

PACIFICA: A Randomized, Controlled Phase 3 Study of Pacritinib Versus Physician's Choice in Patients with Primary or Secondary Myelofibrosis and Severe Thrombocytopenia

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BACKGROUND

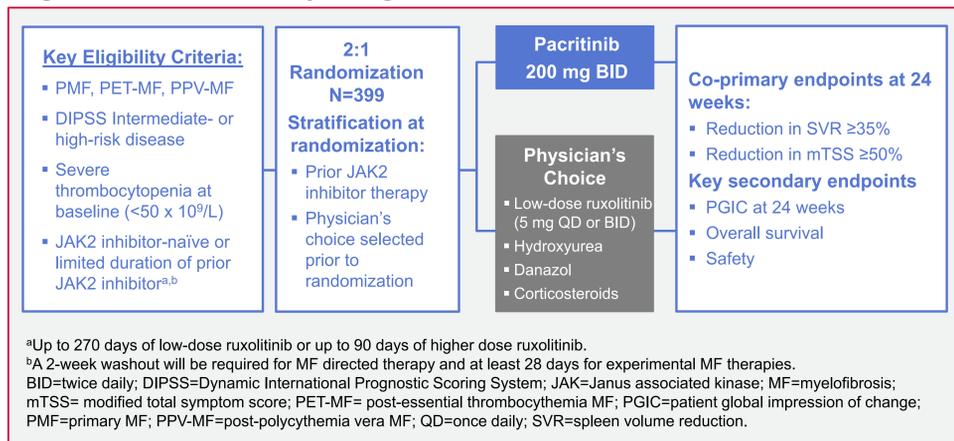
- Myelofibrosis is a serious, life-threatening myeloproliferative neoplasm caused by clonal proliferation of myeloid cells.¹
- Myelofibrosis belongs to the group of *BCR-ABL1* negative myeloproliferative neoplasms.²
- Patients with myelofibrosis and severe thrombocytopenia (platelet counts <50x10⁹/L) are generally older, with more advanced disease and increased risk of bleeding, higher rates of anemia and complex/unfavorable cytogenetics, and shortened overall survival compared to patients with higher platelet counts.³⁻⁵

Pacritinib Development

- Pacritinib is an oral JAK2/IRAK1/ACVR1 inhibitor with minimal activity against JAK1^{6,7} and is approved for patients with myelofibrosis and severe thrombocytopenia in the United States.
- Pacritinib demonstrated clinical activity in myelofibrosis in two phase 3 studies (PERSIST-1, PERSIST-2) and a phase 2 dose-finding study (PAC203), all of which included patients with severe thrombocytopenia.⁸⁻¹⁰
 - In the subset of patients with severe thrombocytopenia in each study, clinical activity was consistent with the overall study population.
- The PACIFICA phase 3 trial (clinical trial identifier: NCT03165734) is designed to evaluate efficacy and safety of pacritinib 200 mg twice daily vs physician's choice (P/C) therapy in patients with myelofibrosis and severe thrombocytopenia.

STUDY DESIGN

Figure 1. PACIFICA Study Design



- Physician's choice includes any one of the following: low-dose ruxolitinib (no more than 10 mg/day), hydroxyurea, danazol, or corticosteroids.
 - Investigators can select an individual P/C agent but cannot combine agents or give them sequentially.
- Patients are treated until disease progression, intolerable adverse events, or withdrawal of consent.
- All patients are followed for survival until 2.5 years after randomization.

STUDY OBJECTIVES

Co-primary Endpoints

- To compare the proportion of patients achieving a ≥35% spleen volume reduction (SVR) and the proportion achieving a ≥50% reduction in modified total symptom score (mTSS) from baseline at Week 24 for pacritinib vs P/C therapy
 - To account for co-primary endpoints, the sample size was adjusted from 348 to 399 patients in order to maintain power to detect a difference between pacritinib and P/C

Secondary Endpoints

- To compare the percentage of patients treated with pacritinib vs P/C who self-assess as "very much improved" or "much improved" at Week 24 as measured by the Patient Global Impression of Change (PGIC)
- To compare the overall survival of patients treated with pacritinib vs P/C therapy
- Safety based on the incidence and severity of treatment-emergent adverse events

Tertiary Endpoints

- Time to achievement of SVR of ≥35% and best response in SVR by magnetic resonance imaging (MRI) or computerized tomography (CT) scan
- Proportion of patients achieving ≥25% SVR from baseline at Week 24
- Hematologic improvement, achievement of red blood cell transfusion independence, improvement in hemoglobin without transfusion and platelet count, and frequency of platelet transfusions)
- Improvement in fatigue as measured by PROMIS v.1.0 – Fatigue – Short Form 7a
- Changes in pharmacodynamic biomarkers, genetic mutation and gene expression, hemoglobin A1c
- Pharmacokinetic profile of pacritinib
- Leukemia-free survival
- Proportion of patients who experience a major adverse cardiac event (MACE)

