSS from baseline to Week 24** is computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 24 TSS - Baseline TSS}}{\text{Baseline TSS}}\right) * 100.$$

Other post-baseline TSS and percent reduction from baseline are similarly defined, except that the post-baseline visit date alone is used as a point of reference at timepoints at which spleen volume is not assessed but a study visit is scheduled and nominal study day alone is used as a point of reference at timepoints at which a study visit is not scheduled. In BAT patients, only post-baseline symptom scores reported prior to crossing over to pacritinib will be used for analysis.

7.2.2 Handling of Missing Values

- If any of the seven individual symptoms scores are missing, the TSS for that day will be considered as missing.
- The baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to the start of study treatment.
- The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Missing TSS at other post-baseline timepoints is similarly handled.

7.2.3 Primary Analyses

The primary analysis of the improvement in TSS will compare the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24. The numbers and percentages of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. The same analyses will be performed based on the evaluable and PP populations as supportive analyses.

7.2.4 Secondary Analyses

The treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count (≤ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact CMH test will be used to test if

treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.
The same analyses will be repeated with the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to other post-baseline time points. In addition, using the evaluable population, descriptive statistics of the percent change in TSS from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

7.2.5 Exploratory Analyses

The percent change from baseline over time in individual symptom scores as measured by the MPN-SAF TSS 2.0 will be evaluated and descriptive statistics of the percent change in individual symptom scores from baseline over time will be presented. The individual symptom scores for each timepoint will be computed as the mean of the daily individual symptom scores obtained during the 28 days prior to that spleen volume scan date. The individual symptom scores at each timepoint will be considered missing if fewer than 20 daily individual symptom scores are available out of the 28 consecutive days prior to that timepoint.

The moving average of TSS will be evaluated as well. The TSS score for a timepoint will be computed as the mean of the 7 daily TSS prior to that timepoint. If fewer than 4 daily TSS are available out of the 7 days, the moving average TSS will be considered missing for that timepoint. A plot of the proportion of patients with a ≥ 50% reduction in TSS from baseline to each timepoint through Week 48 or initial treatment termination, whichever is earlier, will be presented by treatment arm.

The correlation of Week 24 TSS with Week 24 spleen volume and patient global impression assessment (as anchors) will be computed and tested for a significant difference from zero.

7.3 Overall Survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause. OS analysis is planned after long term follow up, i.e., 3 years after the last patient's Week 24 visit or their end date of treatment with the initially assigned study drug, whichever comes first. If a patient is alive or the survival status is unknown by the time of this analysis, survival will be censored at the date the patient was last known to be alive, regardless of whether patients crossed over to a pacritinib regimen from BAT. Though on treatment follow up is limited due to early termination of treatment resulting from the FDA hold and though there is confounding by crossover of BAT patients to a pacritinib regimen, OS will be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median survival time and the corresponding 95% confidence interval, and overall survival curves will be presented by arm. In addition, reasons for censoring will be summarized by arm. The impact of crossover will be evaluated by rank-preserving structural failure time (RPSFT) analysis (Robins and Tsiatis, 1991) and by separating BAT patients who crossover from those who do not.

Additionally, the effect of prognostic factors for MF on OS will be explored using Cox proportional hazards models.

7.4 Progression Free Survival (PFS)

PFS is defined as the time from the start of treatment to the date of progressive disease or death due to any cause (whichever is first reported). PFS will be based on disease progression assessment by the investigator using the definition below. The progression date is the earliest time when any progression is observed. Progression of disease is defined as one or more of the following: splenic progression (defined as in increase in splenic volume of ≥ 25% from baseline based on MRI or CT scan), splenic irradiation, splenectomy, or leukemic transformation (defined as an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%). Patients will be censored at the last progressive disease assessment date if they are alive with no documented progression before analysis. Patients who cross over during the study will be censored at the last assessment date prior to crossing over. Table 1 below provides the rules for progressive disease events and censoring for the primary analysis.

Table--1
PFS Event and Censoring Rules

	Situation	**Date of Event or Censoring**
PFS Event	Progression documented	Earliest date when any progression is observed
	Death	Date of death if no progression
Censor	No post-baseline disease progression assessments	Day 1
	No progression	Date of last progressive disease assessment with evidence of no progression
	Crossover from BAT to Pacritinib	Last progressive disease assessment date prior to the crossover date
	Lost to follow-up	Date of last progressive disease assessment showing no progression

The same analysis methods used for OS (section 7.3) will be used for PFS. Time to progression (time from the start of treatment to the date of progressive disease) may also be evaluated as an exploratory analysis.

7.5 Leukemia Free Survival (LFS)

LFS is defined as the time from the start of treatment to the date of leukemic transformation or death due to any cause. Leukemic transformation is defined as the first date of an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%. Patients will be censored at the date of last assessment for leukemic transformation if they are alive with no documented transformation before analysis. Patients who cross over during the study will be censored at the last assessment date prior to crossing over. Table 2 provides the rules for LFS events and censoring for the analysis of LFS.

Table--2 LFS Event and Censoring Rules		
	Situation	**Date of Event or Censoring**
LFS Event	Leukemic transformation documented	Earliest date when transformation is observed
	Death	Date of death if no leukemic transformation
Censor	No post-baseline disease progression assessments	Day 1
	No leukemic transformation	Date of last assessment with evidence of no leukemic transformation
	Crossover from BAT to Pacritinib	Last assessment date prior to the crossover date
	Lost to follow-up	Date of last assessment showing no leukemic transformation

The same analysis methods used for OS (section 7.3) will be used for LFS.

7.6 Time to Achievement of a ≥ 35% Reduction from Baseline in Spleen Volume

Time to achievement of a ≥ 35% reduction from baseline in spleen volume will be calculated as the time from start of treatment to the date of the first scan with a ≥ 35% reduction from baseline in spleen volume, that is: date of first ≥ 35% reduction – start of treatment date + 1. Patients will be censored at the last radiological assessment date if they have not yet achieved the ≥ 35% reduction from baseline in spleen volume by the Termination visit. The same analysis methods used for OS (section 7.3) will be used for time to achievement of a ≥ 35% reduction from baseline in spleen volume.

7.7 Duration of Maintenance of a ≥ 35% Reduction from Baseline in Spleen Volume

Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume is only defined for responders. The duration will be calculated in the following three ways:

1. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume per IRF assessment to the date of first documented evidence of no longer meeting the ≥ 35% reduction from baseline criteria, that is: duration = Day of < 35% reduction from baseline - Day of first ≥ 35% reduction + 1,
2. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 35% reduction from baseline and ≥ 25% increase from nadir, and
3. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 10% reduction from baseline.

Patients will be censored at the last radiological assessment date if they are alive with no documented loss of response before analysis. The same analysis methods used for OS (section 7.3) will be used for duration of spleen response.

7.8 Best Response in Spleen Volume

Best response in spleen volume is based on the percent change in spleen volume from baseline to any time during the study on initial treatment. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline at any time on study on initial treatment will be presented by treatment arm.

7.9 Percent Change in Spleen Length

Although it is not a study objective, the percent change in spleen length below the left costal margin from baseline will be evaluated as well. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from baseline to Week 24 will be summarized by treatment arm. Patients with a missing Week 24 spleen length, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 50% reduction.
The percent change in spleen length from baseline to post baseline visits will be evaluated as well. Descriptive statistics will be provided by treatment arm. Additionally, the correlation of percent change from baseline in spleen volume and the percent change from baseline in spleen length below the left costal margin will be evaluated.

7.10 Endpoints Relating to RBC Transfusion

A patient is defined as RBC transfusion independent at any time point if that patient had no RBC transfusion in at least 3 months (90 days) preceding that time point as per Gale et al. 2011. The patient is RBC transfusion dependent if, in the 3 months (90 days) preceding, they were transfused with ≥ 2 RBC units per month on average. RBC transfusion independence/dependence is indeterminate if they were transfused with between 0 and 2 RBC units per month on average in that surveillance period (Gale et al. 2011). See Table 3 below. The frequency of RBC transfusion is defined by the number of units of RBC transfused per month over a specific period of time. The analyses planned for endpoints relating to RBC transfusions are defined below.

Table--3
Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	≥ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al. 2011	

7.10.1 Achievement of RBC Transfusion Independence

Achievement of RBC transfusion independence is defined in patients who were RBC transfusion-dependent at baseline, i.e., patients with a baseline RBC transfusion frequency (defined in section 7.10.3) of ≥ 2 units per month. For these patients, achievement of RBC transfusion independence at Week 24 is defined as having had no RBC transfusions in the 3 months (90 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of RBC transfusion independence.

7.10.2 Achievement of Reduced RBC Transfusion Dependence

Achievement of reduced RBC transfusion dependence is defined in patients who were not RBC transfusion independent at baseline, i.e., patients who were either RBC transfusion dependent or indeterminate at baseline. Reduction in RBC transfusion dependence is defined as having a ≥ 50% decrease in the average units of RBC transfusions per month over the 3 months (90 days) prior to their Week 24 visit date compared to baseline units of RBC transfusions per month. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of reduced RBC transfusion dependence.

7.10.3 Frequency of RBC Transfusions

Change from baseline in the frequency of RBC transfusions (units/month) will be summarized by arm over time through Week 24 using descriptive statistics in patients receiving at least one unit of RBC at baseline or while on study treatment. The frequency of RBC transfusions at baseline is defined as the number of units of RBC transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline RBC transfusion frequency is computed as the sum of the number of units of RBC transfusions in the 90 days prior to the informed consent date and the number of units of RBC transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ units\ from\ Transfusion\ History + \#\ units\ from\ IC\ to\ start\ of\ treatment)}{\left(90 + (treatment\ start\ date - IC\ date + 1)\right)\ days} \times 30\frac{days}{month}.$$

At post-baseline timepoints, the frequency of RBC transfusions is defined as the number of units of RBC transfusions per month in the three months (90 days) preceding the visit date. That is,

$$\frac{(\#\ units\ in\ the\ 90\ days\ preceding\ the\ visit\ date)}{90\ days} \times 30\frac{days}{month}.$$

7.11 Endpoints Relating to Platelet Transfusion

There are platelet count thresholds below which American Society of Hematology and American Society of Clinical Oncology guidelines (Schiffer et al and Slichter et al) recommend platelet transfusions, but standard definitions for platelet transfusion independence/dependence do not exist. We define platelet transfusion independence at any time point as having had no platelet transfusions in the month (30 days) preceding that time point. Otherwise, the patient is platelet transfusion dependent. See Table 4 below. The frequency of platelet transfusions is defined by the number of platelet transfusions over a specified period of time. Note that for the purposes of the analysis, platelet transfusion must be given to support platelet counts or to control non-surgical bleeding. Platelets given prophylactically for surgical procedures will not count towards platelet transfusion independence/dependence. The analyses planned for endpoints relating to platelet transfusions are defined below.

