E1343

PK/PD MODELING COMPARING DIVIDED DOSING (200 MG TWICE DAILY) VS SINGLE DOSING (400 MG ONCE DAILY) OF PACRITINIB IN PATIENTS WITH MYELOFIBROSIS ON THE PERSIST-2 PHASE 3 TRIAL

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INTRODUCTION

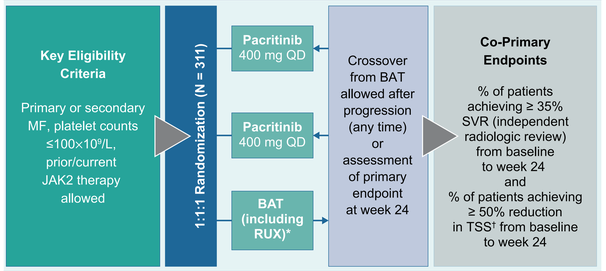
- Myelofibrosis (MF) is a life-threatening hematologic malignancy characterized by splenomegaly and debilitating constitutional symptoms[1-3]
  - Thrombocytopenia is an adverse prognostic variable that increases in prevalence with disease progression and is associated with high symptom burden and shorter survival[3-5]
- Ruxolitinib, a JAK1/2 inhibitor, is approved by FDA for patients with intermediate/high-risk MF and a baseline platelet count ≥ 50×10^9/L
  - Unmet clinical need for patients with baseline or treatment-emergent thrombocytopenia, as well as those relapsed or refractory to ruxolitinib
- Pacritinib, a JAK2/FLT3 inhibitor,[6] has been shown to be clinically active with minimal myelosuppression in patients with MF[7]
- 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[8]
- 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[9]
  - Thus, the twice-daily (BID) dosing regimen with the same total daily dose was considered to achieve higher exposure of pacritinib
- 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[10]
  - 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[11]
  - 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

OBJECTIVE

- Validate the clinical utility of PK/PD modeling to select pacritinib 200 mg BID in the phase 3 PERSIST-2 trial and for further clinical evaluation
  - Compare the PK exposures of pacritinib 200 mg BID and 400 mg QD regimens
  - Summarize safety and efficacy exposure-response relationships

METHODS

Figure 1. Study Schema



*BAT includes any physician-selected treatment MF, and may include any treatment received before study entry.
†TSS, total symptom score by MPN-SAF 2.0 with daily patient reporting of disease-related symptoms by e-diary.

- Blood sampling times in pacritinib-treated patients:
  - For PK/PD analyses in prespecified subset of trial sites: Day 1 of Week 1 (4 h post-dose), Week 3 (pre-dose and 4 h post-dose), Week 12 (pre-dose), and Week 24 (pre-dose)
  - For PK analyses only in remaining trial sites: Weeks 12 and 24 only (pre-dose)
- Plasma pacritinib concentrations measured using validated liquid chromatography-mass spectrometry/mass spectrometry methods
- Results were used to evaluate the relationship between pacritinib exposure and safety and efficacy
- Samples were not collected from patients who crossed over from BAT to pacritinib

RESULTS

- In total, PK samples were collected up to Week 24 from 144 pacritinib-treated patients (78 BID, 64 QD)
- Median pacritinib plasma concentration during Week 1 (4h) was 47% higher with QD vs BID dosing **(Table 1)**
  - At steady state, median Cmin ($Cmin_{ss}$) at Weeks 12 and 24 were higher with BID vs QD dosing by 10% and 15%, respectively
  - Median observed steady-state 4 h concentration (corresponds with $Cmax_{ss}$) at Week 3 was 12% higher with QD vs BID dosing

Table 1. Summary Statistics of Observed Plasma Concentrations

Regimen	Time point	n	Median (range)
200 mg BID	Week 1, 4 h*	36	5367 (713-10714)
	Week 3, 0 h	34	8032 (3536-14935)
	Week 3, 4 h*	36	8444 (4509-15666)
	Week 12, 0 h	71	7028 (83-21463)
	Week 24, 0 h	40	7156 (2730-18248)
400 mg QD	Week 1, 4 h*	38	7905 (1688-13653)
	Week 3, 0 h	36	8338 (1057-17260)
	Week 3, 4 h*	35	9416 (3098-17020)
	Week 12, 0 h	50	6406 (22-18646)
	Week 24, 0 h	38	6215 (118-14381)

*Sample collected at 4 h corresponds approximately to Cmax.

