CTI BioPharma Corp.

PAC203 Protocol

Pacritinib

An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib

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Protocol Synopsis

Name of Investigational Drug	Pacritinib
Protocol ID	PAC203
Protocol Title	An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib
Version	Amendment 6
Study Phase	2

Primary Objective

1. To determine a recommended dosage of pacritinib for further clinical studies

Secondary Objectives

1. To examine the dose–response relationship for efficacy, as measured by spleen volume reduction (SVR) using magnetic resonance imaging (MRI [preferred]) or computed tomography (CT) and total symptom score (TSS) using the MPN-SAF TSS 2.0
2. To examine the dose–response relationship for safety with a focus on adverse events (AE) of interest
3. To further characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of pacritinib

Study Design

This is a dose-finding study in patients with primary or secondary MF (DIPSS risk score of Intermediate-1 to High-Risk) who were previously treated with ruxolitinib. The study is designed to support a pacritinib dosage selection decision. Three dosages will be evaluated, with patients randomized 1:1:1 to pacritinib 100 mg QD, pacritinib 100 mg BID, or pacritinib 200 mg BID. Randomization will be stratified by baseline platelet count (≤50,000/μL; >50,000/μL and ≤100,000/μL; and >100,000/μL). The most recent platelet count obtained prior to start of treatment will be the basis of stratification by baseline platelet count. Assigned treatment will continue until the patient experiences progressive disease, intolerable AEs, withdraws consent, or until the assigned treatment arm is closed. No study treatment crossover will be allowed. All patients should complete all visit procedures through Week 24, including patients who stop pacritinib treatment or have protocol-defined progressive disease prior to Week 24, unless patient withdraws consent, dies, undergoes splenic irradiation or splenectomy, or initiates any non-protocol-directed anti-myelofibrosis treatment. Following regulatory, EC or IRB approval of Amendment 6, study treatment for patients at and beyond the week-24 timepoint will terminate. Study assessments will cease following the End-of-Treatment (EOT) or 30-day post EOT visit, as applicable. Patients who are benefiting from therapy as of study treatment termination may be allowed to continue receiving pacritinib under single patient expanded access or named patient programs at the investigator's discretion and subject to regulatory, Ethics or IRB approval.

The dosage selection process will be based on efficacy and safety parameters, including model-based dose–response.

This study will utilize planned frequent monitoring by an IDMC. At a minimum, the IDMC will consist of 1 board-certified hematologist, 1 board-certified cardiologist, and 1 biostatistician experienced in adaptive design clinical trials. The roles and responsibilities of the IDMC will be fully defined within the IDMC charter, including, but not limited to:

- Review safety data across arms, focusing on bleeding events, cardiac events, and deaths
- Evaluate cumulative safety as described in Section 11
- Make independent recommendations to the Sponsor on study continuation (continue without modification, continue with modification, or terminate) and on patient enrollment (hold or stop enrollment, enroll additional patients, close arm) as described in Section 11
- Make independent recommendation to the Sponsor on pacritinib dosage for further study

The first IDMC meeting is planned to occur once 18 patients have been randomized and treated for 12 weeks and will meet approximately quarterly thereafter. In addition to the IDMC, there will be an Independent

Adjudication Committee (IAC) that will review all grade 4 or 5 cardiac and bleeding events to assess the principal condition that resulted in the outcome. The IAC will provide their assessment to the IDMC. Additional details on the IAC will be provided in the IAC charter.

The determination of a dose or dosages of pacritinib for further study will be based on efficacy, safety, dose–response, and PK/PD exposure–response relationship data after all enrolled patients reach Week 24 (or discontinue the study). Approximately 150 patients total or up to 50 patients per arm may be enrolled. Spleen volume will be measured by MRI (preferred) or CT at baseline and Weeks 12 and 24. Patient-reported disease-related symptoms as assessed by the validated Patient Reported Outcome (PRO) instrument MPN-SAF TSS 2.0 will be collected daily using an electronic diary and evaluated as part of the dose–response relationship. DNA samples will also be collected for analysis of mutations associated with myelofibrosis at baseline and Week 24. In the event of 2 treatment-emergent Common Terminology Criteria for Adverse Events (CTCAE) grade ≥4 cardiac AEs or 2 treatment-emergent CTCAE grade ≥4 hemorrhage AEs in the same treatment arm, suspend study enrollment and the IDMC will be convened to review the events including the IAC's assessment of the events. If the IDMC confirms the nature and grade of the events together with a relationship to study drug, the IDMC may recommend closure of one or more treatment arms. This recommendation is non-binding. The FDA and other Competent Authorities will be notified of any IDMC meeting that is convened under these circumstances and the resultant recommendation will be reported to the FDA within 2 business days. The MHRA will be informed via a substantial amendment. In the event one or more arms are suspended or terminated for a safety observation, randomization into the arm(s) will be halted immediately, however patients who are experiencing benefit, in the opinion of the investigator and Sponsor, and who were randomized to an arm that is suspended or terminated, may continue treatment.

Safety will be monitored with physical examinations, clinical laboratory assessments (including hematologic, chemistry, and coagulation testing), and cardiac monitoring (including ECG and echocardiogram testing); specified study treatment dosage modifications will be followed to address identified abnormalities. Adverse event data will be collected throughout the study.

The Sponsor will collect blood samples for PK assessment from all patients in each dosing arm at the following timepoints:

- Sparse Sampling (all patients): End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 4 hours (± 10 minutes), and 8 hours (± 15 minutes) postdose
- Dense Sampling (performed at selected sites until approximately 6 to 8 patients per dose arm have completed PK evaluation, at which point all further patients will have PK evaluated by sparse sample collection): Week 1 Day 1: 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose) , End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose

The PK parameters, minimum concentration observed, maximum concentration observed, and area under the curve will be determined and summarized using descriptive statistics for each pacritinib dosage arm. Exposure-response analyses will be conducted on both safety and efficacy populations in the study. PD samples will be analyzed for biomarkers associated with the JAK/STAT pathway.

The maximum duration of trial participation for an individual patient will be approximately 24 weeks. The estimated duration of the entire study is approximately 2 years if the maximum number of patients are enrolled. The definition of End of Trial for the PAC203 study is Last Visit of the Last Subject (LVLS).

Number of Centers	Approximately 60 centers globally
Number of Patients	Approximately 150
Inclusion/ Exclusion Criteria	<u>Diagnosis and Inclusion Criteria</u> 1. PMF, PPV-MF, or PET-MF (as defined by Tefferi and Vardiman 2008) 2. DIPSS Intermediate-1, Intermediate -2, or High risk (Passamonti et al 2010) 3. Prior ruxolitinib treatment with failure to benefit or intolerance as defined by at least one of the following:

	a. Treatment for ≥3 months with inadequate efficacy response defined as <10% spleen volume reduction by MRI or <30% decrease from baseline in spleen length by physical examination or regrowth to these parameters following an initial response; and/or b. Treatment for ≥28 days complicated by either i. Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months) ii. National Cancer Institute (NCI) CTCAE grade ≥ 3 AEs of thrombocytopenia, anemia, hematoma, and/or hemorrhage while being treated with a dosage of < 20 mg BID 4. Palpable splenomegaly ≥5 cm below the lower costal margin in the midclavicular line as assessed by physical examination 5. TSS of ≥ 10 on the MPN-SAF TSS 2.0 or patients with a single symptom score of ≥ 5 or two symptoms of ≥ 3, including only the symptoms of left upper quadrant pain, bone pain, itching, or night sweats 6. Age ≥ 18 years old 7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 8. Peripheral blast count of < 10% throughout the screening period 9. Absolute neutrophil count of > 500/μL 10. Adequate liver and renal function, defined by liver transaminases (aspartate aminotransferase [AST]/serum glutamic oxaloacetic transaminase [SGOT] and alanine aminotransferase [ALT]/serum glutamic pyruvic transaminase [SGPT]), ≤ 3 × the upper limit of normal (ULN) (AST/ALT ≤ 5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤ 4× ULN, and creatinine ≤ 2.5 mg/dL 11. Adequate coagulation function, defined by prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), or thrombin time (TT) of ≤ 1.5 × ULN 12. Left ventricular cardiac ejection fraction of ≥ 45% by echocardiogram or multigated acquisition (MUGA) scan 13. If fertile, willing to use effective birth control methods during the study 14. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study 15. Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument 16. Provision of informed consent <u>Exclusion Criteria</u> 1. Life expectancy < 6 months 2. Completed allogeneic stem cell transplant (allo-SCT) or are eligible for and willing to complete allo-SCT 3. History of splenectomy or planning to undergo splenectomy 4. Splenic irradiation within the last 6 months 5. Previously treated with pacritinib 6. Patients receiving high-dose ruxolitinib (more than 10 mg BID or 20 mg QD) who cannot tolerate tapering down ruxolitinib to 10 mg BID or less prior to the first dose of pacritinib as described in Section 6.6 7. Treatment with anticoagulation or antiplatelet agents, except for aspirin dosages of ≤ 100 mg per day, within the last 2 weeks

	8. Treatment with a strong CYP3A4 inhibitor or a strong cytochrome P450 inducer within the last 2 weeks 9. Treatment with medications that can prolong the QTc interval within the last 2 weeks (Appendix 8) 10. Treatment with an experimental therapy within the last 28 days 11. Significant recent bleeding history defined as NCI CTCAE grade ≥ 2 within the last 3 months, unless precipitated by an inciting event (e.g., surgery, trauma, injury) 12. Any history of CTCAE grade ≥ 2 non-dysrhythmia cardiac conditions within the last 6 months. Patients with asymptomatic grade 2 non-dysrhythmia cardiac conditions may be considered for inclusion, with the approval of the medical monitor, if stable and unlikely to affect patient safety. 13. New York Heart Association Class II, III, or IV congestive heart failure 14. Any history of CTCAE grade ≥2 cardiac dysrhythmias within the last 6 months. Patients with non-QTc CTCAE grade 2 cardiac dysrhythmias may be considered for inclusion, with the approval of the medical monitor, if the dysrhythmias are stable, asymptomatic, and unlikely to affect patient safety. 15. QTc prolongation >450 ms or other factors that increase the risk for QT interval prolongation (e.g., heart failure, hypokalemia [defined as serum potassium <3.0 mEq/L that is persistent and refractory to correction], family history of long QT interval syndrome, or concomitant use of medications that may prolong QT interval) 16. Any active gastrointestinal or metabolic condition that could interfere with absorption of oral medication 17. Active or uncontrolled inflammatory or chronic functional bowel disorder such as Crohn's Disease, inflammatory bowel disease, chronic diarrhea, or constipation 18. 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 19. Uncontrolled intercurrent illness, including, but not limited to, ongoing active infection or psychiatric illness or social situation that, in the judgment of the treating physician, would limit compliance with study requirements 20. Known seropositivity for human immunodeficiency virus 21. Known active hepatitis A, B, or C virus infection 22. Women who are pregnant or lactating 23. Concurrent enrollment in another interventional trial
Study Treatments	Pacritinib: Dosage Form: 100 mg capsules Dosage Levels: ▪ 100 mg QD ▪ 100 mg BID ▪ 200 mg BID
Concomitant and Excluded Therapies, Including Procedures	Ruxolitinib should not be administered concurrently with pacritinib at any time. Although there is no washout period required for ruxolitinib prior to the start of dosing with pacritinib, it should be understood that because of the difference in half-life between ruxolitinib (3 hours Jakafi package insert) and pacritinib (approximately 40 hours), there will be a period of 10 to 14 days following the discontinuation of ruxolitinib and the start of dosing with pacritinib, during which pacritinib has not yet

	reached steady state and during which patients may be at increased risk of ruxolitinib withdrawal, particularly after high doses of ruxolitinib (eg, more than 10 mg BID or 20 mg QD). For this reason, patients who are on more than 10 mg BID (or 20 mg QD) of ruxolitinib at the time of consent for this study must taper the ruxolitinib dose down to 10 mg BID or lower and remain stable on the reduced dose for at least 2 weeks prior to starting pacritinib. Tapering should be done per institutional practice and may be done with concurrent addition of prednisone during the screening period. In addition to any steroids used during the screening period, the protocol permits short-term use (up to 14 days) of corticosteroids and/or hydroxyurea as prophylaxis or treatment of symptomatic ruxolitinib withdrawal during the first month of treatment with pacritinib. Supportive care therapies, except when prohibited by any of the below provisions, are permitted, including the use of low-dose aspirin. Corticosteroids (up to 20 mg/day of prednisone or equivalent) and/or hydroxyurea may be used for up to 2 weeks during the first month of treatment with pacritinib to reduce the risk or control symptoms of ruxolitinib withdrawal. Treatments for MF that might be considered supportive care are only allowable with medical monitor approval prior to administration. The following therapies and procedures are prohibited throughout the study: ▪ Chemotherapy, interferon, or other treatment for MF, with the exception of up to 2 weeks of corticosteroids (up to 20 mg/day prednisone or equivalent) and/or 2 weeks of hydroxyurea as needed to reduce the risk of or treat the symptoms of ruxolitinib withdrawal ▪ Antiplatelet or anticoagulation agents, with the exception of ≤ 100 mg/day of aspirin ▪ Growth factor therapies, including erythropoietin and thrombopoietin ▪ Strong CYP3A4 inhibitors and strong CYP450 inducers, except as needed to treat AEs, with medical monitor approval ▪ Any drugs with significant potential for QTc prolongation, except as needed to treat AEs, with medical monitor approval ▪ Splenic irradiation or splenectomy Also refer to the Pacritinib Dosage Modifications section for guidelines on treatment of AEs.
Safety Assessments	Patients will have safety assessment as as described below until approval of Amendment 6, at which point safety assessments will cease following the End-of-Treatment (EOT) or 30-day post EOT visit, as applicable. <u>Adverse Events</u> AEs will be identified and reported to the Sponsor, and the clinically indicated diagnostic, monitoring, treatment, and follow-up measures will be employed. Pregnancy and overdose cases shall be reported as SAEs, irrespective of whether they meet seriousness criteria or not. <u>ECG</u> A 12-lead ECG (collected in triplicate) will be checked at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, and every 3 months while in the follow up period, including QTc calculation (and corrected by the Fredericia method), while on study treatment and 30 days after the last dose of study treatment. Pacritinib dosage modifications and follow-up monitoring for clinically significant ECG changes will be implemented as per the guidelines for “QTc Prolongation, Decreased Cardiac Ejection Fraction, and Other Cardiac Toxicities”. Additional ECG testing shall be done as clinically indicated.

	Ejection Fraction Ejection fraction will be checked at screening, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, and every 6 months while in the follow up period, and 30 days after the last dose of study treatment (such as with echocardiogram or MUGA scan). Pacritinib dosage modifications will be implemented for clinically significant ejection fraction changes as per the guidelines for "QTc Prolongation, Decreased Cardiac Ejection Fraction, and Other Cardiac Toxicities". If pacritinib treatment is resumed after holding for ejection fraction abnormality, ejection fraction should be reassessed about 14 days later, then at least every 3 months as per the above schedule. Additional ejection fraction testing shall be done as clinically indicated. Coagulation Testing Coagulation testing will include protim (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and thrombin time (TT) at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, every 3 months during the follow up period, and 30 days after the last dose of study treatment. Additional coagulation testing should be done as clinically indicated. These results will be taken into account, together with baseline platelet counts and prior medical history of bleeding, to help guide ongoing hematologic monitoring of platelet counts and clinical monitoring for bleeding. Pacritinib dosage modifications will be implemented for clinically significant AEs identified with this testing per the below guidelines for "Pacritinib-Related Nonhematologic Toxicities Other than QTc Prolongation, Decreased Cardiac Ejection Fraction, or Diarrhea". Hematology Hematology parameters including CBC, differential, platelet count and hemoglobin A1C will be evaluated at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, every 3 months during the follow up period, and 30 days after the last dose of study treatment. Blood samples drawn at unscheduled visits for the assessment of hematology parameters should be submitted to the central laboratory for assessment in addition to any local laboratories needed for timely decisions regarding patient care. For patients with baseline platelet count of $\leq$ 50,000/μL, the platelet count will be monitored weekly by the central laboratory for the first 8 weeks then monthly if counts remain $\leq$ 50,000/μL. Samples for platelet counts must be submitted to the central laboratory for analysis, but in addition can be analyzed locally for assessment and management of patients in real time. Additional platelet count testing should be done as clinically indicated. Pacritinib dosage modifications will be implemented for clinically significant AEs identified with this testing per the below guidelines for "Hematologic Toxicities and Related Complications." Serum Chemistry Serum 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, uric acid, and high sensitivity CRP) will be evaluated by a central laboratory at screening, baseline, and as clinically indicated and will include measures of hepatic and renal function and dysfunction. Blood samples drawn at unscheduled visits for serum chemistry evaluation should be submitted to the central laboratory for assessment in addition to any local laboratories needed for timely decisions regarding patient care. Pacritinib dosage modifications will be implemented for clinically significant AEs identified with this testing per the stated guidelines for "Pacritinib-

	Related Nonhematologic Toxicities Other than QTc Prolongation, Decreased Cardiac Ejection Fraction, or Diarrhea".
Pacritinib Dosage Modifications	Pacritinib dosage may be interrupted or modified for hematologic toxicities, hemorrhage, severe infections, cardiac toxicities including QTc interval prolongation and reduction in ejection fraction, diarrhea, and other pacritinib-related nonhematologic toxicities. Pacritinib dosage may also be held for invasive procedures. Refer to Section 6.5 for pacritinib dosage management guidelines.

