Results of PAC203: A Randomized Phase 2 Dose-Finding Study and Determination of the Recommended Dose of Pacritinib in Patients with Myelofibrosis

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ASH 2019, Abstract #667

December 9, 2019

Medications Approved for Myelofibrosis (MF)

- Ruxolitinib and fedratinib (JAK2/JAK1 inhibitors) are approved for MF
  - Neither studied in patients with baseline platelet counts <50,000/µL
  - Neither package insert lists starting dose for patients with platelet counts <50,000/µL[1,2]
- Pacritinib (JAK2/IRAK1 inhibitor) is under development for treatment of MF
  - Studies have included patients with severe thrombocytopenia

[1] JAKAFI (ruxolitinib) FDA package insert
[2] INREBIC (fedratinib) FDA package insert

Myelofibrosis After Ruxolitinib Discontinuation

- Median overall survival in MF is ~5 years[1], but prognosis is worse in 2nd line setting
- Median survival after ruxolitinib discontinuation: 13-14 months[2,3]
  - Worse if platelet count <100,000/µL: OS ~8 months[3]
  - Worse if new mutation on ruxolitinib: OS ~6 months[3]

[1] Cervantes F et al. New prognostic scoring system for primary myelofibrosis based on a study of the IWG-MRT. Blood;113(13):2895-902.
[2] Kuykendall AT et al. Between a Rux and a Hard Place: Evaluating Salvage Treatment and Outcomes in Myelofibrosis after Ruxolitinib Discontinuation. Ann Hematol. 2018;97(3):435-41.
[3] Newberry KJ, et al. Clonal Evolution and Outcomes in Myelofibrosis after Ruxolitinib Discontinuation. Blood. 2017;130(9):1125-31.

Pacritinib: JAK2 Inhibitor for Myelofibrosis

- Pacritinib demonstrated clinical benefit compared to best available therapy (BAT) based on spleen volume response (SVR) in patients with myelofibrosis in two Phase 3 studies[1,2]
- Both studies included patients with severe thrombocytopenia

Baseline Data	PERSIST-1	PERSIST-2
Total study N	327	311
Median platelet count	176,000/µL	55,000/µL
Platelets <50,000/µL, %	16%	45%

- SVR benefit seen in subgroup of patients with severe thrombocytopenia in both studies[3]

[1] Mesa RA, et al. Pacritinib Versus Best Available Therapy for the Treatment of Myelofibrosis Irrespective of Baseline Cytopenias (PERSIST-1): an International, Randomized, Phase 3 Trial. Lancet Haematol. 2017;4(5):e225-36.
[2] Mascarenhas J, et al. Pacritinib vs Best Available Therapy, including Ruxolitinib, in Patients with Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2018;4(5):62-59.
[3] Mascarenhas J, et al. Pacritinib Demonstrates Efficacy Versus Best Available Therapy in Myelofibrosis Patients with Severe Thrombocytopenia in Two Phase 3 Studies. ASH 2019 Abstract #4195.