Table--4
Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

7.11.1 Achievement of Platelet Transfusion Independence

Achievement of platelet transfusion independence is defined in patients who were platelet transfusion-dependent at baseline, i.e., patients who had ≥1 platelet transfusion per month. For these patients, achievement of platelet transfusion independence is defined as having had no platelet transfusions in the month (30 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (section 7.8) will be used for achievement of platelet transfusion independence. Platelet transfusion independence/dependence will also be explored using other cut-offs and the continuous measure of the number of episodes of platelet transfusions.

7.11.2 Frequency of Platelet Transfusions

The change from baseline in the frequency of platelet transfusions (times/month) will be summarized by treatment arm every four weeks through their Week 24 visit date using descriptive statistics in patients receiving at least one platelet transfusion at baseline or while on study treatment. The frequency of platelet transfusions at baseline is defined as the number of platelet transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline platelet transfusion frequency is computed as the sum of the number of transfusions in the 90 days prior to the informed consent date and the number of transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ transfusions\ in\ Transfusion\ History + \#\ transfusions\ from\ IC\ to\ start\ of\ treatment)}{\left(90 + (treatment\ start\ date - IC\ date + 1)\right)\ days} \times 30 \frac{days}{month}.$$

At post-baseline timepoints, frequency of platelet transfusions is defined as the number of platelet transfusions in the month (30 days) preceding the visit date.

7.12 Clinical Improvement in Hemoglobin Level

Clinical improvement in hemoglobin level is defined for the subgroup of patients with baseline hemoglobin level of less than 100 g/L. A clinical improvement in hemoglobin level is defined as having a minimum of 20 g/L increase in hemoglobin level at Week 24 or becoming transfusion independent for 8 weeks or more, i.e., no RBC transfusions in the 8 weeks prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (section 7.8) will be used for clinical improvement in hemoglobin level.

7.13 Clinical Improvement in Platelet Count

Clinical improvement in platelet count is defined for the subgroup of patients with baseline platelet count below 50,000/μL. A clinical improvement in platelet count is defined as a minimum 100% increase from baseline in platelet count at Week 24 and an absolute platelet count of ≥ 50,000/μL for 8 weeks or more prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (section 7.8) will be used for clinical improvement in platelet count.

7.14 Change in JAK2V617F Allele Burden

The percent change from baseline to post-baseline visits in the level of the JAK2V617F mutation, defined as the percent of cells positive for the V617F mutation, will be calculated for each patient and summarized by treatment arm.

7.15 QOL Based on EQ-5D-5L and EORTC QLQ-C30

There are 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as an overall health score recorded on the EQ-5D-5L (Rabin et al. 2011). Each dimension has 5 levels coded 1 through 5 indicating increasing problems or difficulty in that dimension. There should be only one response for each dimension and missing values be coded as 9. The 5 codes are combined (concatenated) to compute a unique health state for each patient. These health states will be converted to country-specific index values (using a bridge to EQ-5D-3L responses and established country-specific index values) to facilitate the computation of quality-adjusted life years (QALYs). The overall health score has a possible value ranging from 0 to 100 and represents the patient's impression of their health, where 0 represents the worst health and 100 represents the best health imagined. Missing overall health scores will be assigned 999. See Table 5.

Table--5 Levels of the EQ-5D-5L Instrument	
EQ-5D-5L Dimensions and Scale	**Levels**
Mobility	1 to 5
Self-care	1 to 5
Usual activities	1 to 5
Pain/discomfort	1 to 5
Anxiety/depression	1 to 5
Overall Health	0 to 100

The frequency distribution of the codes in each dimension will be presented by treatment arm at baseline and at each post-baseline visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24). The overall health score and the index values will be summarized by treatment arm at baseline. The change from baseline in the overall health score and the index values will be summarized by treatment arm at Weeks 8, 16, and 24.

The EORTC QLQ-C30 Version 3 (Fayers et al. 2001) has 30 questions (items) which are combined to form 15 scales for the global health status/quality of life, functional, and symptom assessment of cancer patients. There is 1 global health status/quality of life scale comprising 2 items, each having possible individual scores ranging from 1 to 7 and, hence, a range of 6. There are 5 multi-item functional scales assessing physical, role, emotional, cognitive, and social functioning. Nine symptom scales assess fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Individual scores for the functional and symptom scales range from 1 to 4, with a range of 3. See Table 6.

Table--6 Scales of the EORTC QLQ-C30 Instrument	
EORTC QLQ-C30 Scales	**Scores for Individual Items**
Global Health Status/Quality of Life (2 items)	1 to 7
Functional (15 items)	
Physical	1 to 4
Role	1 to 4
Emotional	1 to 4
Cognitive	1 to 4
Social Functioning	1 to 4
Symptom (13 items)	
Fatigue	1 to 4
Nausea and Vomiting	1 to 4

Table--6 Scales of the EORTC QLQ-C30 Instrument	
EORTC QLQ-C30 Scales	**Scores for Individual Items**
Pain	1 to 4
Dyspnoea	1 to 4
Insomnia	1 to 4
Appetite Loss	1 to 4
Constipation	1 to 4
Diarrhea	1 to 4
Financial Difficulties	1 to 4

The scores for each scale will be set to missing if the answers to more than half of the items in the scale are missing. A raw score for each scale is determined by the average of the individual scores in each scale. The total score for the global health status/quality of life scale and each symptom scale is computed by $\left(\frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each functional scale is computed by $\left(1 - \frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each scale will be summarized by treatment arm at baseline. The change from baseline of the total score in each scale will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.16 Global Impression Assessment

There is 1 domain in the global impression assessment instrument with possible scores ranging from 1 (very much improved) to 7 (very much worse). The scores for the global impression assessment will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.17 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1. The primary hypothesis will be tested at α = 0.05 (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on
    a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24, and
    b. The difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24

individually. The study reaches its primary objective (claims to be successful) when both endpoints reach statistical significance (α = 0.05, 2-sided)

2. If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in a) the QD arm versus the BAT arm and b) the BID arm versus the BAT arm at the 2-sided 0.025 α-level.
    a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be tested at the 2-sided α = 0.025 level.
3. If the p-value is less than α = 0.025, the difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24 will be tested at the 2-sided α = 0.025 level.

7.18 Subgroup Analyses of Efficacy

Subgroup analyses are planned to evaluate any potential impact of demographics or baseline disease characteristics on the primary and secondary endpoints. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Depending on the sample size, other subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), JAK2617F mutation status at baseline (present vs. not present), prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day), RBC transfusion dependency at baseline (dependent vs. not dependent), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and baseline platelet count (< 50,000/μL vs. ≥ 50,000/μL). Additionally, BAT patients treated with ruxolitinib will be analyzed separately.

8 Exposure to Study Treatment

Exposure to initial study treatment will be evaluated by the duration of treatment, cumulative dose, actual dose intensity, and relative dose intensity in the safety population.

Duration of treatment (weeks): is defined as the duration from first day of initial study treatment to the last day of initial study treatment, i.e.,

$$\frac{(\text{Date of last dose of initial study treatment} - \text{date of first dose of initial study treatment} + 1)}{7},$$

Descriptive statistics will be provided for duration of treatment by treatment arm. Duration of treatment will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median duration of treatment and the corresponding 95% confidence interval, and estimated duration of treatment curves will be presented by arm.

Cumulative dose (mg): is defined as the sum of all doses of initial study treatment taken and descriptive statistics will be provided for the pacritinib arms only. The numbers and

percentages of patients with any dose modifications will be provided by treatment arm. Reasons for dose modifications will also be summarized.

Actual dose intensity (ADI, mg/day) = (total dose taken in mg) ÷ (duration of treatment in days) and descriptive statistics will be provided for the pacritinib arms only.

Relative dose intensity (RDI, %) = (ADI) ÷ (planned daily dose) * 100. The planned pacritinib dose is 400 mg/day and descriptive statistics will be provided for the pacritinib arms only.

Exposure to pacritinib after crossover will be analyzed separately (section 10).

Time to crossover will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median time to crossover and the corresponding 95% confidence interval, and estimated time to crossover curves will be presented for the BAT arm. Descriptive statistics for the time to crossover in weeks will be presented for patients who crossed over from BAT to pacritinib, with duration defined as (date of first dose of pacritinib after crossover – date of first dose of initial study treatment + 1)/7. The numbers and percentages of patients taking each BAT therapy will be presented. Additionally, the numbers and percentages of the first BAT therapy taken will be presented.

9 Safety Analysis

Safety analyses include treatment emergent adverse events, clinical labs, ECG, vital signs, performance status, and any abnormal findings observed during the performance of physical examinations by treatment received after randomization through the end of initially assigned study treatment + 30 days. The safety data after patients crossover from BAT to pacritinib will be analyzed separately (section 10).

9.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Analysis of AEs will be based on Treatment Emergent Adverse Events (TEAEs). A TEAE is defined as an adverse event (AE) occurring after the first dose of study treatment and within 30 days after the last study treatment date. In addition, an AE is also considered a TEAE if it is an AE starting more than 30 days after the last study treatment, but the investigator assessed the AE with a relationship to study drug of “Possible”, “Probable”, or “Definite” or if it is an AE with a missing start date but with an end date after the first study drug dose date. An AE occurring after the first dose of study drug that also occurred prior to the first dose of study drug is only considered a TEAE if the AE worsened in grade after the first dose of study drug. An AE occurring after crossover to a pacritinib regimen that also occurred prior to crossover is only considered a TEAE if the AE worsened in grade after crossover.

TEAEs will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE, having a TEAE in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. CTCAE (version 4.0) grades and relationship to study medication will be summarized as appropriate. For summaries by CTC grade or relatedness, only the highest CTC grade or degree of relatedness of each SOC and/or preferred term will be summarized. A patient having the same event more than once will be counted only once and by greatest severity or closest relationship.

In addition, serious TEAEs (SAEs), CTC grade 3 or 4 TEAEs, TEAEs leading to study medication discontinuation, interruption, or dose reduction, TEAEs with an outcome of death, related TEAEs (see section 9.1.3.2 of the protocol), and TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be summarized. A listing of all SAEs will be generated.

The preferred term of TEAEs of all grades and grade 3 or 4 TEAEs will also be presented for each treatment arm by decreasing frequency in the pooled pacritinib arms. These summaries will also be repeated for TEAEs of all grades and grade 3 or 4 TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first).

The numbers and percentages for the causes of all deaths will be presented by treatment arm. A listing of all deaths, both on and off treatment, will also be generated. On treatment deaths are defined as deaths that occur on treatment and within 30 days of treatment discontinuation.

9.1.1 TEAEs of Special Interest

The following TEAEs are considered to be of interest: Diarrhea, Nausea, Vomiting, Neutropenia (including neutrophils decreased), Thrombocytopenia (including platelets decreased), Anaemia (including hemoglobin decreased), Infections and Infestations (SOC), Cardiac AEs, Neurotoxicity, and Haemorrhages. The preferred terms included in Cardiac AEs of special interest are all terms in the Standardised MedDRA Queries (SMQs) of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events. The preferred terms included in the Haemorrhages AEs of special interest are all terms in the SMQ of Haemorrhages. See Appendix 15.1 on page 39 for the preferred terms for neurotoxicity events of special interest.