STATISTICAL METHODS

The following variables will be used to evaluate efficacy and safety.

Efficacy

- The primary efficacy variable for dosage selection is the percent reduction in spleen volume from baseline as measured by MRI or CT at Weeks 12 and 24.
- Other supportive measures for evaluation as part of the dose–response relationship include: the percentage of patients who achieve at least 35% reduction in spleen volume; % TSS reduction from baseline;and the percentage of patients with at least 50% reduction in TSS.

Safety

- The primary safety measure for dosage selection is the percentage of patients with CTCAE grade ≥3 cardiac AEs (Standardized MedDRA Query [SMQ]), CTCAE grade ≥3 hemorrhage AEs (SMQ), CTCAE grade ≥4 thrombocytopenia toxicity (central laboratory based), or CTCAE grade ≥4 anemia toxicity (central laboratory based).
- All other safety data including AEs, death, and clinical laboratory measures will be used as supportive measures for evaluation of pacritinib dose-safety relationship.

There is no formal hypothesis to be tested in this study. Efficacy, safety, and PK/PD data will be summarized by dosage group using descriptive statistics. The dose–response and dose-exposure-response relationship will be explored using a modeling approach.

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Table 1. PAC203 Study Assessments Calendar[20]

Week	Consent and Screen[1]	Randomization and Start of Week 1 (Baseline)[2]	End of Week 4[3]	End of Week 12[4]	End of Week 24[4]	Post -24 Week Follow Up Assessments	End of Treatment[5]	30 Day Post End of Treatment[21]
Day	**-35 to -7**	**1**	**28**	**84**	**168**	**At 3-month intervals following Week 24 visit (ejection fraction assessment will be done at 6-month intervals)**		**+30 days from End of Treatment**
Window (d)		**-1**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-3**
Informed consent[6]	x							
Medical history	x							
Vital signs[7]	x	x	x	x	x	x	x	
Physical exam, including spleen measurement[8]	x	x	x	x	x	x	x	
12-lead ECG[9]	x	x	x	x	x	x	x	x
Ejection fraction assessment (Echo or MUGA)	x		x	x	x	x	x	x
ECOG performance status	x		x	x	x	x	x	
Hematology[10]	x	x	x	x	x	x	x	x
Coagulation testing	x	x	x	x	x	x	x	x
Serum chemistry[11]	x	x	As clinically indicated					
Serum pregnancy test[12]	x		x	x	x		x	
Spleen volume by MRI (preferred modality) or CT[1, 13]	x			x	x	x	x	

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Day	**-35 to -7**	**1**	**28**	**84**	**168**	**At 3-month intervals following Week 24 visit (ejection fraction assessment will be done at 6-month intervals)**		**+30 days from End of Treatment**
Window (d)		**-1**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-3**
Patient-reported outcome instrument: MPN-SAF TSS 2.0[14]	x	x	x	x	x	x	x	
Patient global impression assessment				x	x	x	x	
Pharmacokinetic (PK) assessment[15]		x		x	x			
Pharmacodynamic (PD) assessments[15]		x		x	x			
Dispense pacritinib		x	x	x				
Begin pacritinib dosing		x						
Perform pacritinib accountability[16]			x	x	x		x	
Baseline symptoms and AEs[17]	x	x	x	x	x		x	x
Concomitant medications	x	x	x	x	x		x	x
Transfusion history (RBC and platelets)	x	x	x	x	x		x	

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Day	**-35 to -7**	**1**	**28**	**84**	**168**	**At 3-month intervals following Week 24 visit (ejection fraction assessment will be done at 6-month intervals)**		**+30 days from End of Treatment**
Window (d)		**-1**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-3**
DNA sample		x			x			
Receipt of disease directed therapies[19]							x	

Abbreviations: AEs = adverse events; ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BL = baseline; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; CYP450 = cytochrome P450; DIPSS = Dynamic International Prognostic Scoring System; ECG = electrocardiogram; Echo = echocardiogram; ECOG = Eastern Cooperative Oncology Group; End of Study = 30 days after end of treatment visit; End of Treatment = study treatment end of treatment visit; GI = gastrointestinal; LDH = lactate dehydrogenase; MPN-SAF TSS 2.0 = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (version 2.0); MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QTc = corrected QT interval; SAE = serious adverse event.

1 Screening procedures must be completed between Days -35 and -7, before treatment initiation, with the exception of the screening (baseline) MRI or CT scan, which must be performed between Days -10 and -4.

2 Day 1 assessments are required to be performed prior to initiation of study treatment and can be performed up to 24 hours prior to initiation of study treatment. 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.

3 The study visit at week 4 has a scheduling window of ±3 days; however, all procedures other than MRI or CT should be performed on the same day's visit within ±24 hours.

4 The study visits at weeks 12 and 24 have a scheduling window of ±7 days; however, all procedures other than MRI or CT should be performed on the same day's visit within ±24 hours.

Table 1. PAC203 Study Assessments Calendar[20]

[5]	The End of Treatment visit is scheduled within 7 days after terminating study treatment. A final visit to assess events is scheduled 30 ±3 days after the last dose of study treatment. If treatment ends at a regularly scheduled visit, these procedures may be performed at that time.
[6]	Informed consent must be obtained before any study-specific washout. This may require 2 weeks (A 2-week washout will be required for anticoagulation agents, antiplatelet agents (except aspirin doses of ≤ 100 mg/day), strong CYP3A4 inhibitors, strong CYP450 inducers, and QTc prolonging agents) or 28 days if patient was taking any experimental therapies. Patients not requiring washout may sign the Informed Consent Form at any time prior to screening procedures.
[7]	Vital signs include blood pressure, pulse, respiratory rate, temperature, and body weight.
[8]	Height should be measured only at baseline. Spleen size assessed by physical examination as the distance below the LCM at the midclavicular line.
[9]	A single 12-lead ECG (collected in triplicate) will be performed at screening and ***within*** 1 hour prior to dosing and ***at*** 4 hours (± 10 minutes) post dosing on Day 1 of week 1 and at the end of weeks 4, 12, and 24, 30 days postterm, and as clinically indicated. ECGs will also be collected pre-dose during the post 24-week follow-up visits within 1 hour prior to dosing. The ECGs will be read centrally by blinded independent cardiologist.
[10]	Hematology includes CBC, differential, platelet count and hemoglobin A1C. For patients with baseline platelet count of ≤ 50,000/μL, platelet count will be monitored weekly for the first 8 weeks, then monthly if counts remain ≤ 50,000/μL. These platelet counts must be analyzed by the central laboratory, but local laboratory test results may be used for assessment and management of patients in real time. Samples collected for local testing must also be submitted to the central laboratory and the results captured in the clinical database. Additional hematology testing should be done as clinically indicated.
[11]	Eligibility may be based on local or central laboratory values. Central serum 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, uric acid, and high sensitivity CRP. Any samples collected at any visits must be analyzed by the central laboratory, although local laboratories may additionally be used for patient assessment and management in real time.
[12]	All women of child-bearing potential (WOCBP) must have a pregnancy test at screening. For WOCBP in the UK, the screening pregnancy test must occur no longer than 7 days before the first study drug administration and again at the End of Week 4 visit. Additional pregnancy tests every 12 weeks while on study treatment may be mandated as a country-specific requirement.
[13]	Unscheduled imaging studies may 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. Images generated as part of unscheduled evaluations may also be read locally if treatment discontinuation is being considered. 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. An independent radiologist, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume.

Table 1. PAC203 Study Assessments Calendar[20]

[14] Patient-reported disease-related symptoms as assessed by the MPN-SAF TSS 2.0 will be collected daily up to 48 weeks using an electronic diary starting at least 7 days prior to starting pacritinib treatment. After 48 weeks, the same questionnaire with 7 day recall period (paper) will be used at each visit for the rest of the study.

[15] The Sponsor will collect PK samples from all patients in each dosing arm at the End of Week 12 and End of Week 24 visits: 30 minutes to 0 hours (predose), 4 hours (± 10 minutes), and 8 hours (± 15 minutes) postdose. Dense PK sampling will be performed at selected sites for approximately 6 to 8 patients total per dose arm on Week 1 Day 1: 2 hours (± 5 minutes), 4 hours (±10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose), End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose. In addition, PD samples will be collected on Day 1 (Baseline), Week 12, and Week 24 within 30 minutes prior to 0 hours (predose). Given the sampling schedule, PK and PD samples should be collected before and after the morning dose for patients taking pacritinib twice a day (BID).

[16] 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(s) to every visit. When a patient returns one or more bottles, count the remaining capsules in all bottle(s).

[17] Baseline symptoms and AEs: Patients will be evaluated from the time of signing the Informed Consent Form through 30 days following last dose of study treatment . Each SAE assessed as related to study treatment or study procedures will be collected through 30 days following last dose of study treatment and will be followed until it is resolved, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever occurs first.

[18] Concomitant medications are recorded at the post-24-week follow-up assessments for those patients continuing on pacritinib.

[19] Disease directed therapy includes any therapy that is specifically directed at controlling a disease or its symptoms and does not include standard supportive care, i.e. pain medications. Examples include growth factors, cytotoxics, interferons and other targeted agents.

[20] Study assessments will be performed per schedule until approval of Amendment 6, at which point they cease following the patient's End-of-Treatment, or 30-day post (EOT) visit, as applicable. All patients will require End of treatment visit, however, patients who continue to receive pacritinib under expanded access will not require a 30 Day Post EOT visit.

[21] Following approval of Amendment 6, patients who continue to receive pacritinib under expanded access will not require a 30 Day Post EOT visit.

Special Cases: Modifications to Study Assessments Calendar

All patients should complete all visit procedures through Week 24, including patients who stop pacritinib treatment or have protocol-defined progressive disease prior to week 24, unless patient:

- **withdraws consent**
- **dies**
- **undergoes splenic irradiation, splenectomy, or initiates any non-protocol-directed anti-myelofibrosis treatment**

***Patients who continue on pacritinib after Week 24 will receive efficacy and safety assessment every 3 months up to 2.5 years (with the exception of MRI/CT spleen assessment, which will only be followed up to 2 years and TSS assessment, which will only be followed up to 48 weeks). Study assessments will be performed per schedule until approval of Amendment 6, at which point they cease following the patient's End-of-Treatment, or 30-day post (EOT) visit, as applicable.**

Patients who discontinue pacritinib treatment prior to Week 24 must complete the *End of Treatment* visit within 7 days of stopping the drug and *30 Day Post End of Treatment* visit within 30 days of *End of Treatment* visit.

Patients who discontinue pacritinib treatment prior to Week 24, with or without disease progression, will continue to follow this Study Assessments Calendar through Week 24.

Patients who undergo splenic irradiation, splenectomy, or who initiate any non-protocol-directed anti-myelofibrosis treatment at any time must complete the *End of Treatment* visit within 7 days of stopping the drug and *30 Day Post End of Treatment* visit within 30 days of *End of Treatment* visit, but will not complete any additional visits.

If an arm is closed, patients randomized to that arm will end pacritinib treatment and complete the *End of Treatment* visit within 7 days of stopping the drug and *30 Day Post End of Treatment* visit within 30 days of *End of Treatment* visit.

Unscheduled visits should include physical examination, laboratory tests, and radiographic evaluations as clinically indicated in the judgement of the investigator and these results must be entered into the EDC.

Additional visits may be required for patients with baseline platelet count ≤ 50,000/μL as well as patients who have pacritinib dose modifications due to hematologic, cardiac, diarrhea, or other non-hematologic toxicities in addition to those specified in Section 6.5. Samples drawn for clinical laboratory assessments at unscheduled visits should be submitted to the central laboratory for analysis in addition to any local analysis that may be performed for the purpose of patient management. See Section 6.5 for details.

Abbreviations

Abbreviation	Full Term
AE	adverse event
ALT	alanine aminotransferase (syn: see SGPT)
ASCT	allogeneic stem cell transplantation
AST	aspartate aminotransferase (syn: see SGOT)
AUC	area under the curve
AUC_{inf}	area under the curve to infinite time
AUC_{0-t}	area of the curve up to the last measurable concentration
BAT	best available therapy
BID	twice per day
BUN	blood urea nitrogen
CBC	complete blood count
C_{max}	maximum concentration observed
C_{min}	minimum concentration observed
CRF(s)	case report form(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EPs	erythroid progenitors
ET	essential thrombocythemia
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLT3	fms-like receptor tyrosine kinase 3
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
IC_{50}	50% inhibitory concentration
ICF	informed consent form

Abbreviations

Abbreviation	Full Term
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
ITT	intent-to-treat
i.v.	intravenous
IWG	International Working Group
JAK	Janus kinase
LCM	lower costal margin
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPD	myeloproliferative disease
MPN-SAF TSS 2.0	Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI	National Cancer Institute
PD	pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PK	pharmacokinetic(s)
PMF	primary myelofibrosis
PPV-MF	post-polycythemia vera myelofibrosis
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
QD	once daily
QTc	corrected QT interval
RBC	red blood cell

Abbreviations

Abbreviation	Full Term
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic-oxaloacetic transaminase (syn: see AST)
SGPT	serum glutamic pyruvic transaminase (syn: see ALT)
SMQ	Standardized MedDRA Query
STAT	signal transducers and activators of transcription
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration
TSS	total symptom score
TT	thrombin time
ULN	upper limit of normal
uMPD	unclassifiable myeloproliferative disease
US	United States
WOCBP	Woman of child-bearing potential
WBC	white blood cell

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), MDS/MPDs, 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

MF may present as either a primary myeloproliferative disorder or follow a diagnosis of PV or ET. Regardless of the original diagnosis, PMF, post-polycythemia vera MF (PPV-MF), and post-essential thrombocythemia MF (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 and Green 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; petechiae resulting from thrombocytopenia and/or abnormal platelet function). Gout and renal stones secondary to hyperuricemia are also common (Ahmed and Chang 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 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 red blood cells (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 (IWG) – 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 and Chang 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 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, the JAK 1/2 inhibitor ruxolitinib received approval in the United States (US) 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 studies 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 dosage must be adjusted in patients with platelet counts <200,000/μL. In patients taking ruxolitinib who develop a platelet count <50,000/μL, withholding ruxolitinib is recommended until the platelet count recovers to over 50,000/μL. In clinical studies, 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 dosage 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 dosage modifications for thrombocytopenia were more frequent in the ruxolitinib arm than in the best available therapy arm (41% versus 1%). Disease control is substantially reduced with patients on ruxolitinib who require dose reductions of ruxolitinib to less than 20 mg per day and discontinuation of ruxolitinib is recommended for patients who are taking 5 mg twice daily and who are not responding at 6 weeks (Jakafi package insert, Jakafi SmPC).

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 package insert, Jakafi SmPC).

Patients who are taken off ruxolitinib due to lack of efficacy or toxicity have poor survival which is negatively impacted by starting and ending platelet count. In a recent report from MD Anderson Cancer Center on patient outcome after ruxolitinib discontinuation, median survival was 14 months but was substantially shorter for patients starting ruxolitinib with platelets <260,000/μL (HR = 2.7) or who stopped ruxolitinib at platelet counts <100,000/μL (HR = 4.1) (Newberry et al 2017). In a similar series from the MAYO Clinic, discontinuation rates at 1, 2, and 3 years were 51%, 72% and 89% with the most common causes of disease progression including loss of response (40%) and toxicity with or without loss of response (34%). Survival was dependent on DIPSS scores and was similar for intermediate-2 and high risk patients as compared to patients treated prior to ruxolitinib availability (Tefferi et al 2011).