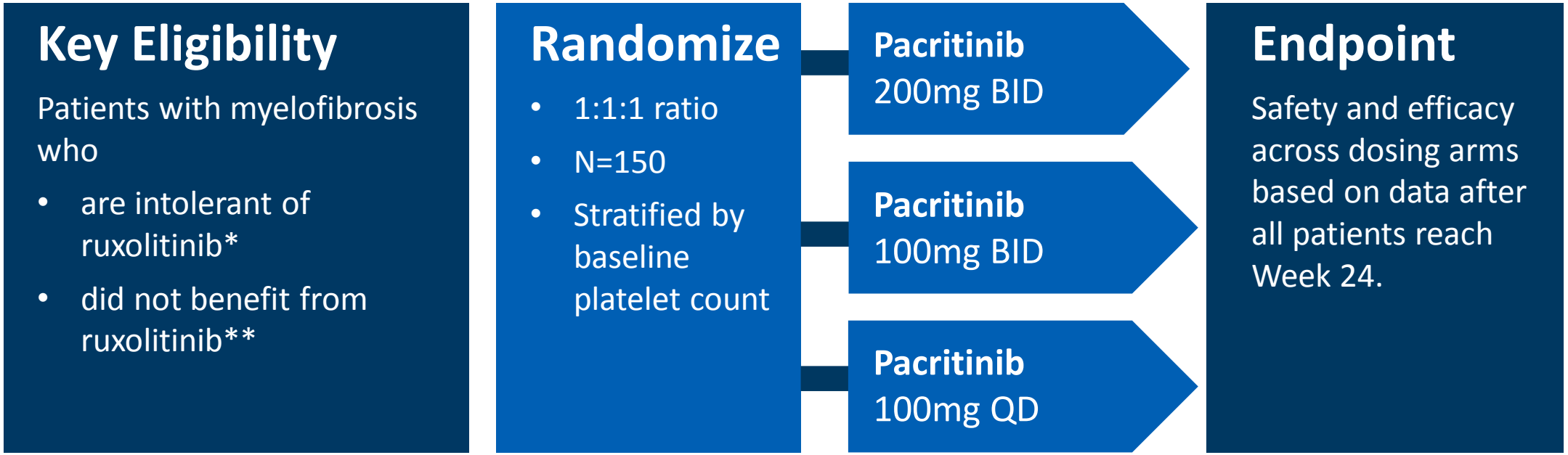
PAC203 Dose-Finding Study: Rationale

- Concern over high-grade cardiac and hemorrhagic events in pacritinib-treated patients on PERSIST-1/-2 led to development of a new dose-finding study (PAC203)

Risk Mitigation for Cardiac and Hemorrhagic Events		
	PERSIST-1 and PERSIST-2	**PAC203 Phase 2**
Exclusion for bleeding	No current grade ≥3 (PERSIST-2 only)	No grade ≥2 bleeding x3 months
Anticoagulants / anti-PLTs	✕	Prohibited starting Day -14
Exclusion for cardiac AEs	No MI x6 months; no grade ≥3 arrhythmia	No grade ≥2 cardiac AE x6 months
Exclusion for heart failure	No NYHA Class III-IV	No NYHA Class II, III, or IV
QT prolonging agent use	✕	Prohibited starting Day -14
ECG monitoring	Weeks 1, 2, and 3	Weeks 1, 4, 12, 24, every 12 weeks
LVEF monitoring	✕	Weeks 1, 4, 12, 24, every 24 weeks

AE, adverse event; **ECG**, electrocardiogram; **LVEF**, left ventricular ejection fraction; **MI**, myocardial infarction; **NYHA**, New York Heart Association; **PLT**, platelet

PAC203 Schema



* **Intolerance**: ruxolitinib for ≥28 days complicated by development of red cell transfusion requirement or grade ≥ 3 anemia, thrombocytopenia, or hemorrhage while on <20mg BID

** **Failure to benefit**: ruxolitinib for ≥3 months with <10% spleen volume reduction or <30% decrease in spleen length, or regrowth to these parameters