- Pacritinib 400 mg QD was associated with higher $Cmax_{ss}$ and lower $Cmin_{ss}$ vs pacritinib 200 mg BID **(Table 2)**

Table 2. Summary of Pacritinib Exposure

	Regimen	n	Geometric Mean (ng/mL)	Ratio	90% CI
$Cmin_{ss}$*	200 mg BID	83	6783	1.12	0.95-1.31
	400 mg QD	34	6076		
$Cmax_{ss}$†	200 mg BID	38	8290	0.93	0.77-1.12
	400 mg QD	36	8930		

*Geometric mean of concentrations from Weeks 3, 12, and 24 pre-dose samples.
†Week 3, 4 h sample.

- Cmin results were more reliable than Cmax on the basis of sample size, and were therefore the focus of safety and efficacy exposure-response relationship analyses
- Events included in the analysis for potential exposure-safety trends are shown in **Table 3**
- For pacritinib 200 mg BID: trend between $Cmin_{ss}$ and any cardiac event, but not for grade ≥ 2 or grade ≥ 3 cardiac events
  - This finding was not reflected in clinical outcomes:
    - Rate of any grade cardiac events (by SMQ) was similar with pacritinib BID (32%), pacritinib QD (32%), and BAT (30%) and most commonly peripheral edema
    - Rate of grade 3/4 cardiac events (by SMQ) was lower with pacritinib BID (7%) vs BAT (9%) or pacritinib QD (13%)
    - No cardiac failure or deaths due to cardiac events with pacritinib BID

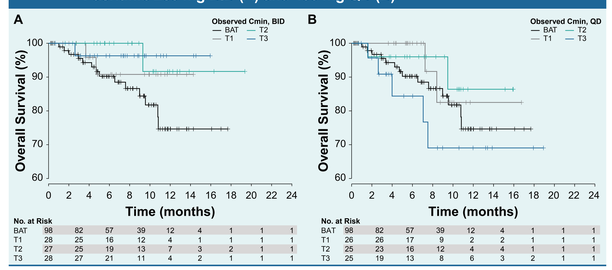
Table 3. Summary of Exposure-Safety Trends for Observed $Cmin_{ss}$

End point	200 mg BID Cmin	400 mg QD Cmin
Death		
Cardiovascular death		
Hemorrhagic death		
Any cardiac events		
Grade ≥ 2 cardiac events		
Grade ≥ 3 cardiac events		
Any hemorrhagic events	X	
Grade ≥ 2 hemorrhagic events		
Grade ≥ 3 hemorrhagic events		
Grade ≥ 2 thrombocytopenia		
Grade ≥ 3 thrombocytopenia		
Grade ≥ 2 anemia		
Grade ≥ 3 anemia		
Any GI event		
Grade ≥ 2 GI event		
Grade ≥ 3 GI event		
Change in QTcF > 30 ms	X	
QTcF > 450 ms		

GI, gastrointestinal.
Note: exposure-safety relationships deemed to have a trend (marked with an X) when the lower bound of the 90% CI for the difference between the event probabilities in the 4th exposure quartile relative to the 1st quartile exceeds 0.

- For pacritinib 200 mg BID: trend between $Cmin_{ss}$ and QT prolongation (change in QTcF > 30 ms)
  - QT prolongation was lower with pacritinib BID (16%) vs pacritinib QD (19%) or BAT (23%)
  - Analysis of QTcF change from baseline vs pacritinib concentration showed no trend
- Of note, incidence of all grade diarrhea was lower with pacritinib BID (48%) vs QD (67%)
  - May be related to decreased pacritinib in the gastrointestinal tract due to higher percent absorption with BID vs QD dosing
- With pacritinib BID, there appears to be a trend for improved overall survival vs BAT regardless of $Cmin_{ss}$ tertile (**Figure 2**, no statistical testing done due to limited OS events)
  - No such trend was evident with pacritinib QD

Figure 2. Overall Survival vs Observed $Cmin_{ss}$ (by Tertile) Relative to BAT for Pacritinib 200 mg BID (A) and 400 mg QD (B).