Patients who discontinue ruxolitinib with intermediate to high risk disease have no effective therapeutic options and a short survival. The current study is designed to test the efficacy and safety of pacritinib in this setting.

1.3 Pacritinib

Pacritinib is a novel JAK2/fms-like receptor tyrosine kinase 3 (FLT3) inhibitor that has demonstrated promising antitumor activity in two mouse models of human malignancies. Preclinical toxicology studies have identified a safe starting dosage for clinical studies. 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, 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 (50% inhibitory concentration [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/F3JAK2V617F cells. Pacritinib treatment at 150 mg/kg orally twice daily (BID) was well tolerated and significantly ameliorated symptoms, with 60% normalization of spleen weight and 92% normalization of liver weight.

Pharmacokinetics in Animals

Pharmacokinetics (PK) following single intravenous (i.v.) or oral administration of pacritinib was evaluated in mice, rats, and dogs. Following oral administration, pacritinib showed rapid absorption in mice (time of maximum concentration [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 hours 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.

1.3.2 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 aspartate transaminase (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 dosages 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 dosages 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.

1.3.3 Summary of Clinical Pharmacology and Phase 1 Studies with Healthy Volunteers with Pacritinib

To date, the Sponsor 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 (SB15182010-004). In addition, the single and multiple dose population PK of pacritinib has been characterized following multiple dose administration of pacritinib in two studies (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 (SB1518-2010-004) in healthy volunteers under fasting conditions, peak plasma concentrations were reached at a median T_{max} ranging from 4.5 to 5.5 hours across the 100 to 400 mg dose range. While between-patient variability was relatively high (28% to 45%), the within-patient variability was low (13% to 15%), highlighting the consistent systemic exposure for pacritinib in individual patients. The mean elimination half-life was approximately 34 hours and was not dependent on dose. The systemic exposure of pacritinib in 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 maximum concentration observed (C_{max}), area of the curve up to the last measurable concentration (AUC_{0-t}), and area under the curve to infinite time (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 studies in patients at pacritinib dosages up to 600 mg once daily (QD) showed slow absorption (T_{max} 4 to 6 hours) and dose-related increases in systemic exposure up to 400 mg QD. The rate of absorption was linear at doses up to 300 mg and thereafter appeared to be rate limited. Therefore, modeling suggested that, at doses of over 200 mg per day, divided doses would yield increased steady study blood levels. Beyond the 400 mg QD dosage, 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 half-life=47 hours), 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.

1.3.4 Overview of Clinical Studies of Pacritinib in Patients with Myelofibrosis

Approximately 967 individuals have received pacritinib in 15 completed studies, which includes 552 patients with myelofibrosis who were assigned to a pacritinib arm. Completed studies include two controlled studies in myelofibrosis, four uncontrolled clinical studies in cancer patients and 9 clinical pharmacology/pharmacokinetic studies. The summary below describes efficacy and safety observations from across the completed controlled (phase 3) studies in myelofibrosis.

Summaries of Each Phase 3 Myelofibrosis Study

PERSIST-1 was the first phase 3 study of pacritinib, comparing the efficacy of 400 mg QD with best available therapy (not including ruxolitinib) in patients with PMF, PPV-MF, or PET-MF. Patients previously treated with JAK2 inhibitors were excluded. There were no exclusion criteria based on platelet count. Three hundred twenty-seven patients (327) were randomized in a 2:1 allocation to pacritinib or best available therapy (BAT). PERSIST-1 demonstrated a statistically significant improvement in the primary endpoint of percent of pacritinib-treated patients achieving a ≥35% reduction in spleen volume at Week 24 compared to baseline, as assessed by centrally read MRI or computed tomography [CT] imaging), compared to best available therapy. Pacritinib efficacy in SVR response was not affected by baseline thrombocytopenia (<50,000/μL or <100,000/μL platelets), compared to BAT (pre-specified subgroup intent-to-treat [ITT] <50,000/μL: 22.9% versus 0% SVR response, respectively; <100,000/μL: 16.7% versus 0% SVR response, respectively), although statistical significance could not be determined in accordance with the pre-specified statistical analysis plan. More patients treated with pacritinib had improved MF-related symptomatology, meeting the predefined TSS response definition (≥50% reduction at Week 24 compared to baseline, as assessed by Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score version 2.0 (MPN-SAF TSS 2.0) than those treated with BAT, but this trend was not statistically significant. In general, safety was similar to that seen in early phase studies, although interim OS results were consistent with a negative trend in survival in pacritinib-treated patients, and there were imbalances in fatal and life-threatening events, including intracranial hemorrhage, and arrhythmias including sudden death.

PERSIST-2 was the second phase 3 study of pacritinib, comparing the efficacy of 400 mg QD and 200 mg BID with best available therapy, including ruxolitinib, in patients with PMF, PPV-MF, or PET-MF and thrombocytopenia (baseline platelet count ≤100,000/μL). Patients previously treated with JAK2 inhibitors were included. There were no exclusion criteria based on platelet count. Three hundred eleven patients (311) were randomized in a 1:1:1 ratio to the 3 treatment arms. Due to Full Clinical Hold on February 8, 2016, only 211 of the accrued patients were evaluable in the ITT (efficacy) population, having been randomized with sufficient time to reach the Week 24 evaluation window, thus limiting the power to detect differences in the efficacy endpoints. PERSIST-2 demonstrated a statistically significant improvement in the coprimary endpoint comparing the pooled pacritinib arms with the BAT arm for the percent of pacritinib-treated patients achieving a ≥35% reduction in spleen volume at Week 24 compared to baseline (SVR response), as assessed by centrally read MRI or CT imaging, compared to best available therapy (18.1% vs. 2.8%, p=0.0011). More patients in the pooled pacritinib had improved MF-related symptomatology, meeting the predefined TSS response definition (≥50% reduction at Week 24 compared to baseline, as assessed by MPN-SAF TSS 2.0, TSS response) than those treated with BAT, but this trend in the second co-primary endpoint was not statistically significant (24.8% vs. 13.9%, p=0.791). Comparing the individual pacritinib treatment arms to BAT, SVR response was nominally significant for BID (21.6%) vs. BAT (p=0.0007), and for QD (14.7%) vs. BAT (p=0.0173). Unlike the pooled coprimary analysis, the BID arm had nominal significance for TSS response vs. BAT (32.4% vs. 13.9%, p=0.0106), but the QD arm did not (17.3%, p=0.6524). Exploratory analyses most relevant to the current study showed that in comparison with the ruxolitinib-treated BAT patients, more pacritinib-treated patients achieved the SVR response than patients treated with either ruxolitinib or other BAT agents (QD 11/75, 14.7%; BID 16/74, 21.6%; ruxolitinib 1/32, 3.1%; other BAT 1/40, 2.5%). Similarly, more pacritinib 200 mg BID (but not 400 mg QD) patients achieved the MPN-SAF TSS2.0 response (pacritinib 24/74, 32.4% vs. ruxolitinib 6/32, 18.8%), despite the increased effect of ruxolitinib compared to all other BAT patients (4/40, 10%).

Interim analyses of the PERSIST-2 study led to Full Clinical Hold due to interim OS results in which the pooled pacritinib treatment arms (QD + BID) were compared with BAT and concerns about fatal intracranial hemorrhage, cardiac failure, and cardiac arrest. Updated analyses based on the locked database demonstrated that the QD dosing arm had a survival decrement compared to BAT (hazard ratio

[HR]=1.18; p=0.6615), but the BID dosing arm had a trend for survival benefit (HR=0.68; p=0.3458). In general, the safety observed in PERSIST-2 was similar to that observed in PERSIST-1, although differences were seen between the QD and BID pacritinib dosing arms. With the exception of hemorrhage, BID dosing generally was associated with lower rates of adverse events (AEs), including grade 3/4 and fatal events. The pacritinib BID arm had greater apparent efficacy for both SVR and reduction in TSS than either pacritinib dosed at 400 mg QD or BAT. Based on these efficacy data, the dose of 200 mg BID has been selected as the upper level dosage regimen for the current dose ranging study.

Most relevant to the current study, the safety impacts of prior JAK2 inhibitor treatment in PERSIST-2 were compared to patients who did not have such prior treatment. Incidences of treatment-emergent AEs (TEAEs) overall followed a similar pattern in the prior JAK2 inhibitor treatment and no prior JAK2 inhibitor treatment subgroups in the pacritinib and BAT treatment arms (pacritinib, 98.1% and 96.3%, respectively; BAT, 90.4% and 87.0%, respectively), with comparable incidence in the QD and BID dosing arms. While thrombocytopenia showed similar rates between subgroups, anemia was increased in the no prior treatment group (pacritinib, 15.5% [13.5% QD and 17.6% BID] and BAT, 11.5% in the prior treatment group, and pacritinib, 35.5% [42.3% QD and 29.1% BID] and BAT, 19.6% in the no prior treatment group). Diarrhea, nausea, and vomiting had increases in incidence in the prior treatment group compared to the no prior treatment group. The percentages of patients who experienced TEAEs of CTCAE grade 3 in the pacritinib QD + BID pooled arms, and BAT arms were 35.9% and 26.9% respectively, in patients with prior treatment and 36.4% and 28.3%, respectively, in patients with no prior treatment. When comparing the incidence of grade 3 events in the QD and BID arm in each subgroup, there was an increased incidence of events in the QD arm in the prior treatment subgroup (44.2% compared to 27.5%) and an increased incidence of events in the BID arm in the no prior treatment subgroup (40.0% compared to 32.7%). The percentage of patients who experienced TEAEs of CTCAE grade ≥3 in the pacritinib and BAT arms were 70.9% and 42.3%, respectively, in patients with baseline prior treatment and 74.8% and 56.5% respectively, in patients with baseline no prior treatment. The rates of grade 3/4 TEAEs in the QD and BID pacritinib groups were similar to that observed in the pacritinib QD + BID pooled arms. The rates of grade 3/4 thrombocytopenia and more notably, anemia events were decreased in the prior treatment group (prior treatment: pacritinib, 12.6% [QD 11.5% and BID 13.7%] and BAT, 9.6%; no prior treatment: pacritinib, 35.5% [QD 42.3% and BID 29.1%] and BAT, 19.6%). Fatal TEAEs occurred at modestly higher rates in the prior treatment group compared to the no prior treatment group in the pacritinib arms, particularly in the pacritinib QD arm, (12.6% [QD 17.3% and BID 7.8%] compared to 9.3% [QD 11.5% and BID 7.3%]). The BAT arm showed a reverse pattern, with fatal events increased in the no prior treatment group compared to the prior treatment group (13.0% versus 5.8%).

Adverse Events in the Myelofibrosis Population:

Overall, amongst the MF subjects treated with pacritinib in the completed controlled and uncontrolled studies, 96% experienced a treatment emergent AE. The most common TEAEs (> 10% of subjects) occurred in the SOCs of gastrointestinal disorders (including diarrhea [66%], nausea [37%], vomiting [24%], abdominal pain [16%] and constipation [13%]), blood and lymphatic system disorders (including anemia [28%] and thrombocytopenia [25%]) and general disorders (fatigue [22%], pyrexia [12%] and decrease appetite [13%]). Events of dizziness (10%), dyspnea, epistaxis and pruritus (all 11%) were also observed.

The most commonly (>10% of all subjects) reported treatment-related TEAEs by preferred term, were in the SOC of gastrointestinal disorders including diarrhea (62%), nausea (31%) and vomiting (18%), and the SOC of blood and lymphatic system disorders, including thrombocytopenia (16%) and anemia (15%). While GI-related events were common, they were generally reversible, of low grade and rarely led to treatment discontinuation. The potential risk of hypersensitivity reaction with pacritinib is low. Pacritinib is contraindicated in patients with a known hypersensitivity to the active substance or to any of

the excipients. Potential mechanisms include an immune-mediated response to pacritinib or any of the excipients of the product.

Safety Observations Across the Controlled Phase 3 Studies:

In the controlled PERSIST-1/-2 studies, patients in the pacritinib arm (42.8% [184/430]) experienced treatment-related grade 3/4 AEs at a higher frequency than patients in the BAT arm (13.7% [28/204]). However, no notable patterns were observed in the type or frequency of specific AEs. The proportion of patients who experienced a treatment related grade 3/4 AE was similar in the 400 mg QD (42.0% [136/324]) arm compared to the 200 mg BID (45.3% [48/106]) arm. The most common treatment related grade 3/4 AEs for both the 400 mg QD and 200 mg BID arms were thrombocytopenia (12.7% and 18.9%, respectively) and anemia (15.4% and 10.4%, respectively). For both treatment arms, all other grade 3/4 TEAEs occurred at a frequency of <6%.

A greater proportion of patients in the pacritinib (50.9%) arm compared to BAT (27.5%), and in the 400 mg QD arm (52.2%) compared to 200 mg BID (47.2%), experienced at least one SAE. The most common SAEs in patients treated with pacritinib by PT were anemia (6.7%), pneumonia (6.3%), disease progression (3.0%), thrombocytopenia and cardiac failure (both 2.8%), and pyrexia and acute renal failure (2.6% each). All of these SAEs occurred at a higher incidence in patients treated with pacritinib compared to BAT. In addition, the incidences of all of these SAEs, except for thrombocytopenia (1.9% of the 400 mg QD arm and 5.7% of the 200 mg BID arm) were similar for the 400 mg QD and 200 mg BID arms

The incidence of deaths reported was higher in the pacritinib arms than in the BAT arm over the entire reporting period for the pooled PERSIST-1/-2 studies, including more than 30 days after last dose of study treatment (27.2% of pacritinib vs. 9.3% of BAT patients) or while on study treatment and within 30 days after treatment (10.9% of pacritinib vs. 5.4% of BAT patients). The higher incidence of deaths in the pacritinib arm was a result of a much higher incidence with 400 mg QD than with 200 mg BID (29.9% vs. 12.7%). In particular, during the period on study treatment or within 30 days after treatment, the difference in deaths between pacritinib and BAT was only seen for the 400 mg QD arm: 12.7% of 400 mg QD died in this period compared to 5.7% of 200 mg BID patients and 5.4% of BAT patients.

The SOCs with the highest number of patients reported in the 400 mg QD arm were general disorders and administration site conditions (4.3%), cardiac disorders (2.5%), and infections and infestations (1.9%). In contrast, for the 200 mg BID arm, the SOCs with the highest number of patients reported were general disorders and administration site conditions (3.8%) and nervous system disorders (2.8%). General disorders and administration site conditions (2.0%) was the most frequently reported SOC in patients treated with BAT.

Thrombocytopenia

While many patients had stable or increasing platelet counts during treatment, some decreases were observed. The incidence of the TEAE of thrombocytopenia was higher during treatment with pacritinib (27.9%) than with BAT (18.6%) in the PERSIST 1/-2 studies. The incidence of thrombocytopenia was generally higher in the 200 mg BID arm compared to the 400 mg QD arm. This was true for all TEAEs (34.0% vs. 25.9%, respectively), related TEAEs (20.8% vs. 16.0%), grade 3/4 TEAEs (21.0% vs. 32.1%), and SAEs (1.9% vs. 5.7%).

Despite thrombocytopenia, most pacritinib patients continued treatment without dose modification. Overall, only 2.5% of patients on 400 mg QD and 1.9% on 200 mg BID, discontinued due to thrombocytopenia and only 2.8% on 400 mg QD and 1.9% on 200 mg BID, had a dose reduction due to thrombocytopenia. In patients with a platelet count below 100,000/μL, only 4.0% of patients on 400 mg QD and 1.9% of patients on 200 mg BID, discontinued due to thrombocytopenia. For those who had dose modifications due to thrombocytopenia, dose reduction or short term interruption allowed treatment continuation. Importantly, treatment emergent thrombocytopenia or worsening of baseline

thrombocytopenia did not appear to be associated with treatment-emergent AEs of bleeding. Hemorrhagic events were reported in pacritinib treated patients with or without severe thrombocytopenia.

Anemia

The TEAE of anemia was higher during treatment with pacritinib (28.1%) than with BAT (17.6%) in the PERSIST-1/-2 studies. However, the incidence of anemia was generally lower in the pacritinib 200 mg BID arm compared to the 400 mg QD arm. This was true for all TEAEs (23.6% vs. 29.6%, respectively), related TEAEs (13.2% vs. 17.9%), grade 3/4 TEAEs (21.7% vs. 26.2%), and TEAEs leading to dose reduction (0.9% vs. 3.7%).