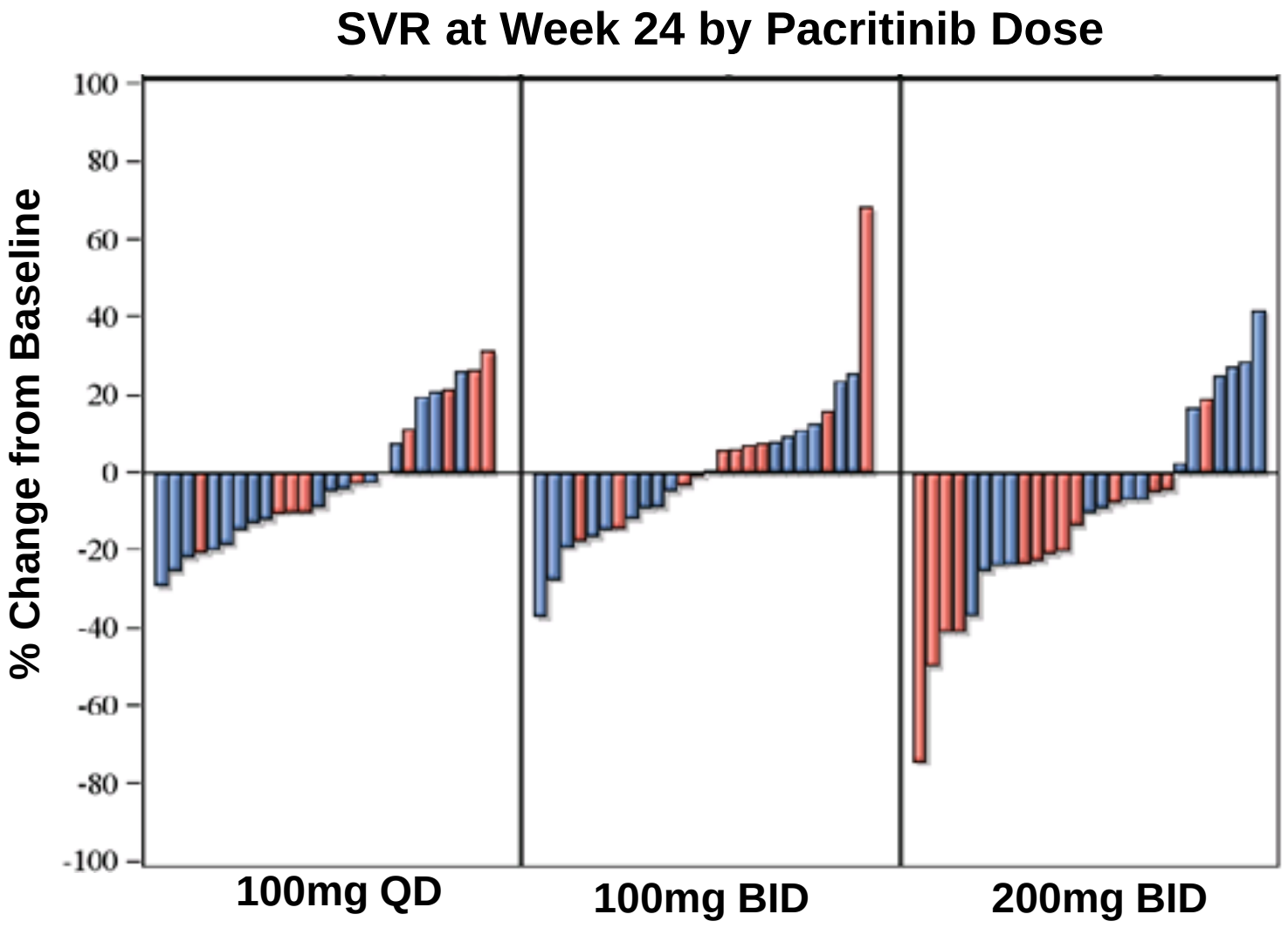
PAC203 Patient Characteristics

Characteristic	All Doses (N=161)
Age (years [median, IQR])	**69 (64-73)**
Platelets (/µL [median, IQR])	**55,000 (36,000-102,000)**
Hemoglobin <10g/dL (%)	**71%**
Peripheral Blasts ≥1% (%)	**58%**
Ruxolitinib duration (years [median, IQR])	**1.7 (0.6-3.3)**
Ruxolitinib exposure Treatment failure Intolerance Both	 **76%** **73%** **50%**
Molecular risk (N=110) High Molecular Risk[1,2] TP53 mutation	 **41%** **7.3%**
Mutations per patient[2] (mean, IQR)	**2.5 [1.25-3.75]**

IQR, inter-quartile range

[1] Tefferi et al. MIPSS70+ Version 2.0: Mutation and Karytype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol. 2018;36(17):1769-70.
[2] O'Sullivan et al. Molecular Analysis in the Pacritinib Dose-Finding PAC203 Study in Patients with Myelofibrosis Refractory or Intolerant to Ruxolitinib. ASH 2019 abstract #4214.