TEAEs of special interest will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE of special interest, having a TEAE of special interest in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. Cardiac and Haemorrhages TEAEs of special interest will also be summarized by SMQ. CTC grade 3 or 4 TEAEs of special interest and those starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be similarly summarized. Additionally, the incidence and prevalence of each TEAE of special interest with 8-week intervals from

baseline will be presented by treatment arm. Incidence and prevalence will also be presented for grade 3 or 4 TEAEs of special interest.

Times to onset and resolution of the first TEAE will also be analyzed for each TEAE of special interest. Time to onset of the first TEAE is defined as the time from start of study drug to the start date of the first occurrence of the TEAE, i.e., time in days is calculated as (start date of first occurrence of the TEAE) – (date of first dose of study treatment) + 1. Subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. Time to resolution of first TEAE is defined as the time from the start date of the first occurrence of the TEAE to its resolution (AE outcome being "recovered/resolved" in CRF). In the absence of resolution, subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. The same analysis methods used for OS (section 7.3) will be used for time to onset of first and time to resolution of these TEAEs of special interest.

9.2 Clinical Laboratory Measurements

Hematology and Chemistry laboratory measures are collected via central lab.

9.2.1 Hematology

The hematology measurements to be analyzed are: hemoglobin, platelet counts, white blood cell counts, neutrophil counts, lymphocyte counts, monocyte counts, and eosinophil counts. When there are non-missing results for both automated and manual hematology differentials, the manual results will be used for analysis if all the hematology results being analyzed are present.

The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each hematology measure. Descriptive statistics of change and percent change from baseline in hematology values will be presented by visit. Plots of the percent change in hemoglobin and platelet counts over time will be presented.

9.2.2 Chemistry

The following clinical chemistry measures will be analyzed: ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, indirect bilirubin, creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid levels. Summaries of the worst CTCAE grade will be presented for ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, creatinine, sodium, potassium, calcium, phosphate, magnesium, albumin, glucose, and cholesterol in either direction of abnormality (i.e., abnormally low or high). The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each chemistry measure. Descriptive statistics of change and percent change from baseline in clinical chemistry values will be presented by visit.

The derived visit window definitions for clinical hematology and chemistry are displayed in Table 7.

Table--7
Analysis Window Definitions for Clinical Chemistry and Hematology Results

Visit	**Nominal Day**	**Range**
Baseline	1 (first dose date)	[-14, 1]
Week 3	15	[2, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.3 Other Clinical Safety

9.3.1 Electrocardiogram (ECG)

The frequency distribution of abnormal ECG measurements on study (after the first study drug treatment through the last dose of study drug) will also be summarized. The proportion of subjects with the following QTc intervals will tabulated by visit (including worst and last on treatment values) and treatment arm:

- A measured value > 450 ms
- A measured value > 480 ms
- A measured value > 500 ms
- > 30 ms above baseline
- > 60 ms above baseline

9.3.2 Vital Sign Measurements

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) of change and percent change from baseline in vital sign measurements, including weight, will be presented by visit.

The frequency distribution of abnormal vital sign measurements (as noted by the investigator) on study (on or after the first day of treatment) will be displayed.

A table summarizing clinically notable blood pressure and weight measurements which are aligned with CTCAE cut-offs, where available, will be displayed. The proportion of subjects whose worst observed values while on study (on or after the first day of treatment) meet the following clinically notable criteria will be tabulated by treatment arm:

- Systolic Blood Pressure
  - < 85 mm Hg
  - ≥ 140 - < 160 mm Hg
  - ≥ 160 mm Hg
- Diastolic Blood Pressure
  - < 50 mm Hg
  - ≥ 90 - < 100 mm Hg
  - ≥ 100 mm Hg
- Weight gain from baseline
  - ≥ 5% - < 10% increase
  - ≥ 10% - < 20% increase
  - ≥ 20% increase
- Weight loss from baseline
  - ≥ 5% - < 10% decrease
  - ≥ 10% - < 20% decrease
  - ≥ 20% decrease

The derived visit window definitions for vital signs are displayed in Table 8.

Table--8
Analysis Window Definitions for Vital Signs Results

Visit	**Nominal Day**	**Range**
Baseline	1 (first dose date)	[-14, 1]
Week 2	8	[2, 11]
Week 3	15	[12, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]

Table--8 Analysis Window Definitions for Vital Signs Results		
Visit	**Nominal Day**	**Range**
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.4 Concomitant Medication

A medication will be considered a concomitant medication if it was taken by the patient at any time on study (on or after the first day of treatment and within 30 days after the last dose of study drug). The following will also be considered concomitant medications:

- Medications missing both start and stop dates.
- Medications having a start date prior to the last dose of study drug and missing the stop date.

Concomitant medications will be summarized by ATC class and preferred term.

9.5 Supplemental Procedures

Procedures received from the first day of treatment to the last day of treatment will be summarized by SOC class and preferred term.

9.6 Subgroup Analysis of Safety

Treatment-emergent adverse events, including all AEs, grade 3/4 AEs, and SAEs, and hematology toxicity will also be summarized by subgroups as appropriate. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Additionally subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), prior treatment with JAK2 inhibitors (yes vs. no), baseline platelet count (< 50,000/μL vs. ≥ 50,000), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and JAK2V617F mutation status at baseline (present vs. not present). Additionally, safety within the subgroup of BAT patients treated with ruxolitinib will be explored.

10 Analysis of Patients who Crossover from BAT to Pacritinib

Selected descriptive efficacy and safety summaries defined above will be repeated for crossover patients. Baseline for these summaries will be considered to be the last assessment prior to or at crossover. The following summaries will be presented for crossover patients.

- **Best response in spleen volume** is based on the percent change in spleen volume from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **The moving average of TSS** as defined in section 7.2.5 for BAT patients after crossover.
- **Best response in spleen length** is based on the percent change in spleen length from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **Exposure to study treatment** as outlined for the pacritinib arms in section 8.
- **Deaths**: the numbers and percentages for each cause of death after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **TEAEs** as outlined in section 9.1 that occur after crossover will be summarized by pacritinib regimen and in the pooled regimens.

Reasons for crossover from BAT to a pacritinib regimen will also be summarized. A listing of all patients who crossover from BAT to a pacritinib regimen will also be generated.

11 Pharmacokinetic and Pharmacodynamic Analysis

The study pharmacokineticist will review the individual concentration-time data prior to the conduct of PK analysis to ascertain the integrity of the concentration-time data set. Population PK/PD analysis will be conducted to characterize the exposure of pacritinib in MF patients following administration of 400 mg QD and 200 mg BID regimens. The PK and PD measures will be summarized with descriptive statistics by pacritinib treatment arm. In addition, the exposure-response relationship for pacritinib will be characterized on key safety (e.g., thrombocytopenia, myelosuppression, anemia, hemorrhage, GI, cardiac failure, and arrhythmia AEs) and the primary and secondary efficacy (i.e., reduction in spleen volume and reduction in TSS) endpoints. The correlation of Week 24 spleen volume and TSS with Week 24 STAT3 phosphorylation will be evaluated as well.

12 Power and Sample Size

It is assumed that the proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. These assumptions were made based on response rates seen

in the COMFORT-I and -II randomized controlled trials and the SB1518-2007-001 and SB1518-2008-003 Phase 2 trials. It is also assumed that the proportion of patients achieving a ≥ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm. These assumptions were made based on response rates seen in the COMFORT-I randomized controlled trial.

With these assumptions, the original sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. For the primary hypothesis (pooled QD/BID vs. BAT), this sample size provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is ≥ 93% to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

Due to the FDA clinical hold, the FAS is being used to evaluate the study objectives. It is estimated that a total of 220 patients meet the FAS definition. With the same assumptions above, this sample size provides 97% and >99% power to test the primary hypothesis (pooled QD/BID vs. BAT) of a treatment difference in spleen volume reduction and a treatment difference in TSS reduction, respectively, at an α-level (2-sided) of 0.05. This sample size also provides 86% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

13 Data Handling Rules

13.1 Definition of Baseline Value

The baseline value for safety analyses will be defined as the last assessment prior to the start of treatment, unless otherwise specified.

13.2 Partial Current MF Diagnosis Date

For patients who have a partial diagnosis date, the 15th of the month will be used if day is missing, and July 15th will be used if both the month and day are missing.

13.3 Partial or Missing AE Onset and Resolution Dates

For AE summaries, the missing day of onset of an adverse event will conservatively be set to:

- First day of the month that the AE occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the AE occurred.
- The 15th of the month and year if the AE month and year are before the month and year of the first treatment.

If the onset date of an adverse event is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 1st of the year if the AE year is before the year of the first study treatment.

If the day of resolution of an adverse event is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year, whichever is earlier. If the day of resolution of an adverse event is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented “as is” in listings.

13.4 Laboratory Results Reported as a Range

Laboratory results that are reported as less than or greater than a certain value (limit of quantification) or as a range of values will be imputed for analysis using the rules described below.

Myeloblast Percentages

- Myeloblast results in the hematology data reported as <X% will be imputed with the value (X-1)% for analysis.
- Myeloblast results in the hematology data reported as ≤X% will be imputed with the value X% for analysis.
- Myeloblast results in the hematology data reported as X-Y% will be imputed with the value Y% for analysis.

Other Laboratory Results

- Laboratory results reported as <X will be imputed with the value (X-1) for analysis. Results reported as <X.Y will be imputed by subtracting one from the

last significant digit (Y). Results reported as <0.1 will be imputed as 0 for analysis as long as the normal range extends to 0.

- Laboratory results reported as >X will be imputed with the value (X+1) for analysis. Results reported as >X.Y will be imputed by adding one to the last significant digit (Y).

14 References

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15 Appendix

15.1 Neurotoxicity Events of Special Interest

The neurotoxicity events of special interest include, but are not limited to, amnesia, blindness, burning sensation, carpal tunnel syndrome, cognitive disorder, confusional state, disturbance in attention, dizziness, dysgeusia, dyskinesia, dysphonia, dysstasia, gait disturbance, facial neuralgia, gait disturbance, headache, hemianopia, hyperaesthesia, hypoaesthesia, incontinence, lethargy, memory impairment, migraine, muscular weakness, myopathy, neck pain, neuralgia, neuropathy peripheral, paraesthesia, Parkinson's disease, peroneal nerve palsy, sensation of heaviness, status epilepticus, syncope, tinnitus, tremor, urinary incontinence, urinary retention, vertigo, vertigo positional, vestibular disorder, VIIth nerve paralysis, vision blurred, visual field defect, and visual impairment. Additional terms will be included as they are identified.

Study PAC326 (PERSIST-2)

Statistical Analysis Plan

Version: 1.2

05 August 2016

A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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Protocol Version: Amendment 2
Protocol Version Date: 31 July 2014

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1. SCOPE

This document describes the statistical analyses and data presentations to be performed for protocol PAC326, "A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis".