Mean (SD) baseline hemoglobin levels for the 400 mg QD and 200 mg BID arms were 103.9 (23.3) g/L and 98.9 (22.0) g/L, respectively, indicating in general, patients were anemic at study entry.

Hemorrhage

Patients with MPNs are at increased risks for thrombosis and major bleeding. Hemorrhagic events have been reported in pacritinib-treated patients with and without severe thrombocytopenia.

The incidence of TEAEs in the SMQ hemorrhages was similar during treatment with pacritinib (33.7%) and BAT (30.4%) in the PERSIST-1/-2 studies. However, the incidence of hemorrhage events was lower in the 400 mg QD arm compared to the 200 mg BID arm for all categories of TEAEs, including SAEs. The most common bleeding events were epistaxis, contusion, hematoma and GI hemorrhage and these events occurred at a similar frequency to patients treated with BAT. Importantly, one of the most common TEAEs in the "watch and wait only" patients was epistaxis (26.3%), indicating a baseline level of bleeding without any therapy, in this MF population. Most events in the SMQ hemorrhages were low grade, however, severe and sometimes life-threatening and fatal hemorrhagic events have been reported across the PERSIST-1/-2 studies. These outcomes comprised predominantly GI bleeding (including gastric variceal hemorrhage, melena, and esophageal hemorrhage) and intracranial hemorrhage, cerebral hemorrhage and meningorrhagia. Overall, hemorrhagic TEAEs resulted in death in seven patients in the PERSIST-1/-2 studies, two treated with pacritinib 200 mg BID, four treated with pacritinib 400 mg QD, and one after crossover from BAT to pacritinib.

The incidence of a new hemorrhage event TEAE was highest at the start of treatment and then diminished with continued treatment in all treatment groups. Serious hematological events occurred in patients with complicated medical histories, severe comorbidities, concomitant antiplatelet use, and myelosuppression. The risk of bleeding episodes did not appear to be related to the degree of thrombocytopenia.

Diarrhea

Patients in the PERSIST-1/-2 studies were evaluated at baseline to assess usual bowel habits and instructed on the need for early intervention for possible GI adverse effects associated with treatment. During each study, standard supportive care measures were provided to control symptoms of GI toxicity.

The incidence of the TEAE of diarrhea was higher during treatment with pacritinib (61.4%) than with BAT (14.2%) in the PERSIST-1/-2 studies. However, the incidence of diarrhea was generally lower in the pacritinib 200 mg BID arm than in the 400 mg QD arm for most categories of TEAEs. This was true for all TEAEs (48.1% vs. 65.7%, respectively), related TEAEs (48.1% vs. 60.2%), grade 3/4 TEAEs (3.8% vs. 6.5%), TEAEs leading to discontinuation (0% vs. 2.5%), and TEAEs leading to dose reduction (0.9% vs. 4.0%). However, the incidence of diarrhea reported as SAEs was similar in both the 200 mg BID and 400 mg QD arms (1.2% vs. 1.9%).

The incidence of diarrhea was highest in the pacritinib groups at the start of treatment and then diminished with continued treatment: 54.3% of patients in the 400 mg QD arm and 40.6% of patients in the 200 mg BID arm reported a new TEAE of diarrhea during the first eight weeks of treatment. Between Weeks 8 and 16, this had decreased to 10.9% of the 400 mg QD arm and 15.3% of the 200 mg BID arm. After Week 16, the incidence was <10% in either arm.

While patients in both pacritinib and BAT treatment arms experienced the onset of diarrhea within the first four weeks, overall the time to onset of the first episode of diarrhea was earlier for patients treated with pacritinib than BAT. Within the pacritinib treatment arms, the 200 mg BID arm was more likely to remain event-free both in the first eight to 12 weeks and over the duration of treatment compared to the 400 mg QD arm. Similar results were seen for the time course of grade 3/4 diarrhea.

Nausea and Vomiting

The incidence of the TEAE of nausea was higher during treatment with pacritinib (32.8%) than with BAT (8.3%) in the PERSIST-1/-2 studies. However, the incidence of nausea was lower in the pacritinib 200 mg BID arm compared to the 400 mg QD arm for related TEAEs (20.8% vs. 29.0%) and those TEAEs leading to dose reduction (0.9% vs. 1.9%). Very few patients in any group reported grade 3/4 TEAEs or SAEs of nausea or nausea AEs leading to discontinuation or dose reduction, and almost all of these were in the 400 mg QD arm.

The incidence of vomiting was higher during treatment with pacritinib (20.7%) than with BAT (5.4%) in the PERSIST-1/-2 studies. However, the incidence of vomiting was lower in the pacritinib 200 mg BID arm than in the 400 mg QD arm for related TEAEs (10.4% vs. 16.4%) and grade 3/4 TEAEs (0% vs. 2.5%). Very few patients in any group reported grade 3/4 TEAEs or SAEs of vomiting or vomiting AEs leading to discontinuation or dose reduction, and almost all of these were in the 400 mg QD arm.

Cardiac Toxicities

The incidence of TEAEs of cardiac disorders was higher during treatment with pacritinib (13.7%) than with BAT (9.8%) in the PERSIST 1/-2 studies. However, the incidence of cardiac disorders was generally lower in the pacritinib 200 mg BID arm than in the 400 mg QD arm. This was true for all TEAEs (10.4% vs. 14.8%, respectively), grade 3/4 TEAEs (3.8% vs. 8.6%), SAEs (4.7% vs. 9.3%), and related SAEs (0.9% vs. 2.2%).

The most commonly reported TEAEs of cardiac disorders were cardiac failure (3.5% of pacritinib patients, with a similar incidence in the 400 mg QD and 200 mg BID arms, and 2.5% of BAT patients) and atrial fibrillation (3.0% of pacritinib patients, all in the 400 mg QD arm, none in the 200 BID arm, and 2.5% of BAT patients). All other cardiac TEAEs occurred with an incidence of <2% in any treatment group. Approximately half of the cardiac events were grade 3/4 in severity in both the pacritinib and BAT arms, but in the pacritinib arm these were mainly in the 400 mg QD arm (8.6% of patients vs. 3.8% of the 200 mg BID arm). Very few of the cardiac events led to discontinuation (1.5% of the 400 mg QD arm, 0.9% of the 200 mg BID arm, and 0.5% of the BAT arm).

Although the rate of serious cardiac events among MF patients was modestly higher than what was expected in the BAT arm, no clear pattern of individual cardiac events or event onset was discernable. Some appeared to be associated with other manifestations of worsening of a pre-existing cardiac condition. In support of this, none of the cardiac events in the BAT arm and only a few in the pacritinib arm were considered to be related to study drug. More specifically, the two most common cardiac events were considered related in four (0.9%) pacritinib patients (all 400 mg QD) with atrial fibrillation and three (0.7%) pacritinib patients (two with 400 mg QD and one with 200 mg BID) with cardiac failure.

While diarrhea was one of the most commonly reported TEAEs for pacritinib-treated patients, severe diarrhea associated with hypokalemia was not observed. Hypokalemia measured by clinical laboratory showed a 2 grade negative shift (0 to 2) in 5.7% of patients in the pacritinib 200 mg BID arm, 7.8% in the 400 mg QD arm, and 2.9% in the BAT arm.

There were 13 cardiac disorder TEAEs leading to death in the PERSIST-1/-2 studies and the incidence was higher in the 400 mg QD arm (8 patients [2.5%]) than either the 200 mg BID arm (no patients) or the BAT arm (2 patients [1.0%]). Of these deaths, only two were reported by the investigator to be related to study treatment (one event of cardiac arrest and one event of congestive cardiac failure).

2 Study Rationale and Objectives

Two phase 2 studies of pacritinib have been conducted in patients with MF. Data from these studies 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 regardless of the degree of thrombocytopenia and in patients who had received prior ruxolitinib. These findings warrant further investigation to confirm the efficacy and safety of pacritinib, in patients who have been previously treated with ruxolitinib including those with thrombocytopenia. Pacritinib may address a significant unmet need as salvage therapy, especially in patients with low platelet counts or red blood cell transfusion requirements who are intolerant of ruxolitinib.

The current study is being proposed to address the Food and Drug Administration (FDA) recommendation to perform a study to determine if a lower dosage of pacritinib might prove optimal in patients with MF. This study is an open-label, randomized, phase 2 study with 3 dosages that aims to identify the most appropriate dosage for future studies based on risk/benefit profile. The 3 dosages include a low dosage (100 mg QD), an intermediate dosage (100 mg BID), and a high dosage with a demonstrated efficacy profile and acceptable safety profile (200 mg BID). These dosage levels have been selected because they span the dose–response curve and allow adequate characterization of dose–response relationship for pacritinib and allow for establishment of a minimally effective dosage that conserves the known effect of pacritinib on the surrogate marker of spleen volume response as determined by independently assessed MRI.

Recruitment to 3 dosages simultaneously is justified based on the large safety database available at the highest planned dosage level from PERSIST-2 (i.e., 200 mg BID), and the planned frequent monitoring by an Independent Data Monitoring Committee (IDMC; see Section 2.2) in addition to rigid entry criteria for patients with pre-existing bleeding episodes and patients with existing cardiac disease, with increased monitoring for cardiac and hemorrhage AEs.

2.1 Justification of Included Patient Population

MF is a serious, life-limiting condition with severe morbidity in advanced stages. Ruxolitinib is the only approved agent for treatment of MF. Patients who are intolerant or who have failed to maintain a robust response to ruxolitinib have no alternative therapies and are at high risk for early mortality.

Overview of Included Patient Population

Patients to be included in this study will have failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy. This requirement is based on the unmet medical need in patients who failed to maintain benefit from the only approved agent. Intolerance is defined by a minimum of 28 days therapy with pre-defined safety issues as previously used in a phase 3 clinical study of a JAK inhibitor in MF patients (https://clinicaltrials.gov/ct2/show/NCT02101268). Suboptimal efficacy is defined based on consensus criteria and is based on a lack of spleen reduction and symptom improvement after 6 months of attempted treatment (Mesa et al 2016).

In addition, patients will be highly symptomatic (Dynamic International Prognostic Scoring System [DIPSS] risk score of Intermediate-1 to High Risk), and have splenomegaly as assessed by physical examination.

Patients must have had no recent cardiac or bleeding history, and meet cardiac and bleeding safety screening evaluations including electrocardiogram (ECG), echocardiogram and coagulation testing

results. Patients with baseline corrected QT interval (QTc) ≥450 ms will be excluded from the study. Patients requiring concomitant medications with a significantly increased risk of QTc prolongation or bleeding will be excluded. Based on the observed limited increase in pacritinib concentration in the cytochrome P450 (CYP3A4) inhibitor interaction study with clarithromycin (Study PAC104), caution should be exercised when coadministering such inhibitors with pacritinib. For the PAC203 clinical study, patients requiring such inhibitors will be excluded (Appendix 5). Based on the substantive pacritinib concentration reduction observed in the cytochrome P450 (CYP450) inducer interaction study with rifampin (Study PAC106), patients requiring such inducers (Appendix 6) will be excluded. Patients are also required to have adequate hepatic and renal organ function and the absence of known medical issues which might affect efficacy assessments, tolerability, or safety on study.

2.2 Independent Data Monitoring Committee

This study will utilize planned frequent monitoring by an IDMC. At a minimum, the IDMC will consist of 1 board-certified hematologist, 1 board-certified cardiologist, and 1 biostatistician experienced in adaptive design clinical studies. The role and responsibilities of the IDMC will be fully defined within the IDMC charter, including, but not limited to:

- Review safety data across arms, focusing on bleeding events, cardiac events, and deaths
- Evaluate cumulative safety as described in Section 11
- Make independent recommendations to the Sponsor on study continuation (continue without modification, continue with modification, or terminate) and on patient enrollment (hold or stop enrollment, enroll additional patients, close arm) as described in Section 11.
- Make independent recommendation to the Sponsor on pacritinib dose or dosages for further study

The IDMC charter will be written in collaboration between the Sponsor and members of the IDMC. In keeping with the terms of the charter, each IDMC meeting will have an open and closed session.

The first IDMC meeting for safety review is planned tooccur once 18 patients have been randomized and treated for 12 weeks and will meet approximately quarterly thereafter. Meeting minutes will be generated from each meeting and provided to the FDA within 10 business days of the meeting conclusion.

In addition to the IDMC, there will be an Independent Adjudication Committee (IAC) that will review all grade 4 or 5 cardiac and bleeding events to assess the principal condition that resulted in the outcome. The IAC will provide their assessment to the IDMC. Additional details on the IAC will be provided in the IAC charter.

2.3 Study Objectives

2.3.1 Primary Objective

The primary objective is to determine a recommended dosage of pacritinib for further clinical studies.

2.3.2 Secondary Objectives

The secondary objectives are as follows:

1. To examine the dose–response relationship for efficacy, as measured by spleen volume reduction (SVR) using MRI (preferred) or CT and TSS using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score version 2.0 (MPN-SAF TSS 2.0)
2. To examine the dose–response relationship for safety with a focus on AEs of interest
3. To further characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of pacritinib

3 Study Design

This is a dose-finding study in patients with PMF, PPV-MF, and PET-MF (DIPSS risk score of Intermediate-1 to High-Risk), who were previously treated with ruxolitinib. The study is designed to support a pacritinib dosage selection decision. Three dosages will be evaluated, with patients randomized 1:1:1 to pacritinib 100 mg QD, pacritinib 100 mg BID, or pacritinib 200 mg BID. Randomization will be stratified by baseline platelet count (≤50,000/μL; >50,000/μL and ≤100,000/μL; and >100,000/μL). The most recent platelet count obtained prior to start of treatment will be the basis of stratification by baseline platelet count. Assigned treatment will continue until the patient experiences progressive disease, intolerable AEs, or withdraws consent, or until the assigned treatment arm is closed. No study treatment crossover will be allowed. All patients should complete all visit procedures through Week 24, including patients who stop pacritinib treatment or have protocol-defined progressive disease prior to Week 24, unless patient withdraws consent, dies, undergoes splenic irradiation or splenectomy, or initiates any non-protocol-directed anti-myelofibrosis treatment. Following regulatory, Ethics or Institution Review Board approval of Amendment 6, study treatment for patients at and beyond the week-24 timepoint will terminate. Study assessments will cease following the End-of-Treatment or 30-day post (EOT) visit, as applicable. Patients who are benefiting from therapy as of study treatment termination may be allowed to continue receiving pacritinib under single patient expanded access or named patient programs at the investigator's discretion and subject to regulatory and Ethics or IRB approval.

The dosage selection process will be based on efficacy and safety parameters, including model-based dose response as described in Section 3.1.

An IDMC consisting of subject matter experts will be convened and chartered to perform an assessment of safety throughout the study. See Section 2.2 for additional information.

The following criteria (non-binding) have been established to guide the decision:

- In the event of the occurrence of 2 treatment-emergent CTCAE grade ≥4 cardiac AEs or 2 treatment-emergent CTCAE grade ≥4 hemorrhage AEs in the same treatment arm, suspend study enrollment and the IDMC will be convened to review the events including the IAC's assessment of the events. If the IDMC confirms the nature and grade of the events together with a relationship to study drug, the IDMC may recommend closure of one or more treatment arms. In the event one or more arms are suspended or terminated for a safety observation, randomization into the arm(s) will be halted immediately, however patients who are experiencing benefit, in the opinion of the investigator and Sponsor, and who were randomized to an arm that is suspended or terminated, may continue treatment.
- The FDA and other Competent Authorities will be notified of any IDMC meeting that is convened under these circumstances, and the resultant decision will be reported to the FDA within 2 business days. The MHRA will be informed via a substantial amendment.
- If closure of an arm occurs, patients will continue to be enrolled into each of the remaining treatment arms.

The determination of dose or dosages of pacritinib for further study will be based on efficacy, safety, dose–response, and PK/PD exposure–response relationship data after all enrolled patients reach Week 24 (or discontinue the study). Approximately 150 patients total or up to 50 patients per arm may be enrolled.

Spleen volume will be measured by MRI (preferred) or CT at baseline and Weeks 12 and 24 (Table 1). Patient-reported disease-related symptoms as assessed by the validated PRO instrument MPN-SAF TSS 2.0 will be collected daily using an electronic diary and evaluated as part of the dose–response relationship. DNA samples will also be collected for analysis of mutations associated with myelofibrosis at baseline and Week 24.

