PACIFICA: A Randomized Phase 3 Study of Pacritinib vs. Physician's Choice in Patients with Myelofibrosis and Severe Thrombocytopenia

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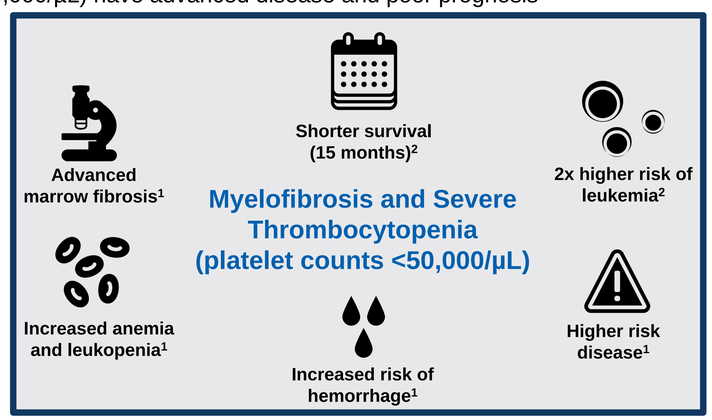
BACKGROUND

Myelofibrosis with Severe Thrombocytopenia

- Patients with myelofibrosis (MF) and severe thrombocytopenia (platelet count <50,000/µL) have advanced disease and poor prognosis[1,2]



- These patients represent an area of serious unmet medical need. Effective treatment options are limited, as approved JAK2 inhibitors generally cannot be given at optimally effective doses due to drug-induced myelosuppression[3]

Pacritinib Development

- Pacritinib is a JAK2/IRAK1 inhibitor with minimal activity against JAK1.[4]
- Pacritinib has demonstrated efficacy in two Phase 3 trials in patients with MF (PERSIST-1 and PERSIST-2),[5,6] including in patients with severe thrombocytopenia[7] (**Abstract #4195 – Monday**)
- The PAC203 Phase 2 dose-finding study was conducted in patients with MF who did not respond to or were unable to tolerate prior ruxolitinib
- Based on results from PAC203, as well as dose-response / exposure-response analysis (**Oral abstract #667 – Monday**)[8], the 200mg BID dose has demonstrated efficacy and will be used in patients with MF and severe thrombocytopenia in the Phase 3 PACIFICA trial

STUDY DESIGN

PACIFICA

Key Eligibility
- Platelet count <50,000/µL
- DIPSS Int-1/-2 or High Risk
- Palpable spleen ≥5cm
- TSS ≥10 (MPN-SAF v2.0)
- Prior JAK inhibitor ≤90 days

Randomize 2:1, N=180

Stratification
- P/C selection
- Prior JAK inhibitor

Pacritinib 200mg BID

vs.

Physician's Choice (P/C)

1° Endpoint
- SVR at 24 weeks

2° Endpoints
- TSS at 24 weeks
- Overall Survival
- PGIC at 24 weeks

- P/C therapy includes any one of: low-dose ruxolitinib (5mg BID or 5mg QD starting), hydroxyurea, thalidomide, lenalidomide, or corticosteroids
- Patients treated until disease progression, toxicity, or withdrawal of consent
- All patient followed for survival until 2.5 years after randomization

STUDY OBJECTIVES

Primary Objective

SVR To compare efficacy of pacritinib vs. P/C therapy based on the proportion of patients with ≥35% **spleen volume response** at Week 24.

Secondary Objectives

TSS To compare the proportion of patients treated with pacritinib vs. P/C with ≥50% reduction in **Total Symptom Score** at Week 24.

OS To compare the **overall survival** of patients treated with pacritinib vs. P/C therapy.

PGIC To compare the proportion 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**.

Tertiary Objectives

- Hematologic improvement (in transfusions, anemia, and thrombocytopenia)
- Improvement in fatigue (PROMIS – Fatigue – Short Form 7a)
- Changes in mutated allelic burden and gene expression

MAJOR ELIGIBILITY CRITERIA

Key Inclusion Criteria

1. Adults with primary or secondary myelofibrosis
2. Platelet count <50,000/µL
3. DIPSS Intermediate-1, Intermediate-2, or High-Risk disease
4. Palpable spleen ≥5cm below costal margin
5. 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, night sweats
6. ECOG performance status 0-2
7. Left ventricular ejection fraction ≥50%
8. Peripheral blasts <10%
9. Adequate hepatic and renal function, coagulation parameters, and neutrophil count

Key Exclusion Criteria

1. Prior splenectomy or allogeneic stem cell transplantation
2. Any myelofibrosis therapy within 14 days prior to Day 1
3. Any prior JAK2 inhibitor treatment for >90 days
4. Grade ≥2 bleeding within prior 3 months unless precipitated by an inciting event
5. Medications that increase bleeding risk within 14 days prior to Day 1
6. Grade ≥2 cardiac conditions within 6 months prior to Day 1 (asymptomatic and stable grade 2 conditions may be considered for inclusion)
7. QTc >450 ms or medications that prolong QT interval within 14 days prior to Day 1
8. NYHA Class II, III, or IV heart failure
9. Active or uncontrolled bowel disorders
10. 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)

STUDY CONDUCT

Study Enrollment

Enrollment start: Sept 30, 2019 **Participating sites**: ~100

Planned Study Footprint

- PACIFICA is in the process of enrolling new sites.
- Anticipated regions of enrollment include North America (United States and Canada), Europe, and countries in the Asia / Pacific region.
- Participating regions may not yet be open to enrollment

STATISTICAL ANALYSIS

Variable	Plan
Sample Size	180
Randomization	2:1 (pacritinib:P/C)
Primary Endpoint	SVR
Power	>80%
alpha	Two-sided 0.05

- Planned subgroup analyses: age, sex, race, Physician's Choice treatment selection (thalidomide and lenalidomide binned into a single category), prior JAK2 inhibitor therapy, and geographic region

CONCLUSIONS

- There is a serious unmet need for safe and effective therapies for patients with MF and severe thrombocytopenia
- The Phase 3 PACIFICA trial will compare efficacy and safety of pacritinib 200mg BID vs. Physician's Choice therapy in this patient population
- The PACIFICA trial is currently open to enrollment

REFERENCES

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CONTACT INFORMATION

Clinicaltrials.gov Identifier: NCT03165734

PACIFICA website: www.PACIFICA-Trial.com

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PosterCast