This statistical analysis plan (SAP) provides a detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of pacritinib in the scope of the study. It provides additional details concerning the statistical analyses that were originally outlined in the protocol. This SAP will be finalized and signed prior to the unblinding of the clinical database. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post hoc in the clinical study report.

The United States Food and Drug Administration (FDA) full clinical hold on 08 February 2016 requiring all patients to discontinue pacritinib has major implications for the statistical analyses that were originally outlined in the protocol. Intent-to-treat (ITT) analyses of efficacy and safety that include follow-up data after 08 February 2016 would produce biased estimates - likely underestimates - of the benefits and risks of pacritinib treatment that would have occurred in a setting of real world adherence. Therefore, to enable analyses to be conducted that preserve the integrity of randomization by following the ITT principle and that are also representative of efficacy and safety in the setting of real world adherence to pacritinib, the following modifications have to be made to the originally planned analyses specified in the protocol:

- For the co-primary endpoints regarding spleen volume and symptom response at Week 24 (as well as for other endpoints assessed at Week 24), ITT analyses will be conducted using all patients randomized at least 22 weeks prior to 08 February 2016. In compliance with the ITT principle, these analyses include all patients having a date of randomization that enabled them to contribute information about a Week 24 endpoint, recognizing the 2-week window that is allowed for patients to reach study visits. This is in alignment with the definition of the full analysis set in ICH E9 – Statistical Principles for Clinical Trials.
- ITT analyses for time-to-event endpoints will be based on follow-up through the truncation date, 08 February 2016.

- ITT analyses of efficacy and safety endpoints that are based on follow-up without truncation, i.e., that will include data after 08 February 2016, will be performed as supportive analyses. While such analyses preserve the integrity of randomization, the corresponding estimates of efficacy and safety will carry a substantive risk for bias since evidence after 08 February 2016 will not reflect real-world adherence to pacritinib treatment.
- All analyses of all efficacy and safety endpoints will take place after the last patient completes the 30-day Post Treatment Termination assessments instead of the Week 24 assessments.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the efficacy of pooled once-daily [QD] and twice-daily [BID] pacritinib dosing arms with that of best available therapy (BAT) in patients with thrombocytopenia and primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The efficacy co-primary endpoints for this analysis are the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) and the proportion of patients achieving a ≥ 50% reduction in the Total Symptom Score (TSS) from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form 2.0 (MPN-SAF TSS 2.0).

2.1.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of QD pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2. To compare the efficacy of BID pacritinib with that of BAT, as assessed by the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 by MRI or CT and the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 on the MPN-SAF TSS 2.0.

2.1.3 Exploratory Objectives

The exploratory objectives are to evaluate treatment effects on the following endpoints:

1. Overall survival (OS)
2. Progression-free survival (PFS)
3. Leukemia-free survival (LFS)
4. Time to achievement of ≥ 35% reduction in spleen volume from baseline by MRI or CT
5. Duration of maintenance of ≥ 35% reduction from baseline in spleen volume
6. Best response in spleen volume by MRI or CT
7. Duration of treatment
8. Achievement of red blood cell (RBC) transfusion independence
9. Achievement of reduced RBC transfusion dependence
10. Clinical improvement in hemoglobin level
11. Frequency of RBC transfusions
12. Achievement of platelet transfusion independence
13. Clinical improvement in platelet count
14. Frequency of platelet transfusions
15. Change in *JAK2V617F* allele burden
16. Quality of life, as measured by the EQ-5D-5L and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 version 3.0.

2.1.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic (PK) and pharmacodynamic (PD) objectives are to assess exposure and exposure-response relationships on PD effect (i.e., pSTAT3 inhibition) and the safety and efficacy of pacritinib.

2.2 Hypotheses

The hypothesis tests described below are based on the ITT population (Section 5.2).

2.2.1 Primary Hypothesis

The primary hypothesis of the study is that treatment with a once- or twice-daily dose of pacritinib results in

1. a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24, and

2. a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

2.2.2 Secondary Hypotheses

The secondary hypotheses of the study are:

- Treatment with a once-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.
- Treatment with a twice-daily dose of pacritinib results in a greater proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 and a greater proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0 than treatment with BAT.

3. SUMMARY OF STUDY DESIGN

This study is a multicenter, randomized, controlled, phase 3 trial. It will compare the efficacy and safety of two dose schedules of pacritinib, in pooled and individual arm analyses versus BAT in patients with thrombocytopenia and PMF, PPV-MF, or PET-MF. A total of 300 eligible patients will be randomized in a 1:1:1 allocation to pacritinib 400 mg dosed QD, pacritinib 200 mg dosed BID, or BAT:

- Pacritinib 400 mg taken orally, QD
- Pacritinib 200 mg taken orally, BID
- BAT

BAT includes any physician-selected treatment for PMF, PPV-MF, or PET-MF, such as approved JAK2 inhibitors (administered according to package insert for patients with thrombocytopenia), and may include any treatment received before study entry. For example, BAT may include ruxolitinib, other approved JAK2 inhibitors, hydroxyurea, glucocorticoids, erythropoietic agents, immunomodulatory agents, mercaptopurine, danazol, interferons, cytarabine, melphalan, or other agents. BAT also includes "no treatment" and symptom-directed treatment without MF-specific treatment.

During the study, patients taking pacritinib may not receive chemotherapy, immunotherapy, corticosteroids, erythropoietic agents, or other treatment for PMF, PPV-MF, or PET-MF. Spleen volume will be measured by MRI or CT at baseline and every 12 weeks thereafter using the same imaging modality, through 48 weeks post randomization or until progression of disease or withdrawal from study treatment. TSS as measured by MPN-SAF TSS 2.0 will be recorded daily through 48 weeks post treatment initiation or until end of study treatment, whichever occurs first.

Patients will also be followed for safety, LFS, OS, frequency of RBC and platelet transfusions, and other exploratory endpoints for 3 years after their Week 24 visit or the end date of treatment with the initially assigned study drug, whichever comes first.

An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pacritinib. No interim efficacy analysis is planned.

4. RANDOMIZATION AND BLINDING

Randomization will be stratified by geographic region (US vs. Canada vs. Europe vs. rest of the world [ROW]), the risk category (intermediate-1 vs. intermediate-2 vs. high risk per Passamonti et al. 2010) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). To be included in the > 100,000/μL group, patients must meet both of the following criteria: 1) rebound platelet count > 100,000/μL and 2) > 50% increase above their first qualifying platelet value after consent. Permuted blocks within strata will be used to restrict treatment allocation. The most recent platelet count obtained prior to randomization on Days -3 to 1 during the screening period will be the basis for stratification. For patients who receive any platelet transfusions during this period, a pre-transfusion platelet count should be obtained within 8 hours prior to transfusion, and this platelet count should be used for stratification. Should more than one such nadir count be obtained prior to randomization, the count obtained closest to randomization will be used for stratification. Should patients receive frequent platelet transfusions and platelet counts, clinical judgment should be used to identify the most appropriate nadir platelet count obtained prior to the last transfusion before randomization.

Although this is an open label study, the double-blind procedure was followed in-house (see the PERSIST-2 Study Blinding Plan). The sponsor (with the exception of pharmacovigilance, site monitoring, clinical document control, and drug supply personnel) and independent radiographic assessors will remain blinded to study treatment assignment, including study drug administration records, until database lock. The clinical database will be unblinded after data review has been completed, protocol violations have been identified, the data have been declared clean and locked, and this SAP has been signed off.

5. ANALYSIS POPULATIONS AND APPROACHES TO ANALYSIS

5.1 ITT Population

The ITT population is defined as all randomized patients. The primary analyses of the efficacy endpoints will be based on data truncated at 08 February 2016, the day of the FDA clinical hold. This means that endpoints assessed at Week 24 will be based on the patients randomized prior to 07 September 2015, 22 weeks prior to 08 February 2016 (with consideration for the 2-week window allowed for study visits) and time-to-event endpoints will be censored at 08 February 2016.

Patients in this population will be analyzed according to the arm to which they were assigned at randomization. This population will be used for the analyses of the efficacy endpoints as well as for the analyses of demographics, baseline characteristics, and medical history.

5.2 Evaluable Population

The evaluable population for each endpoint is defined as all randomized patients who have evaluable baseline and follow up assessments relevant for that endpoint. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The evaluable population will be used for supportive analyses of the efficacy endpoints.

5.3 Per-protocol Population

The per-protocol (PP) population is defined as all randomized patients who receive any study treatment and have no major protocol violations. The major protocol violations that will exclude patients from the PP population are defined as follows:

- Did not meet one of the following inclusion criteria:
  - Inclusion 1: Intermediate-1 or -2 or High risk PMF, PPV-MF, or PET-MF
  - Inclusion 4: Palpable splenomegaly ≥ 5 cm below the LCM by physical examination
  - Inclusion 5: TSS ≥ 13 on the MPN-SAF TSS 2.0, not including the inactivity question
  - Inclusion 8: Peripheral blast count < 10%
  - Inclusion 12: At least 6 months from prior splenic irradiation
  - Inclusion 13: At least 12 months from prior ^{32}P therapy
  - Inclusion 15: At least 2 weeks since any treatment for PMF, PPV-MF, or PET-MF
- Did not meet one of the following exclusion criteria:
  - Exclusion 3: Prior treatment with more than 2 JAK2 inhibitors or with pacritinib
  - Exclusion 6: History of splenectomy or planning to undergo splenectomy
  - Exclusion 10: Inflammatory or chronic functional bowel disorder such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or constipation
  - Exclusion 15: Erythropoietic agent within 28 days prior to randomization
  - Exclusion 16: Thrombopoietic agent within 14 days prior to randomization
- Patients in the pacritinib arms taking any of the BAT treatment options for treatment of MF.
- Visits scheduled outside the analysis window specified for baseline and Week 24 for the relevant endpoint.

Patients in the PP population will be analyzed according to the treatment actually received and their correct strata if there is mis-stratification. The PP population will be used for the supportive analyses of the efficacy endpoints if there is a difference of more than 10% of the patients between the evaluable and PP populations.

5.4 Safety Population

The safety population is defined as all randomized patients who receive at least one dose of study treatment, including patients on the BAT arm treated with watchful waiting. All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received.

5.5 Pharmacokinetic/Pharmacodynamic Evaluable Population

The pharmacokinetic/pharmacodynamic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK or STAT3 phosphorylation analysis.

6. DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

6.1 Demographics and Baseline Characteristics

Descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum) will be provided for those variables measured on a continuous scale. The frequency distribution (counts and percentages (n and %)) will be provided for those variables measured on a nominal scale.

The demographic and baseline characteristics will be analyzed with the following variables in the ITT population.

6.1.1 Demographic Variables

Age, age category (< 65 years vs. ≥ 65 years), gender, race, ethnicity, height, weight, body mass index, ECOG performance status, and geographic region.