Safety will be monitored with physical examinations, clinical laboratory assessments (including hematologic, chemistry, and coagulation testing), and cardiac monitoring (including ECG and echocardiogram testing); specified study treatment dosage modifications will be followed to address identified abnormalities. Adverse event data will be collected throughout the study.

The Sponsor will collect PK samples from patients in each dosing arm at the following timepoints:

- Sparse Sampling (all patients): End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 4 hours (± 10 minutes), and 8 hours (± 15 minutes) postdose
- Dense Sampling (performed at selected sites for approximately 6 to 8 patients total per dose arm, at which point all further patients will have PK evaluated by sparse sample collection): Week 1 Day 1: 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose), End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose

The PK parameters, minimum concentration observed (C_{min}), maximum concentration observed (C_{max}), and area under the curve (AUC) will be determined and summarized using descriptive statistics for each pacritinib dosage arm. Exposure-response analyses will be conducted on both safety and efficacy populations in the study. PD samples will be analyzed for biomarkers associated with the JAK/STAT pathway.

3.1 Rationale for Dosage Selection

The primary objective of the study is to determine a recommended dosage of pacritinib for further clinical development; thus the study is designed to characterize the dose–response relationship for pacritinib in patients with MF. Three dosage levels have been selected based on previous clinical phase 1/2 studies and the phase 3 study PERSIST-2, to span the dose–response curve and allow adequate characterization of dose–response relationships for efficacy and safety of pacritinib. These three dosages include a low dosage (100 mg QD), an intermediate dosage (100 mg BID), and a higher dosage with potentially acceptable efficacy and safety profiles (200 mg BID). As the systemic exposure of pacritinib is linear up to the 300 to 400 mg dosage (see dose-proportionality clinical study report; Study SB1518-2010-004), it is projected that the 100 mg QD regimen would result in pacritinib systemic exposure levels similar to those of a 50 mg BID regimen.

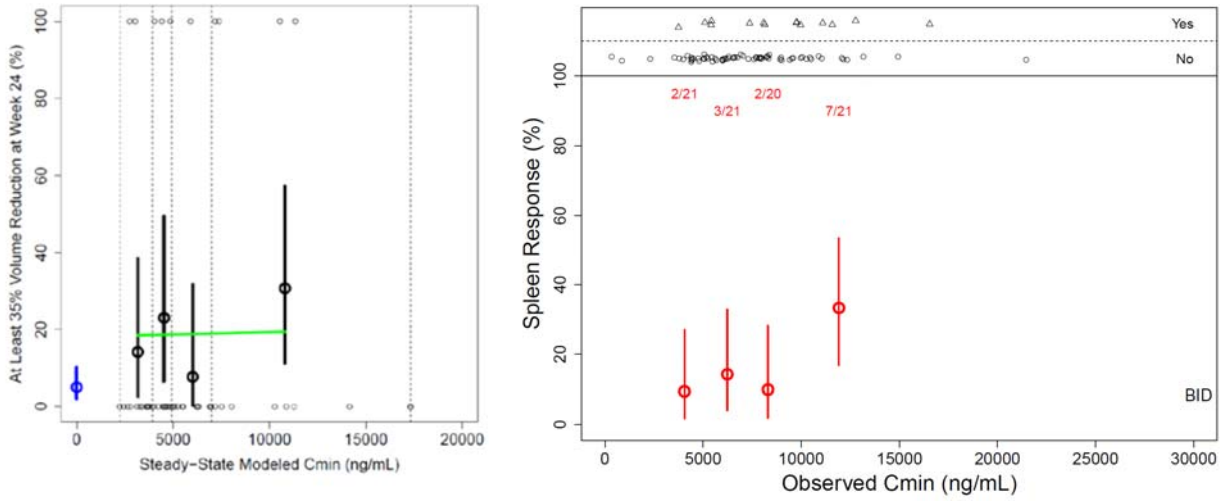
The lowest dosage level selected for the study (100 mg QD) is 4-fold lower than the highest dosage level in the study (200 mg BID) in terms of total daily dose, allowing for adequate separation between dosage levels selected in the study, which should in turn support characterization of the dose–response relationship in the study. The 100 mg QD regimen produced minimal clinical disease responses in 6 patients in phase 1/2 studies and was not associated with any safety concerns, pointing to limited efficacy at the 100 mg QD dosage level. Moreover, integrated exposure-response data from across the clinical program indicate that the exposure-response relationship for pacritinib is relatively steep whereby marked efficacy is only observed at exposure levels higher than those associated with the 100 mg QD

regimen (Figure 1). Median geometric mean C_{min} of pacritinib at steady-state following administration of 200 mg BID regimen in PERSIST-2 was 6,783 ng/mL. Given the observed linearity following single-dose administration of pacritinib capsules up to 400 mg, median steady-state C_{min} levels of pacritinib with administration of 100 mg QD would be projected at around 1,700 ng/mL, where there no evidence for efficacy as measured by SVR as evident from the exposure-response relationship for pacritinib (Figure 1). Overall, the 100 mg QD regimen is likely to show minimal efficacy and is a reasonable choice for the lowest dosage in the study. Dosage levels lower than 100 mg QD are unlikely to offer any advantage in terms of better characterization of the dose–response relationship of pacritinib in the study.

Given the observed incidence of SAEs, the 200 mg BID regimen will be the highest dosage studied in the current study. The 200 mg BID regimen has already demonstrated robust efficacy and a potentially acceptable safety profile in the PERSIST-2 study. An intermediate dosage of 100 mg BID will be tested that is likely to have efficacy based on the phase 1 studies and clinical experience in patients who underwent dose reduction in the phase 3 studies.

Based on the efficacy observed in clinical studies in MF to date, the selected dosage levels of pacritinib are projected to provide reasonable likelihood of efficacy responses while allowing for full characterization of the dose–response and dose-safety relationships for pacritinib.

Figure 1. Exposure-response Relationships on Spleen Volume Response for Pacritinib in Phase 1/2 Studies and PERSIST-2 Study



Phase 1/2 **PERSIST-2**

Source: Section 5.3.5.4, PAC-011-03 Exposure-Response Report, Section 5.3.5.4 PAC-011-03 dataset, and Section 5.3.5.4 PAC-011-04 Dose Justification Memo.

3.2 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 progression events through Week 24. Although the date of the first event is considered the date of progression of disease, subsequent events must also 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 MRI (preferred) or CT scan
- Splenic irradiation
- Splenectomy
- Leukemic transformation, defined as one or more of the following:
  - Increase in peripheral blood blast percentage to ≥20%
  - Bone marrow blast count ≥20% (bone marrow performed as standard of care)

3.3 Treatment Continuation After Progression of Disease

Patients who have progression of disease on MRI (preferred) or CT scan, defined as an increase in splenic volume of ≥25% from baseline on MRI or CT scan, will not be allowed to continue study treatment. Patients should continue the visit schedule through Week 24 (including imaging and all protocol-specified study assessments) despite treatment discontinuation or disease progression prior to Week 24, unless patient withdraws consent, dies, undergoes splenic irradiation or splenectomy, or initiates any non-protocol-directed anti-myelofibrosis treatment.

4 Patient Selection and Withdrawal

4.1 Target Population

4.1.1 Inclusion Criteria

1. PMF, PPV-MF, or PET-MF (as defined by Tefferi and Vardiman 2008; Appendix 4)
2. DIPSS Intermediate-1, Intermediate -2, or High risk (Passamonti et al 2010; Appendix 3)
3. Prior ruxolitinib treatment with failure to benefit or intolerance as defined by at least one of the following:
    a. Treatment for ≥3 months with inadequate efficacy response defined as <10% spleen volume reduction by MRI or <30% decrease from baseline in spleen length by physical examination or regrowth to these parameters following an initial response; and/or
    b. Treatment for ≥28 days complicated by either:
        i. Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months)
        ii. NCI CTCAE grade ≥3 AEs of thrombocytopenia, anemia, hematoma, and/or hemorrhage while being treated with a dosage of <20 mg BID
4. Palpable splenomegaly ≥5 cm below the lower costal margin (LCM) in the midclavicular line as assessed by physical examination
5. TSS of ≥10 on the MPN-SAF TSS 2.0 or patients with a single symptom score of ≥5 or two symptoms ≥3 including only the symptoms of left upper quadrant pain, bone pain, itching or night sweats (Appendix 3)
6. Age ≥18 years old
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 (Appendix 6)
8. Peripheral blast count of <10% throughout the screening period
9. Absolute neutrophil count of >500/μL
10. Adequate liver and renal function, defined by liver transaminases (aspartate aminotransferase [AST]/serum glutamic oxaloacetic transaminase [SGOT] and alanine aminotransferase [ALT]/serum glutamic pyruvic transaminase [SGPT]), ≤3 × the upper limit of normal (ULN) (AST/ALT ≤5 × ULN if transaminase elevation is related to MF), direct bilirubin ≤4× ULN, and creatinine ≤2.5 mg/dL
11. Adequate coagulation function, defined by prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), or thrombin time (TT) of ≤1.5 × ULN
12. Left ventricular cardiac ejection fraction (LVEF) of ≥45% by echocardiogram or multigated acquisition (MUGA) scan
13. If fertile, willing to use effective birth control methods during the study
14. Willing to undergo and able to tolerate frequent MRI or CT assessments during the study
15. Able to understand and willing to complete symptom assessments using a patient-reported outcomes instrument
16. Provision of informed consent

4.1.2 Exclusion Criteria

1. Life expectancy <6 months
2. Completed allo-SCT or are eligible for and willing to complete allo-SCT
3. History of splenectomy or planning to undergo splenectomy
4. Splenic irradiation within the last 6 months
5. Previously treated with pacritinib
6. Patients receiving high-dose ruxolitinib (more than 10 mg BID or 20 mg QD) who cannot tolerate tapering down ruxolitinib to 10 mg BID or less prior to the first dose of pacritinib as described in Section 6.6
7. Treatment with anticoagulation or antiplatelet agents, except for aspirin dosages of ≤100 mg per day, within the last 2 weeks
8. Treatment with a strong CYP3A4 inhibitor or a strong cytochrome P450 inducer within the last 2 weeks (Appendix 5 and Appendix 6, respectively)
9. Treatment with medications that can prolong the QTc interval within the last 2 weeks (Appendix 8)
10. Treatment with an experimental therapy within the last 28 days
11. Significant recent bleeding history defined as NCI CTCAE grade ≥2 within the last 3 months, unless precipitated by an inciting event (e.g., surgery, trauma, injury)
12. Any history of CTCAE grade ≥2 non-dysrhythmia cardiac conditions within the last 6 months. Patients with asymptomatic grade 2 non-dysrhythmia cardiac conditions may be considered for inclusion, with the approval of the medical monitor, if stable and unlikely to affect patient safety.
13. New York Heart Association Class II, III, or IV congestive heart failure (Appendix 7)
14. Any history of CTCAE grade ≥2 cardiac dysrhythmias within the last 6 months. Patients with non-QTc CTCAE grade 2 cardiac dysrhythmias may be considered for inclusion, with the approval of the medical monitor, if the dysrhythmias are stable, asymptomatic, and unlikely to affect patient safety.
15. QTc prolongation >450 ms or other factors that increase the risk for QT interval prolongation (e.g., heart failure, hypokalemia [defined as serum potassium <3.0 mEq/L that is persistent and refractory to correction], family history of long QT interval syndrome, or concomitant use of medications that may prolong QT interval) (Appendix 8)
16. Any active gastrointestinal or metabolic condition that could interfere with absorption of oral medication
17. Active or uncontrolled inflammatory or chronic functional bowel disorder such as Crohn's Disease, inflammatory bowel disease, chronic diarrhea, or constipation
18. 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

19. Uncontrolled intercurrent illness, including, but not limited to, ongoing active infection or psychiatric illness or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
20. Known seropositivity for human immunodeficiency virus
21. Known active hepatitis A, B, or C virus infection
22. Women who are pregnant or lactating
23. Concurrent enrollment in another interventional trial

4.2 Criteria for Withdrawal of Patients

4.2.1 Withdrawal from Study Treatment and Procedures

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 visits through Week 24 required by the protocol, including MRI (preferred) or CT scanning and follow-up for progressive disease, and leukemic transformation. Reasons for discontinuing treatment may include but are not limited to the following:

- Documented disease progression as defined in Section 3.2.
- 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. medical monitor that it is in the patient's best interest to withdraw from study treatment
- Sponsor decision to terminate study
- Death

5 Method of Treatment Assignment and Blinding

Initially, eligible patients will be centrally randomized in a 1:1:1 allocation ratio to pacritinib 100 mg QD, pacritinib 100 mg BID, or pacritinib 200 mg BID using a central interactive web response system. If interim monitoring analysis indicates that any one of the treatment arm meets the stopping criteria (Section 11.9) for efficacy or safety and is thus dropped, then the randomization will be updated to a 1:1 ratio of the two remaining study arms. In the case of two arms being dropped by interim efficacy or safety monitoring, then all eligible patients will be enrolled to the remaining one active arm until up to 30 evaluable subjects are enrolled for that arm.

Randomization will be stratified by geographic region (North America, Europe, versus rest of the world [ROW]) and baseline platelet count (≤50,000/μL; >50,000/μL and ≤100,000/μL; and >100,000/μL). The most recent platelet count obtained prior to start of treatment will be the basis of stratification by baseline platelet count.

A patient's treatment assignment will be known to all except the independent radiographic and cardiology assessors who will remain blinded to patient treatment assignment throughout the study.

6 Study Treatment

6.1 Study Drug Administration

Patients will be supplied with 100 mg capsules of the drug. If assigned to the once per day dosing arm, patients will take 100 mg (1 capsule) of pacritinib QD, at the same time of day, orally, with or without food. Patients assigned to twice per day dosing will take 100 mg (1 capsule) of pacritinib BID at the same times of day, orally, with or without food or 200 mg (2 capsules) of pacritinib BID orally, at the same times of day, with or without food (Table 2).

Table 2. Study Treatment Schedule

Treatment	Dosage/Regimen
Pacritinib 100 mg QD	Pacritinib 100 mg (1 capsule) QD orally, at the same time of day, with or without food
Pacritinib 100 mg BID	Pacritinib 100 mg (1 capsule) BID orally, at the same time of day, with or without food
Pacritinib 200 mg BID	Pacritinib 200 mg (2 capsules) BID orally, at the same time of day, with or without food

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 20°C to 25°C or 68°F to 77°F, with excursions allowed from 15°C to 30°C or 59°F to 86°F. All pacritinib supplies must be kept in a restricted-access area.

6.3 Dosage, Route, and Mode of Administration

Patients in each arm will be supplied with 100-mg capsules of pacritinib. If assigned to the twice per day dosing arms, patients will either take 100 mg (1 capsule) or 200 mg (2 capsules) of pacritinib twice per day, orally, at the same time of day, with or without food. On days when PK and PD samples and ECGs are to be obtained, pacritinib will be administered in the clinic.

6.4 Drug Accountability

At every study visit, patients will return bottles in which pacritinib is supplied with all remaining untaken pacritinib capsules, if any. Patient compliance will be evaluated by pill count.

6.5 Pacritinib Treatment Adjustments for Adverse Events

6.5.1 Treatment Interruption and Discontinuation

Safety parameters including AEs, hematology, cardiac monitoring, and serum chemistry will be assessed according to the protocol. Pacritinib treatment may be withheld for up to 7 days 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.

Pacritinib should be withheld 7 days prior to planned invasive procedures and concurrently with any unplanned invasive procedure. Pacritinib may be restarted after 2 days without active signs or symptoms of active bleeding.

After treatment interruption, patients may resume pacritinib treatment per dose management guidelines below.

6.5.2 Dosage Management Guidelines for Hematologic Toxicity and Related Complications

Myelosuppression is common in patients with MF and this study allows enrollment of patients with severe cytopenias. Patients with complications of myelosuppression may receive standard supportive care, including transient use of granulocyte-colony stimulating factor for the treatment of febrile neutropenia and red blood cell and platelet transfusion as clinically indicated. Patients receiving pacritinib are not allowed to receive erythropoietin for the treatment of anemia or platelet stimulating factors for the treatment of thrombocytopenia.

Hematology parameters, including CBC, differential, and platelet count will be evaluated at regular intervals during the study. These parameters should be monitored more frequently if clinically required. Patients with a baseline platelet count of ≤ 50,000/μL must be monitored weekly by central laboratory assessment for the first 8 weeks, then monthly if counts remain ≤ 50,000/μL. Unscheduled local laboratory test results may be used for assessment and management of patients in real time. Samples collected for local testing must also be submitted to the central laboratory and the results captured in the clinical database.