T, tertile.

- Pacritinib 200 mg BID led to significant improvements over BAT for both co-primary endpoints **(Table 4)**

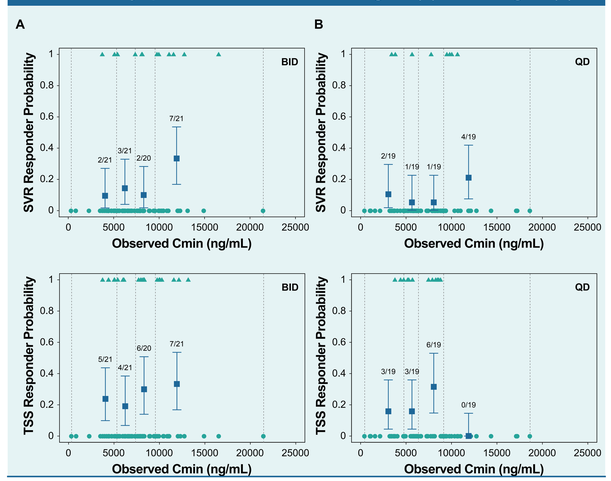
Table 4. Co-Primary Endpoints

Endpoint (Week 24)	Statistics	Pacritinib 200 mg BID (n=74)	Pacritinib 400 mg QD (n=75)	BAT (n=72)
Patients with ≥35% SVR	n (%)	16 (22)	11 (15)	2 (3)
	95% CI*	12.9-32.7	7.6-24.7	0.3-9.7
	P value vs BAT	0.001	0.017	-
Patients with ≥50% reduction in TSS	n (%)	24 (32)	13 (17)	10 (14)
	95% CI*	22.0-44.3	9.6-27.8	6.9-24.1
	P value vs BAT	0.011	0.652	-

*Clopper-Pearson method.

- Treatment with pacritinib BID, but not QD, showed a trend for increased SVR and TSS vs $Cmin_{ss}$ (**Figure 3**)
  - Only 18% of pacritinib QD patients had $Cmin_{ss}$ in the highest quartile for BID patients
  - 82% vs 70% of pacritinib BID vs QD patients had Cminss exceeding the approximate in vitro EC_{50} value (after correcting for protein binding, 5000 ng/mL)

Figure 3. Exposure-Response Relationships for Spleen Volume Reduction and Total Symptom Score for Pacritinib 200 mg BID (A) and 400 mg QD (B)



Note: Exposures are separated into quartiles (dashed vertical lines), and event probabilities per exposure quartile at the mean exposure in that quartile are indicated by the black square points with 95% confidence intervals. The concentrations in patients with events are indicated by the triangles at the top of the plot; concentrations in patients with no events are indicated by the circles at the bottom of the plot.

CONCLUSIONS

- As predicted by PK modeling and simulations analyses, pacritinib 400 mg QD was shown to be associated with higher Cmax and lower Cmin vs pacritinib 200 mg BID in patients with MF from the PERSIST-2 trial
  - Moreover, 200 mg BID regimen demonstrated enhanced efficacy (SVR & TSS reduction) as well as improved OS and reduced AEs compared to the 400 mg QD regimen
- Given the steep exposure-response relationship for pacritinib, it is thought that a relatively small increase of 15% in systemic exposure translated to a marked increase in efficacy and an improved benefit/risk profile of pacritinib 200 mg BID vs 400 mg QD
- The results of PERSIST-2 demonstrate the clinical benefit of pacritinib in patients with MF and thrombocytopenia, including those with prior JAK2 inhibitor therapy
- Further clinical evaluation of pacritinib in patients with MF is ongoing

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