Thrombocytopenia is an adverse prognostic variable that increases in prevalence with progression of disease and is associated with high symptom burden and shorter survival. Ruxolitinib, a JAK1/2 inhibitor, is approved by FDA for patients with intermediate/high-risk MF and a baseline platelet count ≤ 500x10^9/L. Unmet clinical need for patients with baseline or treatment-emergent thrombocytopenia, as well as those refractory or refractory to ruxolitinib. Pacritinib, a JAK2/FLT3 inhibitor, has been shown to be clinically active with minimal myelosuppression in patients with MF.

In the phase 3 PERSIST-1 trial of pacritinib vs best available therapy (BAT, excluding ruxolitinib) in patients with MF, pacritinib 400 mg once daily (QD) demonstrated significant and durable spleen volume reduction (SVR) and symptom control irrespective of baseline platelet count.

In a phase 1/2 study, QD doses ≥ 400 mg did not appreciably increase systemic pacritinib exposure, due to less-than-proportional increase in exposure with dose up.

Thus, the twice-daily (BID) dosing regimen with the same total daily dose was selected. Population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations using data from early phase pacritinib studies predicted higher steady-state exposure.

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Population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations using data from early phase pacritinib studies predicted higher steady-state exposure and total exposure with twice daily vs once daily pacritinib.

Moreover, modeling work predicted enhanced efficacy along with comparable to improved safety profile with BID dosing regimen of pacritinib.

As a result, the phase 3 PERSIST-2 trial of pacritinib vs BAT (including ruxolitinib), in patients with MF and thrombocytopenia evaluated both pacritinib 400 mg QD and 200 mg BID.

Despite identical cumulative daily dosing, patients treated with pacritinib 200 mg BID had improved SVR (P < 0.001) and symptom control (P = 0.011), with numerically reduced adverse events and a trend towards improved survival.

• In total, PK samples were collected up to Week 24 from 144 pacritinib-treated patients (78 BID, 66 QD).

• Median pacritinib plasma concentration during Week 1 (4h) was 47% higher with QD vs BID dosing:
  - At steady state, median Cmin (Cminss) at Weeks 12 and 24 were higher with BID vs QD dosing by 10% and 15%, respectively
  - Median observed steady-state 4h concentration (corresponds with Cmaxss) at Week 3 was 12% higher with QD vs BID dosing

• Pacritinib 400 mg QD was associated with higher Cmaxss and lower Cminss vs pacritinib 200 mg BID (Table 2).