Table 3 indicates required dose interruptions and modifications for hematologic toxicities and complications such as hemorrhage and febrile neutropenia. Of note, if more than one toxicity is experienced simultaneously, the higher-grade toxicity should determine the dose interruption/modification.

Table 3. Treatment Toxicity and Dosage Management: Hematologic Toxicities and Related Complications

Event	CTCAE Grade	Management/Action
Thrombocytopenia	▪ ≥ 2 grade decrease in platelets to grade 3 or 4	▪ Hold pacritinib for up to 7 days until recovery of platelet count to ≤ grade 2. Restart at the next lower dose level. If at 100 mg QD dose level, discontinue.
	▪ For patients starting treatment with grade 3 thrombocytopenia who progress to grade 4 thrombocytopenia that lasts at least 14 days or is complicated by hemorrhage or a new platelet transfusion requirement	▪ Pacritinib may be held for up to 7 days at the treating physician's discretion until recovery of platelets to baseline. Restart either at the same dose or at the next lower dose level.

Table 3. Treatment Toxicity and Dosage Management: Hematologic Toxicities and Related Complications

Event	CTCAE Grade	Management/Action
		▪ If grade 4 thrombocytopenia recurs after restarting drug, pacritinib must be discontinued.
Hemorrhage	▪ Treatment-emergent grade 2 hemorrhage	▪ Hold pacritinib for up to 7 days until hemorrhage resolves. Restart pacritinib at the same dose. ▪ If event recurs, hold until resolution then restart at the next lower dose. If at 100 mg QD dose level, discontinue.
	▪ grade 3	▪ Hold pacritinib for up to 7 days and start at the next lowest dose level once resolved. If at 100 mg QD dose level, discontinue.
	▪ grade 4	▪ Discontinue pacritinib
Febrile neutropenia	▪ grade 4	▪ Hold pacritinib for up to 7 days and start at the next lowest dose level once resolved. If at 100 mg QD dose level, discontinue.
Neutropenic infections, including neutropenic sepsis	▪ grade 4	▪ Hold pacritinib for up to 7 days and start at the next lowest dose level once resolved. If at 100 mg QD dose level, discontinue.

Coagulation Testing

Coagulation testing will include PT, INR, PTT, and TT at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, and 30 days after the last dose of study treatment. Additional coagulation testing should be done as clinically indicated.

These results will be taken into account, together with baseline platelet counts and prior medical history of bleeding, to help guide ongoing hematologic monitoring of platelet counts and clinical monitoring for bleeding. Pacritinib dosage modifications will be implemented for clinically significant AEs identified with this testing per the guidelines in Table 7.

6.5.3 Pacritinib Dosage Management Guidelines for QTc Interval Prolongation, Reduction in Ejection Fraction, and Other Cardiac Toxicities

A 12-lead ECG (collected in triplicate) will be checked at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, including QTc calculation, and 30 days after the last dose of study treatment.

Ejection fraction will be checked (echocardiogram or MUGA scan) at screening, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, every 6 months during the follow up period, and 30 days after the last dose of study treatment. These assessments will be performed until approval of Amendment 6, at which point assessment ceases following the patient's End-of-Treatment, or 30-day post (EOT) visit as applicable. Pacritinib dosage modifications will be implemented for clinically significant ejection fraction changes as per Table 4 and Table 5. For patients with a grade 2 decreased

cardiac ejection fraction at baseline (LVEF 45%-50%), Table 5 should be used for any further decreases in LVEF. If pacritinib treatment is resumed after holding for ejection fraction abnormality, ejection fraction should be reassessed approximately 14 days later, then at least every 3 months as per the above schedule. Additional ejection fraction testing shall be done as clinically indicated.

Treatment should be modified as shown in the following table (Table 4), as recommended by FDA in case of QTc interval prolongation.

Table 4. Pacritinib-Related QTc Prolongation, Decreased Cardiac Ejection Fraction and Other Cardiac Toxicities

CTCAE v4 Toxicity Grade	Management/Action
1	No change.
2 (First occurrence) For patients with grade 2 LVEF decreased at baseline (LVEF 45%-50%) and further decreases in LVEF on study, see Table 5)	▪ Hold pacritinib. ▪ If the toxicity resolves to grade ≤1 within 7 days, treatment may be resumed at the next lower dosage level (or discontinued, if toxicity occurred while taking 100 mg QD). ▪ Toxicity that does not resolve to grade ≤1 within 7 days requires treatment discontinuation.
2 (second occurrence)	Discontinue treatment.
3	Discontinue treatment.
4	Discontinue treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LVEF = left ventricular ejection fraction; QD = once daily; QTc = corrected QT interval.

Table 5. Pacritinib-Related Decreased Cardiac Ejection Fraction for Patients with Grade 2 Ejection Fraction (LVEF 45%-50%) at Baseline

CTCAE v4.0 Toxicity Grade	Management/Action
3	Hold pacritinib for 1 week and reassess LVEF. If LVEF returns to baseline, patient may resume treatment at the next lower dose level; if grade 3 does not resolve, pacritinib should be discontinued.
4	Discontinue treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LVEF = left ventricular ejection fraction

In patients who resume pacritinib treatment after holding treatment for grade 2 QTc interval prolongation, follow-up ECGs (in triplicate) are recommended on Days 1, 7, 14, 28, and 56 after pacritinib restart. After restart of pacritinib, QTc monitoring should follow this schedule with ECGs obtained in triplicate:

- Restart Day 1 at 4 hours (± 1 hour) after ingestion of the first reduced dosage
- 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 2 toxicity does not resolve to grade ≤1 within 7 days, discontinue all treatment with pacritinib. If grade 2 toxicity recurs despite dosage reduction discontinue all treatment with pacritinib.
For grade 3 and 4 QTc prolongation, discontinue all treatment with pacritinib.

Other Cardiac Toxicities

Discontinue treatment with pacritinib for all other grade 3 and 4 cardiac toxicities.

6.5.4 Pacritinib Dosage Management Guidelines for Diarrhea

Treatment with antidiarrheals is advised for all patients who experience new onset diarrhea (Table 6).

Table 6. Treatment Toxicity and Dosage Management: Diarrhea

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 dosage. Concomitant antidiarrheal treatment is required for patients restarting pacritinib at the 100 mg QD dosage level. ▪ If the toxicity recurs after restart at the same dosage level, treatment may only be resumed at the next lower dosage level. ▪ If the toxicity resolves to grade ≤1 or to the baseline grade after more than 7 days, treatment may be resumed only at the next lower dosage level. Discontinuation is required if on hold from the 100 mg QD dosage level. Concomitant antidiarrheal treatment is required for patients restarting pacritinib at the 100 mg QD dosage level. ▪ If the toxicity recurs after restart at the lower dosage level, pacritinib treatment must be discontinued.
4	▪ Hold treatment. ▪ If grade 4 toxicity occurs at the lowest dosage of 100 mg QD, the patient will be discontinued from the study. ▪ If the toxicity resolves to grade ≤1 or to the baseline grade within 7 days, treatment may be resumed, but dosage will be reduced by 1 dosage level from the level at which the toxicity was observed. Concomitant antidiarrheal treatment is required for patients restarting pacritinib at the 100 mg QD dosage level.

6.5.5 Pacritinib Dosage Management Guidelines for Pacritinib-Related Nonhematologic Toxicities Other than QTc Prolongation, Decreased Cardiac Ejection Fraction, Other Cardiac Toxicities or Diarrhea

As defined in Table 7, a maximum of 2 dosage reductions are allowed for pacritinib-related nonhematologic toxicities other than QTc prolongation, decreased cardiac ejection fraction, or diarrhea.

Table 7. Treatment Toxicity and Dosage Management: Pacritinib-Related Nonhematologic Toxicities Other than QTc Prolongation, Decreased Cardiac Ejection Fraction, Other Cardiac Toxicities or Diarrhea

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 dosage, 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 dosage reduction to the next lower dosage.
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 or to the baseline grade within 7 days, treatment may be resumed, but dosage will be reduced by one dosage from the level at which the toxicity was observed. ▪ If grade 4 toxicity occurs at the lowest dosage of 100 mg QD, the patient should be discontinued from the study.

6.6 Concomitant and Excluded Therapies

Ruxolitinib should not be administered concurrently with pacritinib at any time. Although there is no washout period required for ruxolitinib prior to the start of dosing with pacritinib, it should be understood that because of the difference in half-life between ruxolitinib (3 hours Jakafi package insert) and pacritinib (approximately 40 hours), there will be a period of 10 to 14 days following the discontinuation of ruxolitinib and the start of dosing with pacritinib, during which pacritinib has not yet reached steady state and during which patients may be at increased risk of ruxolitinib withdrawal, particularly after high doses of ruxolitinib (eg, more than 10 mg BID or 20 mg QD). For this reason, patients who are on more than 10 mg BID (or 20 mg QD) of ruxolitinib at the time of consent for this study must taper the ruxolitinib dose down to 10 mg BID or lower and remain stable on the reduced dose for at least 2 weeks prior to starting pacritinib. Tapering should be done per institutional practice and may be done with concurrent addition of prednisone during the screening period. In addition to any steroids used during the screening period, the protocol permits short-term use (up to 14 days) of corticosteroids and/or hydroxyurea as prophylaxis or treatment of symptomatic ruxolitinib withdrawal during the first month of treatment with pacritinib.

Supportive care therapies, except when prohibited by any of the below provisions, are permitted, including the use of low-dose aspirin. Corticosteroids (up to 20 mg/day of prednisone or equivalent) and/or hydroxyurea may be used for up to 2 weeks during the first month of treatment with pacritinib to control symptoms of ruxolitinib withdrawal if they occur. Treatments for MF that might be considered supportive care are only allowable with medical monitor approval prior to administration.

The following therapies and procedures are prohibited throughout the study:

- Chemotherapy, interferon, or other treatment for MF, with the exception of up to 2 weeks of corticosteroids (up to 20 mg/day prednisone or equivalent) and/or 2 weeks of hydroxyurea as needed to reduce the risk of or treat the symptoms of ruxolitinib withdrawal
- Antiplatelet or anticoagulation agents, with the exception of ≤ 100 mg/day of aspirin
- Growth factor therapies, including erythropoietin and thrombopoietin
- Strong CYP3A4 inhibitors (Appendix 5) and strong CYP450 inducers (Appendix 6), except as needed to treat AEs, with medical monitor approval
- Any drugs with significant potential for QTc prolongation (Appendix 8), except as needed to treat AEs, with medical monitor approval
- Splenic irradiation or splenectomy

Also refer to the Pacritinib Dosage Management Guidelines (Section 6.5) for guidelines on treatment of AEs.

6.6.1 Management of Gastrointestinal Toxicity

The need for managing gastrointestinal (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.

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 9). At the investigator's discretion, prophylactic use of antidiarrheals 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.

7 Study Assessments

7.1 Criteria for Evaluation

7.1.1 Efficacy

Efficacy assessments will be performed as described below until approval of Amendment 6, at which point assessments cease following the patient's End-of-Treatment, or 30-day post (EOT) visit as applicable.

7.1.1.1 Spleen Volume

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.

Spleen volume will be measured by MRI (preferred) or CT at screening and at the end of weeks 12 and 24 visits. Spleen volume will also be measured at the end of treatment if this does not occur at the end of

Week 24. For patients who continue on pacritinib past Week 24, spleen volume will be assessed by MRI or CT every 3 months up to 2 years. Patients who discontinue treatment (except withdraw of consent or death) will be required to complete the end of treatment visit within 7 days of stopping treatment. Unscheduled imaging studies may 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. An independent radiologist, blinded to all patient and site identifiers and treatment assignments, will measure spleen volume. While images generated as part of unscheduled visits may be read locally if treatment discontinuation is being considered, only the scheduled centrally read images will be used for the efficacy analysis.

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

Patient-reported disease-related symptoms as assessed by the validated PRO instrument MPN-SAF TSS 2.0 (Appendix 5) will be collected daily using an electronic diary and will be evaluated as a part of the dose–response relationship. Patients must begin reporting symptoms via electronic diary at least 7 days before starting pacritinib treatment and will continue until the Week 48 visit. After Week 48, the patient will fill out the questionnaire (Appendix 3) at each follow up visit. The questionnaire is the same PRO instrument and uses a 7 day recall period. The MPN-SAF TSS 2.0 will be translated and available on the eDiary device in several different languages to accommodate an international study.

In addition, the patient global impression assessment questionnaire (Appendix 11) will be completed at the end of Week 12, the end of Week 24 or the end of treatment visit, and every 3 months up to 2.5 years.

7.1.1.4 Other Assessments

Patients will be followed for leukemic transformation and frequency of RBC and platelet transfusions. DNA samples will also be collected for analysis of mutations associated with myelofibrosis at baseline and Week 24.

7.1.2 Safety

Safety assessments will be performed as described below until approval of Amendment 6, at which point assessments cease following the patient's End-of-Treatment, or 30-day post (EOT) visit as applicable.

7.1.2.1 Adverse Events

All AEs, including serious adverse events (SAEs), will be collected during the clinical study from the time the patient signs the informed consent through 30 days following last dose of study treatment. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are to be 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

Hematology parameters including CBC, differential, platelet count, and hemoglobin A1C will be evaluated at screening, baseline, the end of week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, every 3 months during the follow up period, and 30 days after the last dose of study treatment. In addition, for patients with baseline platelet count of ≤ 50,000/μL, the platelet count will be monitored weekly by the central laboratory for the first 8 weeks, then monthly if counts remain ≤ 50,000/μL. Samples collected at any visits for platelet counts must be submitted to the central laboratory for analysis, but in addition can be analyzed locally for assessment and management of patients in real time. Additional platelet count testing should be done as clinically indicated.

7.1.2.3 Coagulation Testing

Coagulation testing will include PT, INR, PTT, and TT at screening, baseline, the end of week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, every 3 months during the follow up period, and 30 days after the last dose of study treatment. Additional coagulation testing should be done as clinically indicated.

These results will be taken into account, together with baseline platelet counts and prior medical history of bleeding, to help guide ongoing hematologic monitoring of platelet counts and clinical monitoring for bleeding.

7.1.2.4 Serum Chemistry

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Serum chemistry parameters (ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin [total, direct, and indirect], creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, blood urea nitrogen (BUN)/urea, albumin, amylase, lipase, glucose, cholesterol, uric acid, and high specificity CRP) will be evaluated by a central laboratory at screening, at baseline, and as clinically indicated. Unscheduled chemistry assessments may be performed locally and/or centrally whenever clinically indicated. Blood samples drawn at unscheduled visits for serum chemistry evaluation should be submitted to the central laboratory for assessment in addition to any local laboratories as needed for timely decisions regarding patient care.

7.1.2.5 ECG Assessment

All patients will have a 12-lead ECG (collected in triplicate)), including QTc calculation corrected by the Fredericia method, at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, and every 3 months while in the follow-up period (pre-dose only for the post-24-week follow-up visit and 30 days after the last dose of study treatment. Additional ECGs may be required in the event patient demonstrates QTc prolongation. See Section 6.5.3 for appropriate pacritinib dose adjustment guidelines and additional ECG requirements. All ECGs will be centrally read by a blinded independent cardiologist.

7.1.2.6 Cardiac Ejection Fraction Assessment

All patients will have ejection fraction checked (echocardiogram or MUGA scan) at screening, the end of Week 4, the end of Week 12, the end of Week 24, or the end of treatment visit, and every 6 months while in the follow up period, and 30 days after the last dose of study treatment. If pacritinib treatment is resumed after holding for ejection fraction abnormality, ejection fraction should be reassessed about

14 days later, then at least every 3 months as per the above schedule. Additional ejection fraction testing shall be done as clinically indicated (see dosage modifications in Section 6.5).

7.1.3 Pharmacokinetics and Pharmacodynamics

The Sponsor will collect PK samples from all patients in each dosing arm at the following timepoints:

- Sparse Sampling (all patients): End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 4 hours (±10 minutes), and 8 hours (±15 minutes) postdose
- Dense Sampling (performed at selected sites for approximately 6 to 8 patients total per dose arm, at which point all further patients will have PK evaluated by sparse sample collection): Week 1 Day 1: 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose), End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose

On the day prior to PK and PD blood sampling, the patient must note the time of dosing and report it to the site during their visit the following day. On the day of PK and PD blood sampling, patients must not take the daily dose of pacritinib prior to the clinic visit. Given the sampling schedule, PK and PD samples should be collected before and after the morning dose for patients taking pacritinib twice per day (BID).

