A Randomized, Controlled Phase 3 Study of Pacritinib Versus Physician's Choice in Patients with Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis, or Post Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Counts <50,000/µL) (PAC-303)

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Sindromi MIELOPROLIFERATIVE CRONICHE target: MIELOFIBROSI

Inclusion Criteria

1. PMF (including pre-fibrotic MF), PPV-MF, or PET-MF (as defined by Tefferi and Vardiman 2008; Appendix 1)
2. Platelet count of <50,000/µL at Screening (Day -35 to Day -3) (based on two measurements taken on different days; both measurements must be <50,000/µL)
3. DIPSS Intermediate-1, Intermediate-2, or High-Risk (Passamonti et al 2010; Appendix 2)
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 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 (Appendix 3). The TSS criteria need only to be met on a single day.
6. If the patient has received prior JAK2 inhibitor treatment, this treatment must meet at least one of the following criteria:
a. Prior treatment with any JAK2 inhibitor, irrespective of dose, with a duration of 90 days or less. The 90-day period starts on the date of first administration of JAK2 inhibitor therapy and continues for 90 calendar days, regardless of whether therapy is administered continuously or intermittently during that interval.
b. Prior treatment with ruxolitinib, at no more than 10 mg total daily dose on any day, with a duration of 270 days or less. The 270-day period starts on the date of first ruxolitinib administration and continues for 270 calendar days, regardless of whether therapy is administered continuously or intermittently. The patient may not have received >10 mg of ruxolitinib on any day during that interval. The 90- or 270-day period may overlap with the Screening period but may not extend into the washout period (14 days prior to treatment Day 1).
7. Age ≥18 years
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 (Appendix 4)
9. Peripheral blast count of <10% throughout the Screening period and prior to randomization
10. Absolute neutrophil count of ≥500/µL
11.Left ventricular cardiac ejection fraction of ≥50% by echocardiogram or multigated acquisition (MUGA) scan
12.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), total bilirubin ≤4 × ULN (in cases where total bilirubin is elevated, direct bilirubin ≤4 × ULN is required), and creatinine ≤2.5 mg/dL
13. Adequate coagulation defined by prothrombin time (PT)/international normalized ratio (INR) and PTT ≤1.5 × ULN

14. If fertile, willing to use effective birth control methods during the study
15. Willing to undergo and able to tolerate frequent MRI or CT scan assessments during the study
16. Able to understand and willing to complete symptom assessments using a patient-reported outcome instrument
17. Provision of informed consent

Exclusion Criteria

1. Life expectancy <6 months
2. Completed allogeneic SCT, or are eligible for and willing to complete other approved available therapy including allogeneic SCT
3. History of splenectomy or planning to undergo splenectomy
4. Splenic irradiation within the last 6 months
5. Previously treated with pacritinib
6. Treatment with any MF-directed therapy within 14 days prior to treatment Day 1
7. Prior treatment with more than one JAK2 inhibitor
8. Treatment with an experimental therapy within 28 days prior to treatment Day 1
9. Systemic treatment with a strong CYP3A4 inhibitor or a strong CYP450 inducer within 14 days prior to treatment Day 1 (Appendix 5 and Appendix 6, respectively). Shorter washout periods may be permitted with approval of the Medical Monitor, provided that the washout period is at least five half-lives of the drug prior to treatment Day 1.
10.Significant recent bleeding history defined as NCI CTCAE grade ≥2 within 3 months prior to treatment Day 1, unless precipitated by an inciting event (eg, surgery, trauma, or injury)
11. Systemic treatment with medications that increase the risk of bleeding, including anticoagulants, antiplatelet agents (except for aspirin dosages of ≤100 mg per day), anti-vascular endothelial growth factor (anti-VEGF) agents, and daily use of COX-1 inhibiting Non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior to treatment Day 1
12.Systemic treatment with medications that can prolong the QT interval within 14 days prior to treatment Day 1. Shorter washout periods may be permitted with approval of the Medical Monitor, provided that the washout period is at least five half-lives of the drug prior to treatment Day 1 (Appendix 8)
13.Any history of CTCAE grade ≥2 non-dysrhythmia cardiac conditions within 6 months prior to treatment Day 1. Patients with asymptomatic grade 2 non-dysrhythmia cardiovascular conditions may be considered for inclusion, with the approval of the Medical Monitor, if stable and unlikely to affect patient safety.
14.Any history of CTCAE grade ≥2 cardiac dysrhythmias within 6 months prior to treatment Day 1. 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.QT corrected by the Fridericia method (QTcF) prolongation >450 ms or other factors that increase the risk for QT interval prolongation (eg, hypokalemia [defined as serum potassium <3.0 mEq/L that is persistent and refractory to correction], or history of long QT interval syndrome)
16.New York Heart Association Class II, III, or IV congestive heart failure (Appendix 7)
17. Any active GI or metabolic condition that could interfere with absorption of oral medication
18.Active or uncontrolled inflammatory or chronic functional bowel disorder such as Crohn's disease, inflammatory bowel disease, chronic diarrhea, or chronic constipation
19.Other malignancy within 3 years prior to treatment Day 1. The following patients may be

eligible despite having had a malignancy within the prior 3 years: patients with curatively treated squamous or basal cell carcinoma of the skin; patients with curatively treated non-invasive cancers; patients with organ-confined prostate cancer with prostate-specific antigen (PSA) <20 ng/mL and National Comprehensive Cancer Network risk of Very Low, Low, or Favorable Intermediate; and patients with curatively treated non-metastatic prostate cancer with negative PSA.
20.Uncontrolled intercurrent illness, including, but not limited to, ongoing active infection, psychiatric illness, or social situation that, in the judgment of the treating physician, would limit compliance with study requirements
21.Active hepatitis B or C virus infection or known active hepatitis A virus infection
22.Human immunodeficiency virus (HIV) infection
23.Women who are pregnant or lactating
24.Concurrent enrollment in another interventional trial
25.Severe thrombocytopenia due to vitamin B12 deficiency, folate deficiency, or viral infection in the opinion of the investigator
26.Known hypersensitivity to pacritinib or any of the following inactive ingredients: microcrystalline cellulose, polyethylene glycol, and magnesium stearate; any contraindication to the “physician’s choice” medicinal product selected by the investigator to be used as the comparator or to loperamide or equivalent antidiarrheal medication.