6.1.2 Baseline Disease Characteristic Variables

Spleen length by physical exam, bone marrow biopsy (cellularity, reticulin and collagen fibrosis staging, and myeloblast percentage), JAK2V617F status, baseline platelet count and category (< 50,000/μL vs. ≥ 50,000/μL), rebound platelet category, baseline hemoglobin and category (< 100 g/L vs. ≥ 100 g/L), current MF diagnosis, time since current MF diagnosis, non-bone marrow diagnostic criteria at initial MF diagnosis, current DIPSS risk category, transfusion history (within 90 days prior to Informed Consent date), red blood cell (RBC) transfusion dependence, platelet transfusion dependence, prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), prior treatment with ruxolitinib (yes vs. no), duration of prior treatment with ruxolitinib (< 6 months vs. ≥ 6 months), and most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day).

6.2 Prior Therapy and Medical History

Prior therapy and medical history are any therapy or diseases that occurred or any medication taken prior to the first day of study drug dosing or prior to the randomization date if patients were never dosed. Prior therapy includes both prior MF and non-MF therapies. Both will be summarized for patients in the ITT population.

For prior MF therapy, number of prior radiation therapies, type of prior radiation therapy, number of prior systemic medical therapy regimens, type of prior systemic medical therapies, and transfusion history for each cellular blood product will be summarized by the frequency distribution (n and %).

Prior non-MF therapies will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term using WHO Drug Dictionary version 01, March 2013.

Medical history will be summarized by frequency distribution (n and %) of system organ class and preferred term by MedDRA dictionary version 16.0 for patients in the ITT population. A listing of medical history will also be generated.

7. EFFICACY ANALYSIS

The efficacy and exploratory endpoints are defined below. Additionally, the planned analyses for these endpoints are described.

7.1 Reduction in Spleen Volume

The first co-primary efficacy endpoint of the study is the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI or CT based on independent radiology facility (IRF) reads. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). Patients with a missing Week 24 spleen volume, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 35% reduction. To test the primary and secondary hypotheses, the treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. These analyses will be performed in the ITT population of patients randomized at least 22 weeks prior to 08 February 2016. The same analyses (serving as supportive analyses) will be performed based on the full ITT cohort without truncation on 08 February 2016, and on the evaluable and PP (if necessary) populations.

As a secondary analysis, the treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count (≤ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact Cochran-Mantel-Haenszel (CMH) test will be used to test if treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.

The proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline to other post-baseline time points will be summarized as well. In addition, using the evaluable population, descriptive statistics of the percent change in spleen volume from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

The post-baseline spleen scan data used for all analyses will be the scans collected at the nominal post-baseline visit or Termination scans collected within 2 weeks (+/- 14 days) of the nominal study day. For example, Termination scans collected within 2 weeks (+/-14 days) of study day 168 (nominal week 24 study day) will be considered the Week 24 scans. Scans collected in BAT patients on or after crossover to pacritinib will be excluded from the primary analysis. Baseline scans are the scans collected at the screening MRI visit.

7.2 Improvement in Total Symptom Score

The second co-primary efficacy endpoint of the study is the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

7.2.1 TSS Algorithm

- **The daily TSS** is the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side.
- **The baseline TSS** is the mean of the daily TSS over the 7 consecutive days prior to the start of treatment. Please note that in the protocol, baseline TSS was defined relative to randomization date with the assumption that treatment would start at randomization. Missing values during these days are handled as described below (Section 7.2.2).
- **The Week 24 TSS** is the mean of the daily TSS obtained during the 28 consecutive days prior to the Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Patients with a missing baseline or Week 24 TSS, including those who meet the criteria for disease progression before Week 24 and those who drop out of the study before Week 24, or patients who cross over to treatment with pacritinib prior to Week 24 will be considered to have not achieved the ≥ 50% reduction. Events occurring prior to Week 24 occurred prior to study day 154.
- The percent reduction in TSS from baseline to Week 24 is computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 24 TSS - Baseline TSS}}{\text{Baseline TSS}}\right) * 100.$$

Other post-baseline TSS and percent reduction from baseline are similarly defined, except that the post-baseline visit date alone is used as a point of reference at timepoints at which spleen volume is not assessed but a study visit is scheduled and nominal study day alone is used as a point of reference at timepoints at which a study visit is not scheduled. In BAT patients, only post-baseline symptom scores reported prior to crossing over to pacritinib will be used for analysis.

7.2.2 Handling of Missing Values

- If any of the seven individual symptoms scores are missing, the TSS for that day will be considered as missing.
- The baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to the start of study treatment.
- The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Missing TSS at other post-baseline timepoints is similarly handled.

7.2.3 Primary Analyses

The primary analysis of the improvement in TSS will compare the proportion of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24. The numbers and percentages of patients achieving a ≥ 50% reduction in TSS from baseline to Week 24 will be summarized by the 3 arms (QD, BID, and BAT). The treatment differences in the proportions comparing the pooled pacritinib arms (QD + BID) to the BAT arm, comparing the QD arm to the BAT arm, and comparing the BID arm to the BAT arm will be tested using the Fisher exact test, and the 95% (97.5% for individual PAC arm comparisons) confidence intervals based on the Agresti-Caffo method will be provided. These analyses will be performed in the ITT population of patients randomized at least 22 weeks prior to 08 February 2016. The same analyses will be performed based on the full ITT, evaluable, and PP (if necessary) populations as supportive analyses.

7.2.4 Secondary Analyses

The treatment differences in the proportions comparing the pooled pacritinib arms to BAT, QD to BAT, and BID to BAT will be tested within strata defined by region (US vs. Canada vs. Europe vs. ROW), risk category (intermediate-1 vs. intermediate-2 vs. high), and by rebound platelet count ($\leq$ 100,000/μL vs. > 100,000/μL), in the strata with sufficient patients for valid statistical testing. The exact CMH test will be used to test if treatment differences are preserved across strata. A sensitivity analysis may be performed to evaluate the impact of any mis-stratification.

The same analyses will be repeated with the proportion of patients achieving a $\geq$ 50% reduction in TSS from baseline to other post-baseline time points. In addition, using the evaluable population, descriptive statistics of the percent change in TSS from baseline to post-baseline visits will be presented by treatment arm.

Treatment differences comparing the individual pacritinib arms will also be explored.

7.2.5 Exploratory Analyses

The percent change from baseline over time in individual symptom scores as measured by the MPN-SAF TSS 2.0 will be evaluated and descriptive statistics of the percent change in individual symptom scores from baseline over time will be presented. The individual symptom scores for each timepoint will be computed as the mean of the daily individual symptom scores obtained during the 28 days prior to that spleen volume scan date. The individual symptom scores at each timepoint will be considered missing if fewer than 20 daily individual symptom scores are available out of the 28 consecutive days prior to that timepoint.

The moving average of TSS will be evaluated as well. The TSS score for a timepoint will be computed as the mean of the 7 daily TSS prior to that timepoint. If fewer than 4 daily TSS are available out of the 7 days, the moving average TSS will be considered missing for that timepoint.

The correlation of Week 24 TSS with Week 24 spleen volume and patient global impression assessment (as anchors) will be computed and tested for a significant difference from zero. The effect of the usage of pain medication on symptom scores will also be explored based on the patient-reported pain medication log.

7.3 Overall Survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause. By original plan, the OS analysis was to include long term follow-up, i.e., follow-up until 3 years after the last patient's Week 24 visit. As a result of the FDA clinical hold, the primary analysis of survival data will be based on a truncation of follow-up on 08 February 2016. It is noteworthy that, even with this truncation, the effect of pacritinib will be confounded by crossover of BAT patients to a pacritinib regimen.

OS will be estimated using the Kaplan-Meier product-limit method. Reasons for censoring will be summarized by treatment arm. The effect of the following prognostic factors for OS will also be explored using Cox proportional hazards (PH) models: DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and individual components, baseline platelet count (< 50,000/μL vs. ≥ 50,000 and continuously), MF type (primary vs. secondary), time since diagnosis, JAK2 mutation status/allele burden, ECOG performance, MF fibrosis staging, and number of risk factors. Cox PH models will also be used to explore modification of the effect of treatment on OS.

As supportive analyses of OS, these analyses will be repeated without truncating follow-up on the day of the FDA clinical hold.

7.4 Progression Free Survival (PFS)

PFS is defined as the time from the start of treatment to the date of progressive disease or death due to any cause (whichever is first reported). PFS will be based on disease progression assessment by the investigator using the definition below. The progression date is the earliest time when any progression is observed. Progression of disease is defined as one or more of the following: splenic progression (defined as in increase in splenic volume of ≥ 25% from baseline based on MRI or CT scan), splenic irradiation, splenectomy, or leukemic transformation (defined as an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%). Patients will be censored at the earlier of the FDA clinical hold date (08 February 2016) or the last progressive disease assessment date if they are alive with no documented progression before analysis. Table 1 below provides the rules for progressive disease events and censoring for the primary analysis.

Table 1. PFS Event and Censoring Rules

	Situation	Date of Event or Censoring
PFS Event	Progression documented	Earliest date when any progression is observed
	Death	Date of death if no progression
Censor	No post-baseline disease progression assessments	Day 1
	No progression	Earlier of the FDA clinical hold date (08FEB2016) or date of last progressive disease assessment with evidence of no progression
	Lost to follow-up	Earlier of the FDA clinical hold date (08FEB2016) or date of last progressive disease assessment showing no progression

PFS will be estimated using the Kaplan-Meier product-limit method. Survival times will be censored on the day of the FDA clinical hold, 08 February 2016. Reasons for censoring will be summarized by treatment arm. As supportive analyses, these analyses will be repeated without censoring on the day of the FDA clinical hold.

7.5 Leukemia Free Survival (LFS)

LFS is defined as the time from the start of treatment to the date of leukemic transformation or death due to any cause. Leukemic transformation is defined as the first date of an increase in peripheral blood blast percentage to ≥ 20% sustained for ≥ 8 weeks and/or a bone marrow blast count ≥ 20%. Patients will be censored at the earlier of the FDA clinical hold date (08FEB2016) or the date of last assessment for leukemic transformation if they are alive with no documented transformation before analysis. Table 2 provides the rules for LFS events and censoring for the analysis of LFS.

Table 2. LFS Event and Censoring Rules

	Situation	Date of Event or Censoring
LFS Event	Leukemic transformation documented	Earliest date when transformation is observed
	Death	Date of death if no leukemic transformation
Censor	No post-baseline disease progression assessments	Day 1
	No leukemic transformation	Earlier of the FDA clinical hold date (08FEB2016) or date of last assessment with evidence of no leukemic transformation
	Lost to follow-up	Earlier of the FDA clinical hold date (08FEB2016) or date of last assessment showing no leukemic transformation

The same analysis methods used for PFS (Section 7.4) will be used for LFS.

7.6 Time to Achievement of a ≥ 35% Reduction from Baseline in Spleen Volume

Time to achievement of a ≥ 35% reduction from baseline in spleen volume will be calculated as the time from start of treatment to the date of the first scan with a ≥ 35% reduction from baseline in spleen volume, that is: date of first ≥ 35% reduction – start of treatment date + 1. Patients will be censored at the earlier of the FDA clinical hold date (08FEB2016) or the last radiological assessment date if they have not yet achieved the ≥ 35% reduction from baseline in spleen volume by the Termination visit. The same analysis methods used for PFS (Section 7.4) will be used for time to achievement of a ≥ 35% reduction from baseline in spleen volume.