Results will be used to evaluate the relationship between drug exposure and safety and efficacy as well as biomarkers associated with the JAK/STAT pathway.

7.1.4 Informed Consent, Screening, and Washout of Prohibited Concomitant Medications 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.

Informed consent must be obtained before any protocol-defined assessments including drug washout. The informed consent process should be documented in the patient's medical chart. A 2-week washout will be required for anticoagulation agents, antiplatelet agents except aspirin dosages of ≤100 mg/day, strong CYP450 inducers, and QTc prolonging agents. A 28-day washout period will be required for any experimental therapies.

The screening evaluations listed below are to be carried out **between 35 and 7 days prior to the start of treatment, with the exception of MRI or CT scan, which must be performed between 10 and 4 days prior to the start of the study.**

- Medical history
- Vital signs, including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (collected in triplicate)
- Ejection fraction assessment (Echocardiogram or MUGA)
- ECOG performance status
- Hematology: CBC with differential, platelet count and hemoglobin A1C

- Coagulation testing including PT, INR, PTT, and TT
- 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, uric acid, and high specificity CRP
- Serum pregnancy test for women of childbearing potential (WOCBP). For WOCBP in the UK, the screening pregnancy test must occur no longer than 7 days before the first study drug administration. 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.
- MRI (preferred) or CT scan (without contrast) for measurement of spleen volume (to be performed between Days -10 and -4 prior to the start of treatment).
- Begin collecting patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary. Patient must complete daily for 7 consecutive days prior to starting treatment.
- Baseline symptoms and AEs
- Concomitant medications
- Transfusion history (RBC and platelets)

7.1.5 Randomization and Start of Week 1 (Baseline; -1 day)

Randomization: Patient must first sign informed consent, then complete all screening procedures, and meet all eligibility criteria.

- Vital signs, including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight
- Physical examination, including height, clinical signs and symptoms, and spleen measurement
- 12-lead ECG (collected in triplicate)
- Hematology: CBC with differential, platelet count and hemoglobin A1C; patients with baseline platelet count of ≤ 50,000/μL, platelet count will be monitored weekly by the central laboratory for the first 8 weeks, then monthly if counts remain ≤ 50,000/μL. Blood samples drawn at unscheduled visits for the assessment of hematology parameters should be submitted to the central laboratory for assessment in addition to any local laboratories as needed for timely decisions regarding patient care. Additional hematology testing should be done as clinically indicated.
- Coagulation testing including PT, INR, PTT, and TT
- 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, uric acid, and high sensitivity CRP. Blood samples drawn at unscheduled visits for the assessment of serum chemistry parameters should be submitted to the central laboratory for assessment in addition to any local laboratories as needed for timely decisions regarding patient care.

- Continue collecting patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary daily
- For patients participating in dense PK sampling: PK sample at 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose)
- PD sample within 30 minutes prior to 0 hours (predose)
- DNA sample
- Dispense pacritinib
- Begin pacritinib dosing
- Baseline symptoms and AEs
- Concomitant medications
- Transfusion history (RBC and platelets)
- Provide prescription for loperamide (Imodium®) or a similarly effective antidiarrheal drug

7.1.6 End of Week 4, Study Day 28 (± 3 days)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (collected in triplicate)
- Ejection fraction assessment (Echocardiogram or MUGA)
- ECOG performance status
- Hematology: CBC with differential, platelet count and hemoglobin A1C
- Coagulation testing including PT, INR, PTT, and TT
- Serum chemistry as clinically indicated
- Serum pregnancy test for women of childbearing potential within the United Kingdom
- Continue collecting patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary daily
- Dispense pacritinib
- Perform pacritinib accountability
- AEs
- Concomitant medications
- Transfusion history (RBC and platelets)

7.1.7 End of Week 12, Study Day 84 (± 7 days)

- Vital signs, including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (collected in triplicate)
- Ejection fraction assessment (Echocardiogram or MUGA)
- ECOG performance status
- Hematology: CBC with differential, platelet count and hemoglobin A1C
- Coagulation testing including PT, INR, PTT, and TT

- Serum chemistry as clinically indicated
- Serum pregnancy test, if mandated by country-specific requirement
- MRI (preferred) or CT scan (without contrast) for measurement of spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue collecting patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary daily
- Patient global impression assessment
- For all patients: PK samples at 30 minutes to 0 hours (predose), 4 hours (± 10 minutes), and 8 hours (±15 minutes) postdose
- For patients participating in dense PK sampling: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose
- PD sample within 30 minutes prior to 0 hours (predose)
- Dispense pacritinib
- Pacritinib accountability
- AEs
- Concomitant medications
- Transfusion history (RBC and platelets)

7.1.8 End of Week 24, Study Day 168 (± 7 days), or End of Treatment

- Vital signs, including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight
- Physical examination, including spleen measurement
- 12-lead ECG (collected in triplicate)
- Ejection fraction assessment (Echocardiogram or MUGA)
- ECOG performance status
- Hematology: CBC with differential, platelet count, and hemoglobin A1C
- Coagulation testing including PT, INR, PTT, and TT
- Serum chemistry as clinically indicated
- Serum pregnancy test, if mandated as a country-specific requirement
- MRI (preferred) or CT scan (without contrast) for measurement of spleen volume (for each patient, the same imaging modality should be used throughout the study)
- Continue collecting patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary daily
- Patient global impression assessment
- For all patients: PK samples at 30 minutes to 0 hours (predose), 4 hours (±10 minutes), and 8 hours (±15 minutes) postdose
- For patients participating in dense PK sampling: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose
- PD sample within 30 minutes prior to 0 hours (predose) [collected at Week 24; not collected at End of Treatment]
- Dispense pacritinib (for patients continuing to receive treatment)
- Perform pacritinib accountability
- AEs

- Concomitant medications
- Transfusion history (RBC and platelets)
- DNA Sample [collected at Week 24; not collected at End of Treatment]

7.1.9 30-Day Post End of Treatment (30 ±3 days After End of Treatment)

For patients who transition to and continue treatment under an expanded access program, the 30-Day Post End of Treatment assessment will not be performed.

- 12-lead ECG (collected in triplicate)
- Ejection fraction assessment (Echocardiogram or MUGA)
- Hematology: CBC with differential, platelet count and hemoglobin A1C
- Coagulation testing including PT, INR, PTT, and TT
- Serum chemistry as clinically indicated
- Last time point for collection of patient-reported disease-related symptoms on MPN-SAF TSS 2.0 via electronic diary. Patient to return electronic diary device during visit.
- Last time point for collection and follow-up of nonserious AEs (related or not related) and SAEs deemed not related to study treatment or procedures.
- Concomitant medications

8 Pharmacokinetic and Pharmacodynamic Analysis

8.1 Blood Sample Collection, Handling, and Shipping

Blood samples for PK and PD analyses should be collected in appropriate blood collection tubes as defined in the study manuals. On the days when blood samples for PK and PD analyses are collected, patients should be instructed not to take pacritinib at home. The time/date when the prior dose was administered must be recorded in the source documents and on the appropriate eCRF page. The Sponsor will provide the investigator with sample collection kits as well as a manual containing details for the preparation of blood samples to be collected. Shipping supplies and instructions will also be provided.

8.2 Pharmacokinetic and Pharmacodynamic Assessments

The Sponsor will collect PK samples from all patients in each dosing arm at the following timepoints:

- Sparse Sampling (all patients): End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 4 hours (±10 minutes), and 8 hours (± 15 minutes) postdose
- Dense Sampling (performed at selected sites for approximately 6 to 8 patients total per dose arm, at which point all further patients will have PK evaluated by sparse sample collection): Week 1 Day 1: 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose and 24 hours postdose (within 30 minutes before the Day 2 dose), End of Week 12 and End of Week 24: 30 minutes to 0 hours (predose), 2 hours (± 5 minutes), 4 hours (± 10 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) postdose

Given the sampling schedule, PK and PD samples should be collected before and after the morning dose for patients taking pacritinib twice a day (BID). The PK parameters, minimum concentration observed, maximum concentration observed, and area under the curve will be determined and summarized using

descriptive statistics for each pacritinib dosage arm. Exposure-response analyses will be conducted on both safety and efficacy populations in the study. PD samples will be analyzed for biomarkers associated with the JAK/STAT pathway.

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:
  - A laboratory or other test result that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring
  - Requires discontinuation, dosage reduction, or delay of study drug
  - Requires that the patient receive specific corrective or supportive therapy
  - Clinically significant changes noted during physical examinations, cardiac monitoring, imaging studies, biopsies, and other safety assessments, whether or not these procedures were required by the protocol

Progressive disease is not an AE.

9.1.2 Reporting Adverse Events

Adverse events will be collected as described below until approval of Amendment 6, at which point assessments cease following the patient's End-of-Treatment, or 30-day post (EOT) visit as applicable.

All baseline conditions and AEs will be collected during the clinical study from the time the patient signs the informed consent through 30 days following last dose of study drug.

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 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.

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. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting investigator (e.g., "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 can be 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 on the death eCRF.

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 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 (i.e., 4.01, 4.02 and above) may be used at the discretion of the Sponsor. Central laboratory values will be used to grade and record AEs in EDC.

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) 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.

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.

9.1.3.3 Outcome

AEs will be characterized according to the outcomes described in Table 8.

Table 8. 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 patient 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:

- Dosage not changed
- Dosage reduced
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

9.1.4 Serious Adverse Events

9.1.4.1 Definition of a Serious Adverse Event

A SAE is an AE that, at any dosage, 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 (Items 1 to 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 dosage of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. All cases of drug overdose, irrespective of seriousness or association with AE(s), must be reported to the Sponsor within 24 hours. Determination of seriousness will be reached in consultation with the Safety Physician, CTI BioPharma Corp. Pharmacovigilance US Headquarters or designee. Additional instructions for reporting cancer/overdose information will be provided by the Sponsor in the study binder.

9.1.4.2 Exceptions

Hospitalizations not reported as SAEs include admissions for:

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

9.1.4.3 Reporting Serious Adverse Events to the Sponsor

AEs, including SAEs, irrespective of causal relationship, will be collected during the clinical study from the time the patient signs the informed consent through 30 days following the last dose of study drug. The site will notify the Sponsor of the SAE via the EDC system by recording the event on the SAE eCRF and checking the appropriate box on the eCRF indicating that the event meets SAE criteria. The EDC system will send an auto-generated email notification to CTI BioPharma Corp Pharmacovigilance that an SAE has been identified and will be reported. The site must send the paper SAE form via email (SAE@CTIbiopharma.com) within 24 hours of the site's first awareness of an SAE.

Special Considerations:

- SAEs considered to be related (i.e., assessed as possibly 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 unlikely related to study drug or study procedures shall be followed for 30 days after the 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 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 brief narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be provided as soon as the information becomes available and provided to CTI Pharmacovigilance via email at SAE@CTIbiopharma.com or fax (1-866-660-8967).

Source documents should be submitted 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 assess SAEs for expedited reporting against the most current approved version of the Investigator Brochure. Until an AE is identified in the Reference Safety Information of the IB or SmPC, 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 Institutional Review Board (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 patient 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 patient 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 Reporting Form. Additional instructions for reporting pregnancy information will be provided by the Sponsor in the study binder.

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 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 study 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 Sections 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.

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. In addition, any laboratory test samples collected at unscheduled visits will be submitted to the central laboratory, although laboratory tests performed for patient management in real time may be analyzed locally.

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 dosage modifications and for evaluation of signs and symptoms. Samples collected at unscheduled visits that are analyzed in a local laboratory must also be submitted to the central laboratory and the results entered into the EDC. Treatment decisions (such as dose delays) and adverse events may be based on either local or central laboratory results. For reporting purposes, central lab values are to be used to grade adverse events.

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 interpretations, radiology assessments, and other tests.

9.3 Vital Signs and Physical Examination

Vital signs (including blood pressure, pulse, respiratory rate, temperature, and body weight) and physical examinations (including spleen measurement) will be obtained at screening, baseline, the end of week 4, the end of Week 12, the end of Week 24 or the end of treatment visit. Height will be measured only at baseline.

9.4 Safety Surveillance

9.4.1 Routine Pharmacovigilance Monitoring

The Sponsor's pharmacovigilance committee will monitor safety data every month during the clinical study by examining the incidence and severity of AEs, changes in laboratory results, and other data (such as aggregate analysis of data from other pacritinib studies) as appropriate. The committee will communicate clinically important increases in the rate of serious adverse reactions to the IDMC (see Section 2.2), investigators, and regulatory agencies, as appropriate. A clinically important increase will be considered an increase in frequency and/or severity in an event which leads to a serious outcome and exceeds the rate(s) of the reported event listed in the Investigator Brochure reference safety information.

Single events assessed as serious, unexpected and related will continue to be reported on an expedited basis per regulatory requirement.

10 Data Management

The CTI BioPharma Corp. 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 patient 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 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.

CTI BioPharma Corp. 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 BioPharma Corp. staff or designee.

11 Statistical Analysis Plan

Statistical analysis of the study data will be the responsibility of CTI BioPharma Corp. Biostatistics Department or its designee. This section describes the statistical methodology used in the analysis of the primary safety and efficacy endpoints to aid the decision of dosage determination. Other supportive analyses will be specified in a separate statistical analysis plan (SAP). The SAP will be finalized before the first patient is randomized.

11.1 Variables for the Analysis

Efficacy

- The primary efficacy variable for dosage selection is the percent reduction in spleen volume from baseline as measured by MRI (preferred) or CT at Weeks 12 and 24.
- Other supportive measures for evaluation as part of the dose–response relationship include: the percentage of patients who achieve at least 35% reduction in spleen volume; % TSS reduction from baseline; and the percentage of patients with at least 50% reduction in TSS.
- Long term efficacy is evaluated using percent reduction in spleen volume from baseline as measured by MRI or CT, percent reduction in TSS from baseline, percent reduction in spleen length by physical exam and the patient global impression assessment.

Safety

- The primary safety measure for dosage selection is the percentage of patients with CTCAE grade ≥3 cardiac AEs (Standardized MedDRA Query [SMQ]), CTCAE grade ≥3 hemorrhage AEs (SMQ), CTCAE grade ≥4 thrombocytopenia toxicity (central laboratory based), or CTCAE grade ≥4 anemia toxicity (central laboratory based).
- All other safety data including AEs, death, and clinical laboratory measures will be used as supportive measures for evaluation of pacritinib dose-safety relationship and for long term safety evaluation.

11.2 Hypotheses

The primary objective of this study is to explore the dose–response relationship for pacritinib among primary and secondary MF patients to determine a recommended dosage for further clinical studies. There is no formal statistical hypothesis to be tested.

11.3 Analysis Populations

11.3.1 Full Analysis Set

The full analysis set (FAS) is defined as all randomized patients who received at least one dose of study treatment. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The FAS will serve as the population for the analyses of efficacy, in keeping with the intent-to-treat (ITT) principle.

11.3.2 Safety Population

The safety population is defined as all randomized patients who received at least one 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.

11.3.3 Pharmacokinetic/Pharmacodynamic Evaluable Population

The PK/PD evaluable population is defined as all randomized patients who received any dose of study treatment and have the necessary baseline and post-baseline measurements to provide interpretable results for the specific parameters of interest. 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

Summary statistics and 95% confidence intervals of the percent change in spleen volume by visit and the proportion of patients achieving a ≥35% reduction at Weeks 12 and 24 will be generated for each arm for the final locked data. The same analysis will be repeated for percent change in TSS and the proportion of patients achieving a ≥50% reduction in TSS at Weeks 12 and 24.

In addition, analyses of the dose–response and dose-exposure-response relationship will be performed using a modeling approach. The details of the analysis will be described in the SAP.

11.5 Multiplicity

No formal statistical hypothesis testing will be performed, thus no multiplicity adjustment is needed.

11.6 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 and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients with an event. AE data for hemorrhagic and cardiac events will be identified based on SMQs and analyzed as a SMQ group by treatment arm. Incidences of hemorrhagic and cardiac AE data by SMQs over 8-week interval will be summarized by treatment arm. 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.

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 summarized in shift tables comparing the worst post-baseline visit to baseline.

