The Impact of Pacritinib on Myelofibrosis Symptoms in Patients With Moderate and Severe Thrombocytopenia: a Retrospective Analysis of Patients in the PERSIST-2 Study

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INTRODUCTION

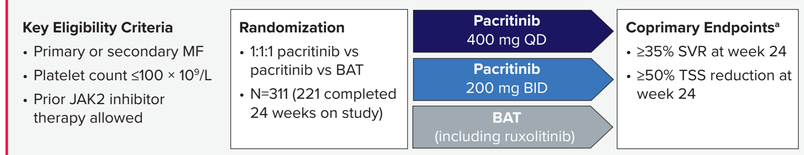
Symptoms of Myelofibrosis With Thrombocytopenia

- Thrombocytopenia is a marker of advanced disease among patients with myelofibrosis (MF) and represents an area of unmet medical need.
- Compared with patients who have higher platelet count, those with moderate and severe thrombocytopenia (platelet count ≤100 × 10^9/L) generally have worse quality of life and higher symptom burden.[1]
  - Physical function symptoms (fatigue and inactivity) are particularly severe in patients with platelet count ≤100 × 10^9/L.[1]

Pacritinib Therapy for Cytopenic Myelofibrosis

- Pacritinib is an oral Janus kinase (JAK) 2/interleukin-1 receptor–associated kinase 1 (IRAK1) inhibitor that does not inhibit JAK1.[2]
- Pacritinib demonstrated superior spleen volume response versus best available therapy (BAT) in patients with MF who have moderate or severe thrombocytopenia (platelet count ≤100 × 10^9/L) in the phase 3 PERSIST-2 study.[3]
- Unlike the studies in which JAK1/2 inhibitors were approved, which relied on a modified total symptom score (mTSS) that excluded "tiredness," PERSIST-2 included tiredness as part of the TSS.
  - The percentage of patients in PERSIST-2 with TSS response was 25% for the pooled pacritinib arms versus 14% for BAT (*P*=0.08).

Figure 1. PERSIST-2 Study Design



[a]The primary analysis compared pooled pacritinib (400 mg QD and 200 mg BID) versus BAT.
BAT=best available therapy; BID=twice daily; MF=myelofibrosis; QD=once daily; SVR=spleen volume response; TSS=total symptom score.

OBJECTIVES

- To retrospectively analyze symptom benefit in patients treated in PERSIST-2 based on mTSS, to allow direct comparison with other JAK inhibitor studies.
- To analyze the impact of pacritinib versus BAT (including ruxolitinib) on symptom severity, including the symptoms tiredness and inactivity.

METHODS

- The analysis included patients in the intention-to-treat (ITT) efficacy population from PERSIST-2; the symptoms evaluated and scoring details are shown in **Table 1**.
- The mTSS response was determined using the percentage of patients with score reduction ≥50% from baseline to week 24.
- Wilcoxon's rank sum test was used to compare differences in scores between pacritinib and BAT.

Table 1. MF Symptoms Evaluated in TSS vs mTSS

	Tiredness	Inactivity	Early satiety	Abdominal pain	Left rib pain	Night sweats	Itching	Bone pain
Evaluated	X	X	X	X	X	X	X	X
TSS	X		X	X	X	X	X	X
mTSS			X	X	X	X	X	X

MF=myelofibrosis; mTSS=modified total symptom score; TSS=total symptom score.

RESULTS

Baseline Patient Characteristics

- The analysis included 74 patients randomized to pacritinib 200 mg twice daily (BID) and 72 to BAT; an additional 75 patients were randomized to pacritinib 400 mg once daily (dose no longer in development).
- Key baseline characteristics for the population are shown in **Table 2**.

Table 2. Key Baseline Characteristics

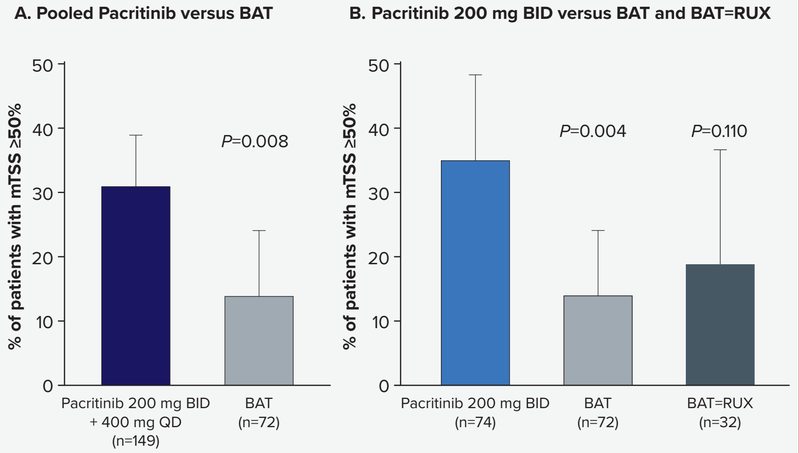
	Pacritinib 200 mg BID (n=74)	BAT (n=72)	BAT=RUX (n=32)
Mean age, years	66.1	67.3	68.8
Platelet count × 10^9/L, median (IQR)	55.0 (36.0-92.0)	56.0 (29.0-81.0)	61.0 (35.0-91.0)
Hemoglobin <10 g/dL, n (%)	44 (59.5)	41 (56.9)	16 (50.0)
Transfusion dependent[a] or transfusion indeterminate[b], n (%)	36 (48.6)	35 (48.6)	13 (40.6)