7.7 Duration of Maintenance of a ≥ 35% Reduction from Baseline in Spleen Volume

Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume is only defined for responders. The duration will be calculated in the following three ways:

1. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume per IRF assessment to the date of first documented evidence of no longer meeting the ≥ 35% reduction from baseline criteria, that is: duration = Day of < 35% reduction from baseline - Day of first ≥ 35% reduction + 1,
2. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 35% reduction from baseline and ≥ 25% increase from nadir, and
3. the time from the date of the scan with a ≥ 35% reduction from baseline in spleen volume to the date of the first documented evidence of a < 10% reduction from baseline.

Patients will be censored at the earlier of the FDA clinical hold date (08 February 2016) or the last radiological assessment date if they are alive with no documented loss of response before analysis. The same analysis methods used for PFS (Section 7.4) will be used for duration of spleen response.

7.8 Best Response in Spleen Volume

Best response in spleen volume is based on the percent change in spleen volume from baseline to any time during the study on initial treatment. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from baseline at any time on study on initial treatment will be presented by treatment arm.

7.9 Percent Change in Spleen Length

Although it is not a study objective, the percent change in spleen length below the left costal margin from baseline will be evaluated as well. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from baseline to Week 24 will be summarized by treatment arm. Patients with a missing Week 24 spleen length, including those who meet the criteria for disease progression and crossover to treatment with pacritinib or who drop out of the study before Week 24 (prior to study day 154) will be considered to have not achieved the ≥ 50% reduction.

The percent change in spleen length from baseline to post baseline visits will be evaluated as well. Descriptive statistics will be provided by treatment arm. Additionally, the correlation of percent change from baseline in spleen volume and the percent change from baseline in spleen length below the left costal margin will be evaluated.

7.10 Endpoints Relating to RBC Transfusion

A patient is defined as RBC transfusion independent at any time point if that patient had no RBC transfusion in at least 3 months (90 days) preceding that time point as per Gale et al. 2011. The patient is RBC transfusion dependent if, in the 3 months (90 days) preceding, they were transfused with ≥ 2 RBC units per month on average. RBC transfusion independence/dependence is indeterminate if they were transfused with between 0 and 2 RBC units per month on average in that surveillance period (Gale et al. 2011). See Table 3 below. The frequency of RBC transfusion is defined by the number of units of RBC transfused per month over a specific period of time. The analyses planned for endpoints relating to RBC transfusions are defined below.

Table 3. Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	≥ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al. 2011	

7.10.1 Achievement of RBC Transfusion Independence

Achievement of RBC transfusion independence is defined in patients who were RBC transfusion-dependent at baseline, i.e., patients with a baseline RBC transfusion frequency (defined in Section 7.10.3) of ≥ 2 units per month. For these patients, achievement of RBC transfusion independence at Week 24 is defined as having had no RBC transfusions in the 3 months (90 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (Section 7.8) will be used for achievement of RBC transfusion independence.

7.10.2 Achievement of Reduced RBC Transfusion Dependence

Achievement of reduced RBC transfusion dependence is defined in patients who were not RBC transfusion independent at baseline, i.e., patients who were either RBC transfusion dependent or indeterminate at baseline. Reduction in RBC transfusion dependence is defined as having a ≥ 50% decrease in the average units of RBC transfusions per month over the 3 months (90 days) prior to their Week 24 visit date compared to baseline units of RBC transfusions per month. The same analysis methods used for best response in spleen volume (Section 7.8) will be used for achievement of reduced RBC transfusion dependence.

7.10.3 Frequency of RBC Transfusions

Change from baseline in the frequency of RBC transfusions (units/month) will be summarized by arm over time through Week 24 using descriptive statistics in patients receiving at least one unit of RBC at baseline or while on study treatment. The frequency of RBC transfusions at baseline is defined as the number of units of RBC transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline RBC transfusion frequency is computed as the sum of the number of units of RBC transfusions in the 90 days prior to the informed consent date and the number of units of RBC transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ units\ from\ Transfusion\ History + \#\ units\ from\ IC\ to\ start\ of\ treatment)}{\left(90 + (treatment\ start\ date - IC\ date + 1)\right)\ days} \times 30\frac{days}{month}.$$

At post-baseline timepoints, the frequency of RBC transfusions is defined as the number of units of RBC transfusions per month in the three months (90 days) preceding the visit date. That is,

$$\frac{(\#\ units\ in\ the\ 90\ days\ preceding\ the\ visit\ date)}{90\ days} \times 30\frac{days}{month}.$$

7.11 Endpoints Relating to Platelet Transfusion

There are platelet count thresholds below which American Society of Hematology and American Society of Clinical Oncology guidelines (Schiffer et al and Slichter et al) recommend platelet transfusions, but standard definitions for platelet transfusion independence/dependence do not exist. We define platelet transfusion independence at any time point as having had no platelet transfusions in the month (30 days) preceding that time point. Otherwise, the patient is platelet transfusion dependent. See Table 4 below. The frequency of platelet transfusions is defined by the number of platelet transfusions over a specified period of time. Note that for the purposes of the analysis, platelet transfusion must be given to support platelet counts or to control non-surgical bleeding. Platelets given prophylactically for surgical procedures will not count towards platelet transfusion independence/dependence. The analyses planned for endpoints relating to platelet transfusions are defined below.

Table 4. Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

7.11.1 Achievement of Platelet Transfusion Independence

Achievement of platelet transfusion independence is defined in patients who were platelet transfusion-dependent at baseline, i.e., patients who had ≥1 platelet transfusion per month. For these patients, achievement of platelet transfusion independence is defined as having had no platelet transfusions in the month (30 days) prior to their Week 24 visit date. The same analysis methods used for best response in spleen volume (Section 7.8) will be used for achievement of platelet transfusion independence. Platelet transfusion independence/dependence will also be explored using other cut-offs and the continuous measure of the number of episodes of platelet transfusions.

7.11.2 Frequency of Platelet Transfusions

The change from baseline in the frequency of platelet transfusions (times/month) will be summarized by treatment arm every four weeks through their Week 24 visit date using descriptive statistics in patients receiving at least one platelet transfusion at baseline or while on study treatment. The frequency of platelet transfusions at baseline is defined as the number of platelet transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline platelet transfusion frequency is computed as the sum of the number of transfusions in the 90 days prior to the informed consent date and the number of transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ transfusions\ in\ Transfusion\ History + \#\ transfusions\ from\ IC\ to\ start\ of\ treatment)}{\big(90 + (treatment\ start\ date - IC\ date + 1)\big)\ days} \times 30\frac{days}{month}.$$

At post-baseline timepoints, frequency of platelet transfusions is defined as the number of platelet transfusions in the month (30 days) preceding the visit date.

7.12 Clinical Improvement in Hemoglobin Level

Clinical improvement in hemoglobin level is defined for the subgroup of patients with baseline hemoglobin level of less than 100 g/L. A clinical improvement in hemoglobin level is defined as having a minimum of 20 g/L increase in hemoglobin level at Week 24 or becoming transfusion independent for 8 weeks or more, i.e., no RBC transfusions in the 8 weeks prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (Section 7.8) will be used for clinical improvement in hemoglobin level.

7.13 Clinical Improvement in Platelet Count

Clinical improvement in platelet count is defined for the subgroup of patients with baseline platelet count below 50,000/μL. A clinical improvement in platelet count is defined as a minimum 100% increase from baseline in platelet count at Week 24 and an absolute platelet count of ≥ 50,000/μL for 8 weeks or more prior to the Week 24 visit. The same analysis methods used for best response in spleen volume (Section 7.8) will be used for clinical improvement in platelet count.

7.14 Change in JAK2V617F Allele Burden

The percent change from baseline to post-baseline visits in the level of the JAK2V617F mutation, defined as the percent of cells positive for the V617F mutation, will be calculated for each patient and summarized by treatment arm.

7.15 QOL Based on EQ-5D-5L and EORTC QLQ-C30

There are 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as an overall health score recorded on the EQ-5D-5L (Rabin et al. 2011). Each dimension has 5 levels coded 1 through 5 indicating increasing problems or difficulty in that dimension. There should be only one response for each dimension and missing values be coded as 9. The 5 codes are combined (concatenated) to compute a unique health state for each patient. These health states will be converted to country-specific index values (using a bridge to EQ-5D-3L responses and established country-specific index values) to facilitate the computation of quality-adjusted life years (QALYs). The overall health score has a possible value ranging from 0 to 100 and represents the patient's impression of their health, where 0 represents the worst health and 100 represents the best health imagined. Missing overall health scores will be assigned 999. See Table 5.

Table 5. Levels of the EQ-5D-5L Instrument

EQ-5D-5L Dimensions and Scale	Levels
Mobility	1 to 5
Self-care	1 to 5
Usual activities	1 to 5
Pain/discomfort	1 to 5
Anxiety/depression	1 to 5
Overall Health	0 to 100

The frequency distribution of the codes in each dimension will be presented by treatment arm at baseline and at each post-baseline visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24). The overall health score and the index values will be summarized by treatment arm at baseline. The change from baseline in the overall health score and the index values will be summarized by treatment arm at Weeks 8, 16, and 24.

The EORTC QLQ-C30 Version 3 (Fayers et al. 2001) has 30 questions (items) which are combined to form 15 scales for the global health status/quality of life, functional, and symptom assessment of cancer patients. There is 1 global health status/quality of life scale comprising 2 items, each having possible individual scores ranging from 1 to 7 and, hence, a range of 6. There are 5 multi-item functional scales assessing physical, role, emotional, cognitive, and social functioning. Nine symptom scales assess fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Individual scores for the functional and symptom scales range from 1 to 4, with a range of 3. See Table 6.

Table 6. Scales of the EORTC QLQ-C30 Instrument

EORTC QLQ-C30 Scales	Scores for Individual Items
Global Health Status/Quality of Life (2 items)	1 to 7
Functional (15 items)	
Physical	1 to 4
Role	1 to 4
Emotional	1 to 4
Cognitive	1 to 4
Social Functioning	1 to 4
Symptom (13 items)	
Fatigue	1 to 4
Nausea and Vomiting	1 to 4
Pain	1 to 4
Dyspnoea	1 to 4
Insomnia	1 to 4
Appetite Loss	1 to 4
Constipation	1 to 4
Diarrhea	1 to 4
Financial Difficulties	1 to 4

The scores for each scale will be set to missing if the answers to more than half of the items in the scale are missing. A raw score for each scale is determined by the average of the individual scores in each scale. The total score for the global health status/quality of life scale and each symptom scale is computed by $\left(\frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each functional scale is computed by $\left(1 - \frac{\text{Raw Score - 1}}{\text{Range}}\right) * 100$. The total score for each scale will be summarized by treatment arm at baseline. The change from baseline of the total score in each scale will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.16 Global Impression Assessment

There is 1 domain in the global impression assessment instrument with possible scores ranging from 1 (very much improved) to 7 (very much worse). The scores for the global impression assessment will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument through Week 24 (Weeks 8, 16, and 24) using descriptive statistics.