11.7 Determination of Sample Size

The determination of sample size for this dosage finding study was not only driven by a targeted predictive probability, but also to ensure adequate precision to evaluate efficacy using percent reduction of spleen volume from baseline. Based on past clinical experience (e.g., 10% SVR deemed as the minimum clinically meaningful reduction), variance in percent reduction in spleen volume (standard

deviation around 20%) from PERSIST-1 and PERSIST-2 studies, and the need for exploratory modeling analysis of pacritinib dose–response and dose–exposure-response relationship, a maximum of 30 evaluable patients per treatment arm are adequate to evaluate efficacy.

With 50 patients per arm, if the true incidence rate for a specified safety event is 5% among patients per each arm, then the chance of observing at least 1 event among 50 patients will be 92%. At the end of the study, for each treatment group, if none of the 50 patients experience an AE, then the true incidence rate of the AE is no greater than 3.2% with 80% confidence (no greater than 4.5% with 90% confidence).

Approximately 150 patients are planned for enrollment (up to 50 patients per arm).

11.8 Interim Analyses

No additional analysis will be performed in this study following the first interim analysis performed on 29 June 2018.

11.9 Safety Stopping Criteria

In the event of the occurrence of 2 treatment-emergent CTCAE grade ≥4 cardiac AEs or 2 treatment-emergent CTCAE grade ≥4 hemorrhage AEs in any of the individual treatment arms, study enrollment will be suspended until the IDMC has adjudicated the events. If the IDMC confirms the nature and grade of the events together with a relationship to study drug, the IDMC may recommend closure of one or more treatment arms. This recommendation is non-binding. The FDA and other competent authorities will be notified of any IDMC meeting that is convened under these circumstances, and the resultant decision will be reported to the FDA within 2 business days. The MHRA will be informed via a substantial amendment. After the first IDMC meeting, patients will continue to be enrolled into each of the remaining treatment arms to further evaluate safety and efficacy at doses carried forward. In the event one or more arms are suspended or terminated for a safety observation, randomization into the arm(s) will be halted immediately, however patients who are experiencing benefit, in the opinion of the investigator and Sponsor, and who were randomized to an arm that is suspended or terminated, may continue treatment.

12 Pharmacokinetic and Pharmacodynamic Analyses

The PK parameters, minimum concentration observed, maximum concentration observed, and area under the curve will be determined and summarized using descriptive statistics for each pacritinib dosage arm. Exposure-response analyses will be conducted on both safety and efficacy populations in the study. PD samples will be analyzed for biomarkers associated with the JAK/STAT pathway.

13 Independent Data Monitoring Committee

See Section 2.2 for a description of the composition and responsibilities of the IDMC.

14 Study Administration and Investigator Obligations

For studies conducted outside the US under a US Investigational New Drug (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 BioPharma 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 informed consent form (ICF) to each site for submission and approval by site's Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC). CTI BioPharma Corp. or its designee must review and approve any proposed deviations from the sample ICF. Patients must be re-consented to the most current IRB/REB/IEC approved version of the ICF during their participation in the study. The investigator must provide the final IRB/REC/IEC approved ICF 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, Sponsor representative, or regulatory agency 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/REB/IEC 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. or designee may monitor each site by phone to keep abreast of patient status and to answer questions.

In order for the investigator to participate in this study, the study monitor must have direct access to source data for 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 immediately forward copies of audit reports.

14.6 Record Retention

US FDA regulations (21CFR§312.62[c]) and the International Council on Harmonization (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, 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/Research Ethics Board/Independent Ethics Committee

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/REB/IEC approval letter stating that the study protocol and ICF 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 curriculum vitae for the principal investigator, and a copy of an IRB/REB/IEC approved ICF 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 10 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. In addition, substantial amendments made to this protocol will require approval by the appropriate regulatory authority prior to implementation.

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 study.

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Appendix 1 - 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** 4. 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, and unexplained fever (>37.5 degrees C)

	Major Criteria	Minor/Additional Criteria
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 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, and unexplained fever (>37.5 degrees C)

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

1 Source: Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 2008;22:14-22.

2 Source: Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia 2008;22:437-8.

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 2 - Dynamic International Prognostic Scoring System in Primary Myelofibrosis

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

Source: Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010;115:1703-8.

Appendix 3 - Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score Version 2.0 (MPN-SAF TSS 2.0) – 24-Hour Recall Period

This form should be used from study screening to Week 48

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)

For assessing eligibility, the TSS is the sum of the individual symptom scores for tiredness, early satiety, abdominal discomfort, night sweats, pruritis, bone pain, and pain under ribs on the left side. The inactivity symptom score should not be included in the TSS calculation for eligibility.

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score version 2.0 (MPN-SAF TSS 2.0) – 7 day recall period

This form is used at each visit from Week 48 visit to the end of the study

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 7 days:	
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 4 - Eastern Cooperative Oncology Group Performance Status Scale Grade Description

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 (e.g., 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.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Appendix 5 - Selected Strong 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, please discuss this with the medical monitor.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://www.pharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.

Appendix 6 – Selected Strong Inducers of CYP450

carbamazepine
efavirenz
nevirapine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

This list is not comprehensive. When considering using an agent that could be a potential CYP450 inducer, please discuss this with the medical monitor.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://www.pharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.

Appendix 7 - The Stages of Heart Failure, New York Heart Association 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 M, Fox AC, Devereaux RB. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little Brown and Company; 1994. p. 253-256.	

Appendix 8 - Medications with Significant Arrhythmogenic Potential

Use of the following drugs is prohibited, due to the potential for QT interval prolongation.[a]	
Alkylating agent	Bendamustine (Treanda, Treakisym, Ribomustin, Levact)
Alpha 1 blocker	Alfuzosin (Uroxatral)
Analgesic	Hydrocodone-ER (Hysingla™ ER, Zohydro ER); Tramadol (Crispin, Ralivia ER, Ralivia Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol)
Anesthetic	Propofol (Diprivan, Propoven); Sevoflurane (Ultane, Sojourn)
Antianginal	Bepridil (Removed from Market) (Vascor)
Antiarrhythmic	Amiodarone (Cordarone, Pacerone, Nexterone); Disopyramide (Norpace); Dofetilide (Tikosyn); Dronedarone (Multaq); Flecainide (Tambocor, Almarytm, Apocard, Ecrinal, Flécaine); Ibutilide (Corvert); Procainamide (Pronestyl, Procan); Quinidine (Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora); Sotalol (Betapace, Sotalex, Sotacor); Pilsicainide (Only on Non-US Market) (Sunrythm)
Antibiotic	Azithromycin (Zithromax, Zmax); Bedaquiline (Sirturo); Ciprofloxacin (Cipro, Cipro-XR, Neofloxin); Clarithromycin (Biaxin, Prevpac); Delamanid (Only on Non US Market) (Deltyba); Erythromycin (E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth); Gatifloxacin (Removed from Market) (Tequin); Gemifloxacin (Factive); Grepafloxacin (Removed from Market) (Raxar); Levofloxacin (Levaquin, Tavanic); Moxifloxacin (Avelox, Avalox, Avelon); Norfloxacin (Removed from Market) (Noroxin, Ambigram); Ofloxacin (Floxin); Roxithromycin (Only on Non US Market) (Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin); Sparfloxacin (Removed from Market) (Zagam); Telavancin (Vibativ); Telithromycin (Ketek);
Anticancer	Arsenic trioxide (Trisenox); Capecitabine (Xeloda); Lenvatinib (Lenvima); Tamoxifen (Nolvadex [discontinued 6/13], Istubal, Valodex); Vandetanib (Caprelsa); Cabozantinib (Cometriq); Epirubicin (Ellence, Pharmorubicin, Epirubicin Ebewe); Fluorouracil (5-FU) (Adrucil, Carac, Efudex, Efudix, others); Midostaurin (Rydapt); Necitumumab (Portrazza); Tipiracil and Trifluridine (Lonsurf)
Anticoagulant	Betrixaban (Bevyxxa)
Anticonvulsant	Ezogabine (Retigabine) (Potiga, Trobalt); Felbamate (Felbatol)
Antidepressant	SNRI: Venlafaxine (Effexor, Efexor) SSRI: Citalopram (Celexa, Cipramil); Escitalopram (Cipralex, Lexapro, Nexito, Anxiset-E [India], Exodus [Brazil], Esto [Israel], Seroplex, Elicea, Lexamil, Lexam, Entact [Greece], Losita [Bangladesh], Reposil [Chile], Animaxen [Colombia], Esitalo [Australia], Lexamil [South Africa]) Tetracyclic: Mirtazapine (Remeron) Tricyclic: Clomipramine (Anafranil); Desipramine (Pertofrane, Norpramine); Imipramine (melipramine) (Tofranil); Nortriptyline (Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen); Trimipramine (Surmontil, Rhotrimine, Stangyl)
Antiemetic	Dolasetron (Anzemet); Granisetron (Kytril, Sancuso, Granisol); Ondansetron (Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv,

Use of the following drugs is prohibited, due to the potential for QT interval prolongation.[a]	
	Setronax); Palonosetron (Aloxi); Tropisetron (Only on Non US Market) (Navoban, Setrovel)
Antifungal	Fluconazole (Diflucan, Trican); Pentamidine (Pentam)
Antihistamine	Astemizole (Removed from Market) (Hismanal); Terfenadine (Removed from Market) (Seldane)
Antihypertensive	Isradipine (Dynacirc); Ketanserin (Only on Non US Market) (Sufrexal); Moexipril/HCTZ (Uniretic, Univasc); Nicardipine (Cardene)
Antilipemic	Probucol (Removed from Market) (Lorelco)
Antimalarial	Artenimol+piperaquine (Only on Non-US Market) (Eurartesim); Chloroquine (Aralen); Halofantrine (Only on Non-US Market) (Halfan); Primaquine phosphate
Antimania	Lithium (Eskalith, Lithobid)
Antimycobacterial	Clofazimine (Only on Non-US Market) (Lamprene)
Antinausea	Domperidone (Only on Non-US Market) (Motilium, Motillium, Motinorm Costi, Nomit)
Antineoplastic agent	Inotuzumab ozogamicin (Besponsa); Oxaliplatin (Eloxatin)
Antipsychotic	Cyamemazine (cyamepromazine) (Only on Non-US Market) (Tercian); Haloperidol (Haldol [US & UK], Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol [Germany], Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol); Levomepromazine (methotrimeprazine) (Only on Non-US Market) (Nosinan, Nozinan, Levoprome); Levosulpiride (Only on Non-US Market) (Lesuride, Levazeo, Enliva [with rabeprazole]; Mesoridazine (Removed from Market) (Serentil); Perphenazine (Trilafon, Etrafon/Triavil, Decentan); Pimozide (Orap); Pipamperone (Only on Non-US Market) (Dipiperon [E.U], Propitan [Japan], Dipiperal, Piperonil, Piperonyl); Prothipendyl (Only on Non-US Market) (Dominal, Largophren, Timoval, Timovan, Tumovan); Thioridazine (Mellaril, Novoridazine, Thioril); Benperidol (Only on Non-US Market) (Anquil, Glianimon)
Antipsychotic/antiemetic	Chlorpromazine (Thorazine, Largactil, Megaphen); Droperidol (Inapsine, Droleptan, Dridol, Xomolix); Promethazine (Phenergan)
Antipsychotic, atypical	Aripiprazole (Abilify, Aripiprex); Asenapine (Saphris, Sycrest); Clozapine (Clozaril, Fazaclo, Versacloz); Iloperidone (Fanapt, Fanapta, Zomaril); Melperone (Only on Non-US Market) (Bunil, Buronil, Eunerpan); Paliperidone (Invega, Xepilon); Pimavanserin (Nuplazid); Risperidone (Risperdal); Sertindole (Only on Non-US Market) (Serdolect, Serlect); Sulpiride (Only on Non-US Market) (Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor); Sultopride (Only on Non-US Market) (Barnetil, Barnotil, Topral); Zotepine (Only on Non-US Market) (Losizopilon, Lodopin, Setous and Zoleptil)
Antiretroviral	Efavirenz (Sustiva and others)
Antisense oligonucleotide	Nusinersen (Spinraza)
Antiviral	Rilpivirine (Edurant, Complera, Eviplera); Saquinavir (Invirase [combo])
Beta-3 adrenergic antagonist	Mirabegron (Myrbetriq)
Cholinesterase inhibitor	Donepezil (Aricept)

Use of the following drugs is prohibited, due to the potential for QT interval prolongation.[a]	
Cyclin dependent kinase inhibitor	Ribociclib (Kisqali)
Dopamine 2 and 5HT2a antagonist	Flupentixol (Only on Non-US Market) (Depixol, Fluanxol)
Dopamine agonist	Apomorphine (Apokyn, Ixense, Spontane, Uprima)
Estrogen agonist/antagonist	Toremifene (Fareston)
GI stimulant	Cisapride (Removed from Market) (Propulsid)
Glucosylceramide synthase inhibitor	Eliglustat (Cerdelga)
Gonadotropin receptor agonist/antagonist	Leuprolide (Lupron, Eligard, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap and others)
Gonadotropin releasing hormone agonist/antagonist	Degarelix (Firmagon, Ferring)
Histone deacetylase inhibitor	Panobinostat (Farydak); Romidepsin (Istodax); Vorinostat (Zolinza)
Imaging contrast agent	Perflutren lipid microspheres (Definity, Optison)
Imunosuppressant	Tacrolimus (Prograf, Advagraf, Protopic)
Kinase inhibitor	Ceritinib (Zykadia); Crizotinib (Xalkori); Dabrafenib (Tafinlar); Lapatinib (Tykerb, Tyverb); Nilotinib (Tasigna); Sunitinib (Sutent); Vemurafenib (Zelboraf)
Local anesthetic	Cocaine
Microtubule inhibitor	Eribulin mesylate (Halaven)
Muscle relaxant	Terodiline (Only on Non-US Market) (Micturin, Mictrol [not bethanechol]); Tizanidine (Zanaflex, Sirdalud); Tolterodine (Detrol, Detrusitol)
Norepinephrine reuptake inhibitor	Atomoxetine (Strattera)
Opioid agonist	Levomethadyl acetate (Removed from Market) (Orlaam); Methadone (Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon)
Opioid receptor modulator	Buprenorphine (Butrans, Belbuca, Bunavail, Buprenex, Suboxone, Zubsolv)
Oxytocic	Oxytocin (Pitocin, Syntocinon)
Phosphodiesterase 3 inhibitor	Anagrelide (Agrylin, Xagrid); Cilostazol (Pletal)
Phosphodiesterase 5 inhibitor	Vardenafil (Levitra)
Progesterone antagonist	Mifepristone (Korlym, Mifeprex)
Proteasome inhibitor	Bortezomib (Velcade, Bortecad)
Psychedelic	Ibogaine (Only on Non-US Market)
Sedative	Dexmedetomidine (Precedex, Dexdor, Dexdomitor)

Use of the following drugs is prohibited, due to the potential for QT interval prolongation.[a]	
Selective D2, D3 dopamine antagonist	Tiapride (Only on Non-US Market) (Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl, Tiaprim, Tiaprizal, Sereprid, Tiapridex)
Somatostatic analog	Pasireotide (Signifor)
Sphingosine phospate receptor modulator	Fingolimod (Gilenya)
Tyrosine kinase inhibitor	Bosutinib (Bosulif); Dasatinib (Sprycel); Osimertinib (Tagrisso); Pazopanib (Votrient); Sorafenib (Nexavar)
Vasoconstrictor	Terlipressin (Only on Non US Market) (Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others)
Vasodilator, Coronary	Papaverine HCl (Intra-coronary)
Vesicular monamine transporter 2 inhibitor	Deutetrabenazine (Austedo); Valbenazine (Ingrezza); Tetrabenazine (Nitoman, Xenazine)
Viral protease inhibitor	Lopinavir and ritonavir (Kaletra, Aluvia)
Source: CredibleMeds Filtered QT Drug List Rev March 01 2018 (AZCERT.ORG)	

Appendix 9 - 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 10 - Investigator Responsibilities, Required Documentation, and Signature

CTI BioPharma Corp. 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), Research Ethics Board (REB), 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/REB/IEC approval letter referencing the protocol (and amendments, if applicable).
  - IRB/REB/IEC Membership List: A list of the IRB/REB/EC members, their respective titles or occupations, and their institutional affiliations.
  - A sample copy of the IRB/REB/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

Appendix 11 - Patient Global Impression Assessment

Patient Global Impression Assessment

Patient Number: _____
Today's date (day/month/year): _____/_____/_____

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your myelofibrosis symptoms are:	1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse