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

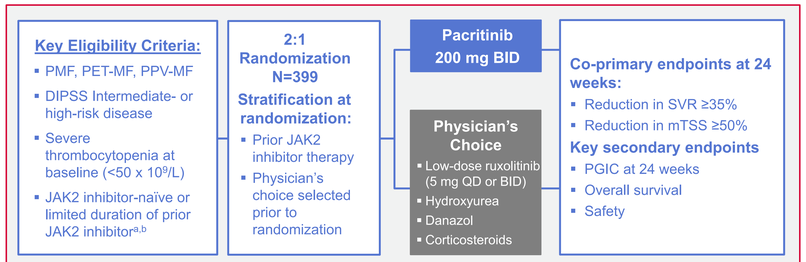
- Myelofibrosis is a serious, life-threatening myeloproliferative neoplasm caused by clonal proliferation of myeloid cells.[1]
- Myelofibrosis belongs to the group of *BCR-ABL1* negative myeloproliferative neoplasms.[2]
- Patients with myelofibrosis and severe thrombocytopenia (platelet counts <50x10^9/L) 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



[a]Up to 270 days of low-dose ruxolitinib or up to 90 days of higher dose ruxolitinib.
[b]A 2-week washout will be required for MF directed therapy and at least 28 days for experimental MF therapies.
BID=twice daily; DIPSS=Dynamic International Prognostic Scoring System; JAK=Janus associated kinase; MF=myelofibrosis; mTSS= modified total symptom score; PET-MF= post-essential thrombocythemia MF; PGIC=patient global impression of change; PMF=primary MF; PPV-MF=post-polycythemia vera MF; QD=once daily; SVR=spleen volume reduction.

- 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 10^9/L
- DIPSS Intermediate-1, Intermediate-2, or high-risk disease[11]
- 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

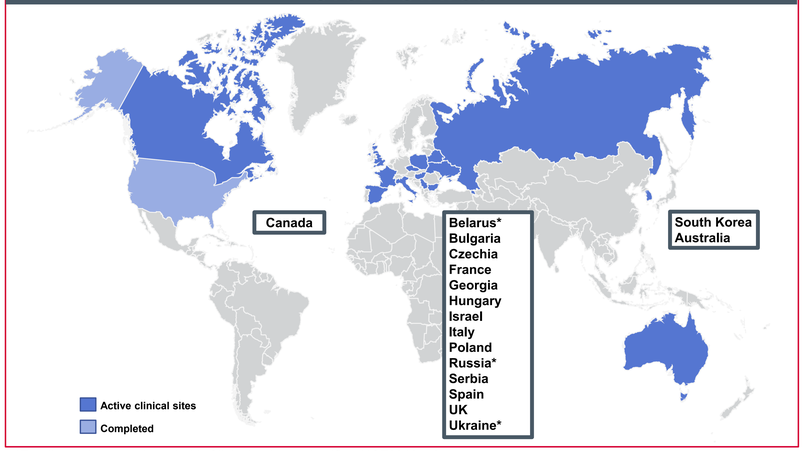
Table 1. Key Statistical Plan Variables

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.

ACKNOWLEDGEMENTS: This study is supported by CTI BioPharma Corp. We would like to extend our thanks to the patients, their families, the investigators and their staff members who are making this trial possible.

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