7.17 Multiplicity

The primary and secondary hypotheses tests will be performed in the following manner in order to ensure an overall Type I error at 5%.

1. The primary hypothesis will be tested at $\alpha = 0.05$ (2-sided) in the pooled pacritinib arms (QD + BID) versus the BAT arm on:

   a. The difference in proportions of patients achieving a $\geq$ 35% reduction in spleen volume at Week 24; and

   b. The difference in proportions of patients achieving a $\geq$ 50% reduction in TSS at Week 24.

   The study reaches its primary objective (claims to be successful) when statistical significance ($\alpha = 0.05$, 2-sided) is reached for <u>both</u> endpoints.

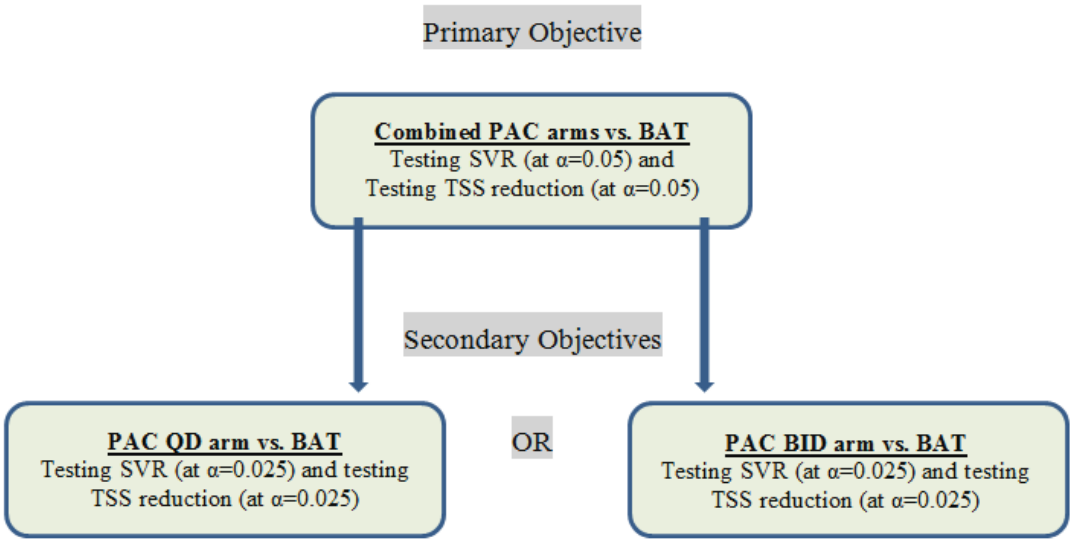
2. If the study reaches the primary objective, the secondary hypotheses will be tested concurrently in i) the QD arm versus the BAT arm and ii) the BID arm versus the BAT arm at the 2-sided 0.025 α-level on:

a. The difference in proportions of patients achieving a ≥ 35% reduction in spleen volume at Week 24; and
b. The difference in proportions of patients achieving a ≥ 50% reduction in TSS at Week 24.

Success at a given dose is achieved when statistical significance (α = 0.025, 2-sided) is reached for both endpoints.

The following diagram provides a graphical view of this testing procedure.

Figure 1. Testing Procedure for Primary and Secondary Hypotheses



7.18 Subgroup Analyses of Efficacy

Subgroup analyses are planned to evaluate any potential impact of demographics or baseline disease characteristics on the primary and secondary endpoints. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Depending on the sample size, other subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), JAK2617F mutation status at baseline (present vs. not present), prior treatment with JAK2 inhibitors (yes vs. no), duration of prior treatment with JAK2 inhibitors (< 6 months vs. ≥ 6 months), most recent dose of ruxolitinib (< 10 mg/day vs. ≥ 10 mg/day), RBC transfusion dependency at baseline (dependent vs. not dependent), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and baseline platelet count (< 50,000/μL vs. ≥ 50,000/μL). Additionally, BAT patients treated with ruxolitinib will be analyzed separately.

8. EXPOSURE TO STUDY TREATMENT

Exposure to initial study treatment will be evaluated by the duration of treatment, cumulative dose, actual dose intensity, and relative dose intensity in the safety population.

Duration of treatment (weeks): is defined as the duration from first day of initial study treatment to the last day of initial study treatment, i.e.,

$$\frac{(\textit{Date of last dose of initial study treatment} - \textit{date of first dose of initial study treatment} + 1)}{7},$$

Descriptive statistics will be provided for duration of treatment by treatment arm. Duration of treatment will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median duration of treatment and the corresponding 95% confidence interval, and estimated duration of treatment curves will be presented by arm.

Cumulative dose (mg): is defined as the sum of all doses of initial study treatment taken and descriptive statistics will be provided for the pacritinib arms only. The numbers and percentages of patients with any dose modifications will be provided by treatment arm. Reasons for dose modifications will also be summarized.

Actual dose intensity (ADI, mg/day) = (total dose taken in mg) ÷ (duration of treatment in days) and descriptive statistics will be provided for the pacritinib arms only.

Relative dose intensity (RDI, %) = (ADI) ÷ (planned daily dose) * 100. The planned pacritinib dose is 400 mg/day and descriptive statistics will be provided for the pacritinib arms only.

Exposure to pacritinib after crossover will be analyzed separately (Section 10).

Time to crossover will also be analyzed using the Kaplan-Meier product-limit method. Summary statistics, including median time to crossover and the corresponding 95% confidence interval, and estimated time to crossover curves will be presented for the BAT arm. Descriptive statistics for the time to crossover in weeks will be presented for patients who crossed over from BAT to pacritinib, with duration defined as (date of first dose of pacritinib after crossover – date of first dose of initial study treatment + 1)/7. The numbers and percentages of patients taking each BAT therapy will be presented. Additionally, the numbers and percentages of the first BAT therapy taken will be presented.

9. SAFETY ANALYSIS

Safety analyses include treatment emergent adverse events, clinical labs, ECG, vital signs, performance status, and any abnormal findings observed during the performance of physical examinations by treatment received after randomization through the end of initially assigned study treatment + 30 days. The safety data after patients crossover from BAT to pacritinib will be analyzed separately (Section 10).

9.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Analysis of AEs will be based on Treatment Emergent Adverse Events (TEAEs). A TEAE is defined as an adverse event (AE) occurring after the first dose of study treatment and within 30 days after the last study treatment date. In addition, an AE is also considered a TEAE if it is an AE starting more than 30 days after the last study treatment, but the investigator assessed the AE with a relationship to study drug of "Possible", "Probable", or "Definite" or if it is an AE with a missing start date but with an end date after the first study drug dose date. An AE occurring after the first dose of study drug that also occurred prior to the first dose of study drug is only considered a TEAE if the AE worsened in grade after the first dose of study drug. An AE occurring after crossover to a pacritinib regimen that also occurred prior to crossover is only considered a TEAE if the AE worsened in grade after crossover.

TEAEs will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE, having a TEAE in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. CTCAE (version 4.0) grades and relationship to study medication will be summarized as appropriate. For summaries by CTC grade or relatedness, only the highest CTC grade or degree of relatedness of each SOC and/or preferred term will be summarized. A patient having the same event more than once will be counted only once and by greatest severity or closest relationship.

In addition, serious TEAEs (SAEs), CTC grade 3 or 4 TEAEs, TEAEs leading to study medication discontinuation, interruption, or dose reduction, TEAEs with an outcome of death, related TEAEs (see Section 9.1.3.2 of the protocol), and TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be summarized. A listing of all SAEs will be generated.

The preferred term of TEAEs of all grades and grade 3 or 4 TEAEs will also be presented for each treatment arm by decreasing frequency in the pooled pacritinib arms. These summaries will also be repeated for TEAEs of all grades and grade 3 or 4 TEAEs starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first).

The numbers and percentages for the causes of all deaths will be presented by treatment arm. A listing of all deaths, both on and off treatment, will also be generated. On treatment deaths are defined as deaths that occur on treatment and within 30 days of treatment discontinuation.

9.1.1 TEAEs of Special Interest

The following TEAEs are considered to be of interest: Diarrhea, Nausea, Vomiting, Neutropenia (including neutrophils decreased), Thrombocytopenia (including platelets decreased), Anaemia (including hemoglobin decreased), Infections and Infestations (SOC), Cardiac AEs, Neurotoxicity, and Haemorrhages. The preferred terms included in Cardiac AEs of special interest are all terms in the Standardised MedDRA Queries (SMQs) of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events. The preferred terms included in the Haemorrhages AEs of special interest are all terms in the SMQ of Haemorrhages. See Appendix 15.1 for the preferred terms for neurotoxicity events of special interest.

TEAEs of special interest will be summarized by presenting, for each treatment arm, the number and percentage of patients having any TEAE of special interest, having a TEAE of special interest in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. Cardiac and Haemorrhages TEAEs of special interest will also be summarized by SMQ. CTC grade 3 or 4 TEAEs of special interest and those starting prior to the Week 24 visit, crossover to pacritinib, or discontinuation of initial treatment (whichever comes first) will be similarly summarized. Additionally, the incidence and prevalence of each TEAE of special interest with 8-week intervals from baseline will be presented by treatment arm. Incidence and prevalence will also be presented for grade 3 or 4 TEAEs of special interest.

Times to onset and resolution of the first TEAE will also be analyzed for each TEAE of special interest. Time to onset of the first TEAE is defined as the time from start of study drug to the start date of the first occurrence of the TEAE, i.e., time in days is calculated as (start date of first occurrence of the TEAE) – (date of first dose of study treatment) + 1. Subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. Time to resolution of first TEAE is defined as the time from the start date of the first occurrence of the TEAE to its resolution (AE outcome being "recovered/resolved" in CRF). In the absence of resolution, subjects will be censored at the earliest of the following dates: last dose (if treatment discontinued) + 30 days, lost to follow-up date, and death date. The same analysis methods used for OS (Section 7.3) will be used for time to onset of first and time to resolution of these TEAEs of special interest.

9.2 Clinical Laboratory Measurements

Hematology and Chemistry laboratory measures are collected via central lab.

9.2.1 Hematology

The hematology measurements to be analyzed are: hemoglobin, platelet counts, white blood cell counts, neutrophil counts, lymphocyte counts, monocyte counts, and eosinophil counts. When there are non-missing results for both automated and manual hematology differentials, the manual results will be used for analysis if all the hematology results being analyzed are present.

The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each hematology measure. Descriptive statistics of change and percent change from baseline in hematology values will be presented by visit. Plots of the percent change in hemoglobin and platelet counts over time will be presented.