[a]Tranfusion dependence is defined as an average of ≥2 RBC units/month in the prior 90 days.
[b]Tranfusion indeterminate is defined as an average of <2 RBC units/month in the prior 90 days.
BAT=best available therapy; BID=twice daily; RBC=red blood cells, RUX=ruxolitinib.

PERSIST-2 Met the Coprimary Endpoint Based on Symptom Improvement With the Modified TSS

- Significantly more patients achieved a mTSS response with pooled pacritinib versus BAT (31% vs 14%; *P*=0.008) (**Figure 2A**).
- More patients achieved a mTSS response with pacritinib 200 mg BID versus BAT (35% vs 14%; *P*=0.004) and BAT=RUX (35% vs 19%; *P*=0.110) (**Figure 2B**).
- Among patients receiving BAT, mTSS response rates were modestly higher for patients who received ruxolitinib prior to week 24 (19% [6/32]) compared with those who did not (10% [4/40]), although both were lower than response rates with pacritinib 200 mg BID (35%).

Figure 2. mTSS Response Rates (Week 24)



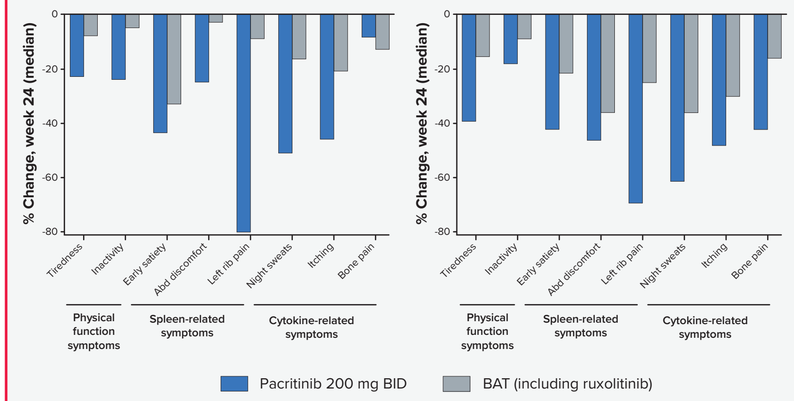
BAT=best available therapy; BID=twice daily; mTSS=modified total symptom score; QD=once daily; RUX=ruxolitinib; TSS=total symptom score.

REFERENCES: 1. Scotch AH, et al. *Leuk Res*. 2017;63:34-40. **2.** Singer JW et al. *J Exp Pharmacol.* 2016;8:11-19. **3.** Mascarenhas J, et al. *JAMA Oncol.* 2018;4:652-659.

Symptom Reduction With Pacritinib

- Patients in the pacritinib 200 mg BID arm experienced greater percent reductions in individual MF symptoms between baseline and week 24 compared with BAT (**Figure 3**).
  - Improvement was seen in patients with both moderate and severe thrombocytopenia.
- The severity of physical function symptoms was reduced more with pacritinib 200 mg BID compared with BAT by week 24.
  - Median reduction in tiredness: 30% versus 13% (*P*=0.026).
  - Median reduction in inactivity: 22% versus 7% (*P*=0.099).

Figure 3. Percent Change in Individual Symptom Scores



BAT=best available therapy; BID=twice daily.

CONCLUSIONS

- The symptom benefit of pacritinib in patients with MF who have moderate and severe thrombocytopenia was demonstrated in the PERSIST-2 study.
- A significant symptom benefit was observed in patients treated with pacritinib 200 mg BID compared with BAT, including ruxolitinib.
  - The mTSS response rate of 35% in patients with moderate and severe thrombocytopenia is comparable to that reported for approved JAK1/2 inhibitors, which were studied in patients with higher platelet counts.
- Pacritinib may address the unmet need for symptom control in patients with cytopenic MF.

ACKNOWLEDGMENTS: This poster was presented at the 2021 American Society of Hematology Annual Meeting. Copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without permission from ASH and CTI BioPharma. This study was supported by CTI BioPharma. Medical writing and editorial assistance was provided under the direction of the authors by MedThink SciCom, and funded by CTI BioPharma.

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