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Adults (age ≥ 18) with primary or secondary myelofibrosis
- Platelet count <50 x 10⁹/L
- DIPSS Intermediate-1, Intermediate-2, or high-risk disease¹¹
- Palpable spleen ≥5 cm below left costal margin
- TSS ≥10 (MPN-SAF TSS 2.0) or 1 symptom ≥5 or 2 symptoms ≥3 including only the symptoms of left upper quadrant pain, bone pain, itching, or night sweats
- Eastern Cooperative Oncology Group performance status 0-2
- Left ventricular ejection fraction ≥50%
- Peripheral blasts <10%
- Adequate hepatic and renal function, coagulation parameters, and neutrophil count

Key Exclusion Criteria

- Prior or planned splenectomy or allogeneic stem cell transplantation
- Any myelofibrosis therapy within 14 days prior to treatment Day 1
- Any prior JAK2 inhibitor treatment for ≥270 days of low-dose ruxolitinib or up to 90 days of any JAK2 inhibitor or treatment with more than one JAK2 inhibitor
- Medications that increase bleeding risk within 14 days prior to treatment Day 1

- Grade ≥2 bleeding within prior 3 months unless precipitated by an inciting event
- Grade ≥2 cardiac conditions within 6 months prior to treatment Day 1 (asymptomatic and stable grade 2 conditions may be considered for inclusion)
- QTc >450 msec or medications that prolong QT interval within 14 days prior to treatment Day 1
- New York Heart Association Class II, III, or IV congestive heart failure
- Active or uncontrolled bowel disorders
- Non-myelofibrosis malignancy within prior 3 years other than curatively treated basal or squamous skin cancer, cervical carcinoma in situ, breast carcinoma in situ, or non-metastatic prostate cancer (prostate cancer under watch-and-wait strategy may be considered for inclusion)

STATISTICAL ANALYSIS

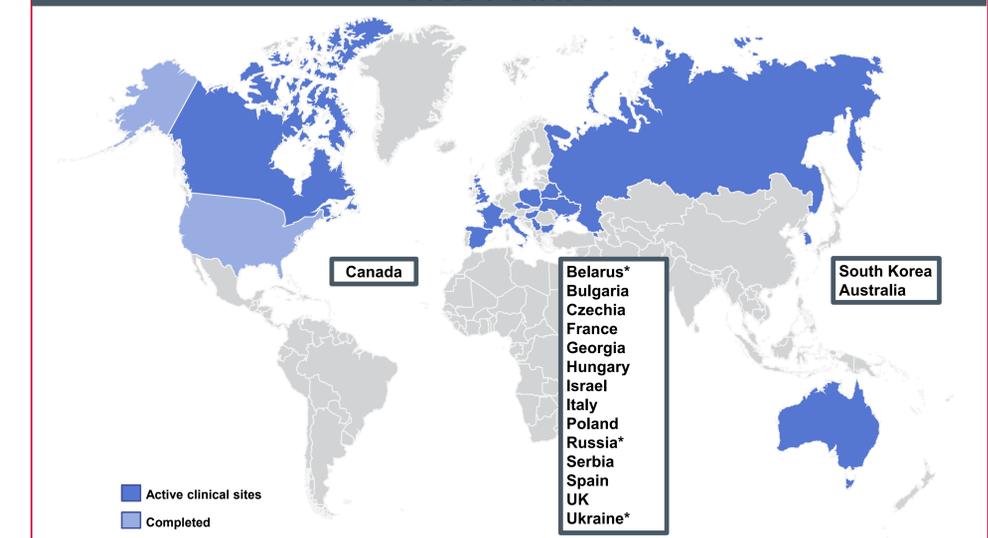
Table 1. Key Statistical Plan Variables

| Variable | Plan |
|-----------------------------|------------------------|
| Co-Primary Endpoints | SVR and mTSS |
| Sample size | 399 |
| Randomization | 2:1 (pacritinib : P/C) |
| Power | 85% |
| Alpha | Two-sided 0.05 |

mTSS=modified total symptom score; SVR=spleen volume reduction.

- Planned subgroup analyses include:
 - Age, sex, race, P/C treatment (proposed prior to randomization), prior JAK2 inhibitor therapy, and geographical location (North America, Europe, and rest of the World)
- Given US approval, currently enrolling outside of the US
- Approximately 100 clinical sites worldwide

STUDY STATUS



*Enrollment is currently on hold. Clinicaltrial.gov identifier: NCT03165734.

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