9.2.2 Chemistry

The following clinical chemistry measures will be analyzed: ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, indirect bilirubin, creatinine, LDH, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, BUN/urea, albumin, amylase, lipase, glucose, cholesterol, and uric acid levels. Summaries of the worst CTCAE grade will be presented for ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, creatinine, sodium, potassium, calcium, phosphate, magnesium, albumin, glucose, and cholesterol in either direction of abnormality (i.e., abnormally low or high). The numbers and percentages of the shifts in CTC grade from baseline to Week 24, last post-baseline grade, and worst post-baseline grade will be presented for each chemistry measure. Descriptive statistics of change and percent change from baseline in clinical chemistry values will be presented by visit.

The derived visit window definitions for clinical hematology and chemistry are displayed in Table 7.

Table 7. Analysis Window Definitions for Clinical Chemistry and Hematology Results

Visit	Nominal Day	Range
Baseline	1 (first dose date)	[-14, 1]
Week 3	15	[2, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.3 Other Clinical Safety

9.3.1 Electrocardiogram (ECG)

The frequency distribution of abnormal ECG measurements on study (after the first study drug treatment through the last dose of study drug) will also be summarized.

The proportion of subjects with the following QTc intervals will tabulated by visit (including worst and last on treatment values) and treatment arm:

- A measured value > 450 ms
- A measured value > 480 ms
- A measured value > 500 ms
- > 30 ms above baseline
- > 60 ms above baseline

9.3.2 Vital Sign Measurements

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) of change and percent change from baseline in vital sign measurements, including weight, will be presented by visit.

The frequency distribution of abnormal vital sign measurements (as noted by the investigator) on study (on or after the first day of treatment) will be displayed.

A table summarizing clinically notable blood pressure and weight measurements which are aligned with CTCAE cut-offs, where available, will be displayed. The proportion of subjects whose worst observed values while on study (on or after the first day of treatment) meet the following clinically notable criteria will be tabulated by treatment arm:

- Systolic Blood Pressure
  - < 85 mm Hg
  - ≥ 140 - < 160 mm Hg
  - ≥ 160 mm Hg

- Diastolic Blood Pressure
  - < 50 mm Hg
  - ≥ 90 - < 100 mm Hg
  - ≥ 100 mm Hg
  - Weight gain from baseline
  - ≥ 5% - < 10% increase
  - ≥ 10% - < 20% increase
  - ≥ 20% increase
- Weight loss from baseline
  - ≥ 5% - < 10% decrease
  - ≥ 10% - < 20% decrease
  - ≥ 20% decrease

The derived visit window definitions for vital signs are displayed in Table 8.

Table 8. Analysis Window Definitions for Vital Signs Results

Visit	Nominal Day	Range
Baseline	1 (first dose date)	[-14, 1]
Week 2	8	[2, 11]
Week 3	15	[12, 21]
Week 4	28	[22, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 125]
Week 20	140	[126, 153]
Week 24	168	[154, 209]
Week 36	252	[210, 293]
Week 48	336	[294, 377]
Week 60	420	[378, 461]
Week 72	504	[462, 545]
Week 84	588	[546, 629]
EOT	Last dose date	[Last dose date, Last dose date + 7]

9.4 Concomitant Medication

A medication will be considered a concomitant medication if it was taken by the patient at any time on study (on or after the first day of treatment and within 30 days after the last dose of study drug). The following will also be considered concomitant medications:

- Medications missing both start and stop dates.
- Medications having a start date prior to the last dose of study drug and missing the stop date.

Concomitant medications will be summarized by ATC class and preferred term.

9.5 Supplemental Procedures

Procedures received from the first day of treatment to the last day of treatment will be summarized by SOC class and preferred term.

9.6 Subgroup Analysis of Safety

Treatment-emergent adverse events, including all AEs, grade 3/4 AEs, and SAEs, and hematology toxicity will also be summarized by subgroups as appropriate. Subgroups based on stratification factors include region (North America vs. Europe vs. ROW), DIPSS risk category (intermediate-1 vs. intermediate-2 vs. high risk) and by rebound platelet count (≤100,000/μL vs. > 100,000/μL). Additionally subgroups may include, but are not limited to, gender, age group (< 65 years vs. ≥ 65 years), race (Caucasian vs. non-Caucasian), prior treatment with JAK2 inhibitors (yes vs. no), baseline platelet count (< 50,000/μL vs. ≥ 50,000), baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and JAK2V617F mutation status at baseline (present vs. not present). Additionally, safety within the subgroup of BAT patients treated with ruxolitinib will be explored.

10. ANALYSIS OF PATIENTS WHO CROSSOVER FROM BAT TO PACRITINIB

Selected descriptive efficacy and safety summaries defined above will be repeated for crossover patients. Baseline for these summaries will be considered to be the last assessment prior to or at crossover. The following summaries will be presented for crossover patients.

- **Best response in spleen volume** is based on the percent change in spleen volume from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 35% reduction in spleen volume from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **The moving average of TSS** as defined in Section 7.2.5 for BAT patients after crossover.
- **Best response in spleen length** is based on the percent change in spleen length from crossover baseline to any time on pacritinib after crossover. The numbers and percentages of patients achieving a ≥ 50% reduction in spleen length from crossover baseline to any time on pacritinib after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **Exposure to study treatment** as outlined for the pacritinib arms in Section 8.
- **Deaths**: the numbers and percentages for each cause of death after crossover will be presented by pacritinib regimen and in the pooled regimens.
- **TEAEs** as outlined in Section 9.1 that occur after crossover will be summarized by pacritinib regimen and in the pooled regimens.

Reasons for crossover from BAT to a pacritinib regimen will also be summarized. A listing of all patients who crossover from BAT to a pacritinib regimen will also be generated.

11. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

The study pharmacokineticist will review the individual concentration-time data prior to the conduct of PK analysis to ascertain the integrity of the concentration-time data set. Population PK/PD analysis will be conducted to characterize the exposure of pacritinib in MF patients following administration of 400 mg QD and 200 mg BID regimens. The PK and PD measures will be summarized with descriptive statistics by pacritinib treatment arm. In addition, the exposure-response relationship for pacritinib will be characterized on key safety (e.g., thrombocytopenia, myelosuppression, anemia, hemorrhage, GI, cardiac failure, and arrhythmia AEs) and the primary and secondary efficacy (i.e., reduction in spleen volume and reduction in TSS) endpoints. The correlation of Week 24 spleen volume and TSS with Week 24 STAT3 phosphorylation will be evaluated as well.

12. POWER AND SAMPLE SIZE

It is assumed that the proportion of patients achieving a ≥ 35% reduction in spleen volume at Week 24 will be 5% in the BAT arm, 25% in the QD pacritinib arm, and 25% in the BID pacritinib arm. These assumptions were made based on response rates seen in the COMFORT-I and -II randomized controlled trials and the SB1518-2007-001 and SB1518-2008-003 Phase 2 trials. It is also assumed that the proportion of patients achieving a ≥ 50% reduction in TSS at Week 24 is 5% in the BAT arm, 45% in the QD pacritinib arm, and 45% in the BID pacritinib arm. These assumptions were made based on response rates seen in the COMFORT-I randomized controlled trial.

With these assumptions, the original sample size of 300 patients (100 in the QD pacritinib arm, 100 in the BID pacritinib arm, and 100 in the BAT arm) is planned for the study. For the primary hypothesis (pooled QD/BID vs. BAT), this sample size provides > 99% power to detect a treatment difference in spleen volume reduction and a treatment difference in TSS reduction at an α-level (2-sided) of 0.05.

This sample size also provides 96% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

Assuming a 10% dropout rate, there is ≥ 93% to detect the treatment differences specified above. A Fisher exact test is used for the purpose of sample size calculation.

The patients randomized at least 22 weeks prior to the FDA clinical hold are being used to evaluate the study objectives. It is estimated that a total of 220 patients meet this definition. With the same assumptions above, this sample size provides 97% and >99% power to test the primary hypothesis (pooled QD/BID vs. BAT) of a treatment difference in spleen volume reduction and a treatment difference in TSS reduction, respectively, at an α-level (2-sided) of 0.05. This sample size also provides 86% power to detect a treatment difference in spleen volume reduction and > 99% power to detect a treatment difference in TSS reduction at an α-level (2-sided) of 0.025 for testing the secondary hypotheses independently, i.e., when comparing the endpoints in the QD pacritinib arm with the BAT arm and comparing the endpoints in the BID pacritinib arm with the BAT arm.

13. DATA HANDLING RULES

13.1 Definition of Baseline Value

The baseline value for safety analyses will be defined as the last assessment prior to the start of treatment, unless otherwise specified.

13.2 Partial Current MF Diagnosis Date

For patients who have a partial diagnosis date, the 15th of the month will be used if day is missing, and July 15th will be used if both the month and day are missing.

13.3 Partial or Missing AE Onset and Resolution Dates

For AE summaries, the missing day of onset of an adverse event will conservatively be set to:

- First day of the month that the AE occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the AE occurred.
- The 15th of the month and year if the AE month and year are before the month and year of the first treatment.

If the onset date of an adverse event is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 1st of the year if the AE year is before the year of the first study treatment.

If the day of resolution of an adverse event is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year, whichever is earlier. If the day of resolution of an adverse event is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented "as is" in listings.

13.4 Laboratory Results Reported as a Range

Laboratory results that are reported as less than or greater than a certain value (limit of quantification) or as a range of values will be imputed for analysis using the rules described below.

Myeloblast Percentages

- Myeloblast results in the hematology data reported as <X% will be imputed with the value (X-1)% for analysis.
- Myeloblast results in the hematology data reported as ≤X% will be imputed with the value X% for analysis.
- Myeloblast results in the hematology data reported as X-Y% will be imputed with the value Y% for analysis.

Other Laboratory Results

- Laboratory results reported as <X will be imputed with the value (X-1) for analysis. Results reported as <X.Y will be imputed by subtracting one from the last significant digit (Y). Results reported as <0.1 will be imputed as 0 for analysis as long as the normal range extends to 0.
- Laboratory results reported as >X will be imputed with the value (X+1) for analysis. Results reported as >X.Y will be imputed by adding one to the last significant digit (Y).

14. REFERENCES

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15. APPENDIX

15.1 Neurotoxicity Events of Special Interest

The neurotoxicity events of special interest include, but are not limited to, amnesia, blindness, burning sensation, carpal tunnel syndrome, cognitive disorder, confusional state, disturbance in attention, dizziness, dysgeusia, dyskinesia, dysphonia, dysstasia, gait disturbance, facial neuralgia, gait disturbance, headache, hemianopia, hyperaesthesia, hypoaesthesia, incontinence, lethargy, memory impairment, migraine, muscular weakness, myopathy, neck pain, neuralgia, neuropathy peripheral, paraesthesia, Parkinson's disease, peroneal nerve palsy, sensation of heaviness, status epilepticus, syncope, tinnitus, tremor, urinary incontinence, urinary retention, vertigo, vertigo positional, vestibular disorder, VIIth nerve paralysis, vision blurred, visual field defect, and visual impairment. Additional terms will be included as they are identified.