Spleen Volume Response (SVR) at Week 24



Dose Group	Patients with ≥35% SVR
100mg QD	0/52 (0%)
100mg BID	1/55 (1.8%)
200mg BID PLT <50,000/µL	5/54 (9.3%) 4/24 (17%)

Baseline platelet level

- <50,000/µL
- ≥50,000/µL

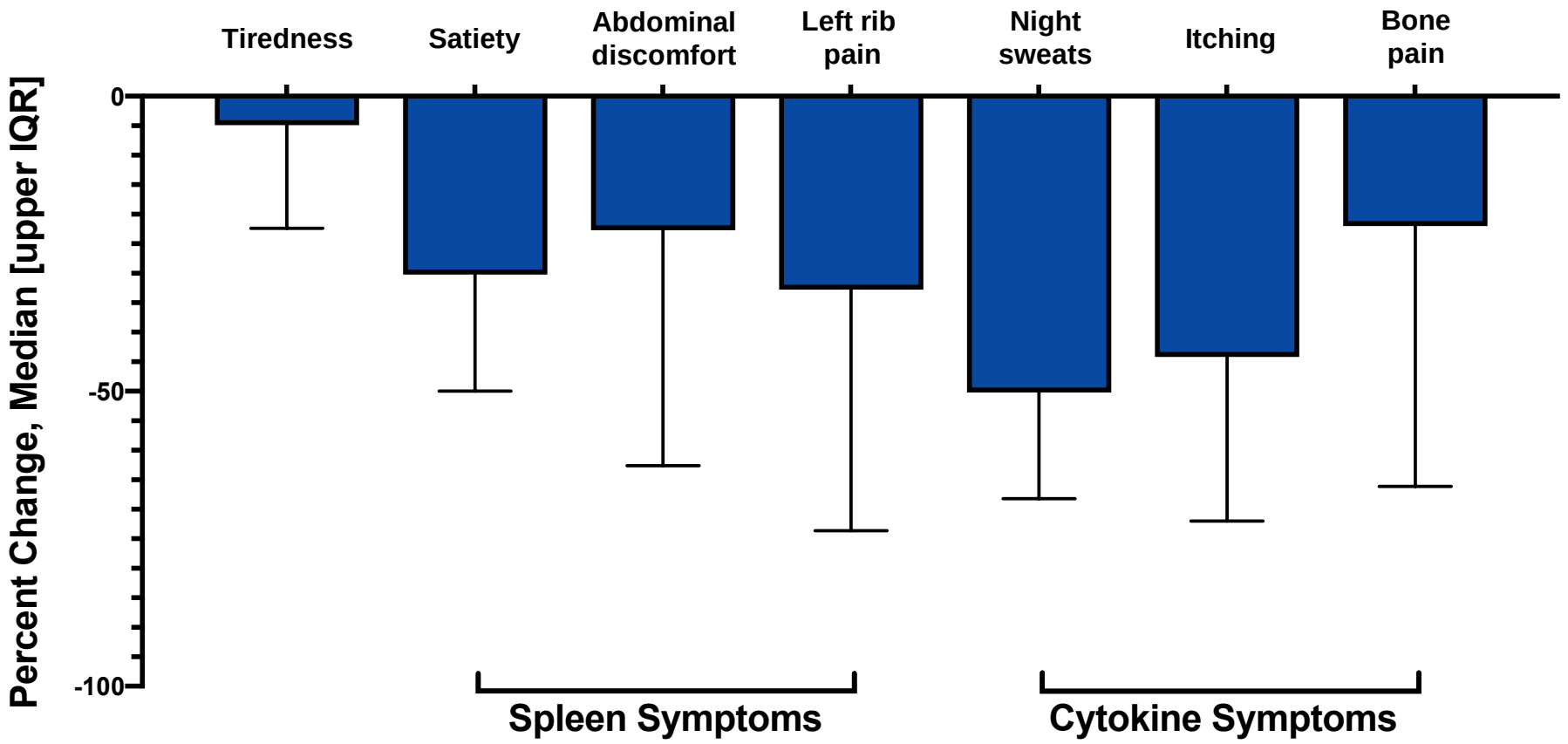
Symptom Improvement at Week 24

Patients with improvement Total Symptom Score (TSS) at Week 24

Dose Group	≥50% TSS reduction	Median TSS reduction (IQR)
100mg QD	4/52 (7.7%)	-3% (-30% to 29%)
100mg BID	4/55 (7.3%)	-16% (-44% to 1%)
200mg BID	4/54 (7.4%)	-27% (-39% to 1%)

IQR, inter-quartile range

Improvement of Individual Symptoms at Week 24



Data shown for 200mg BID arm

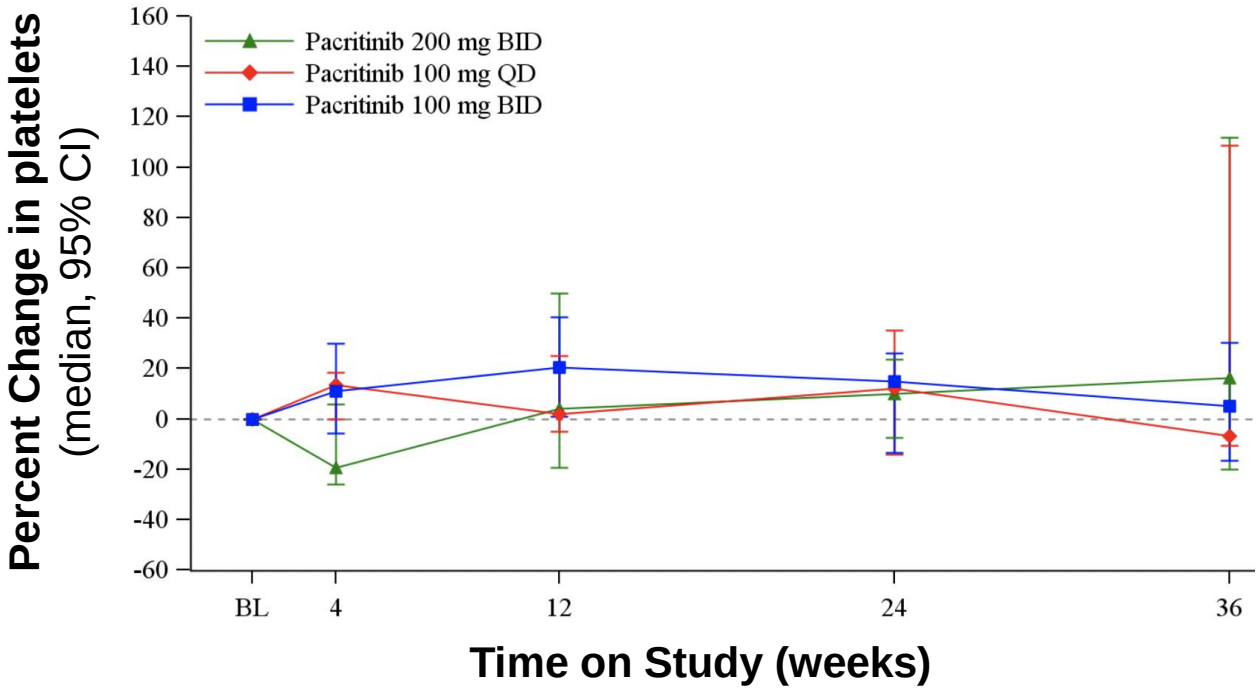
Treatment-Emergent Adverse Events (>12%)

TEAE Term*	100mg QD N=52	100mg BID N=55	200mg BID N=54
Diarrhea	10 (**19.2%**)	12 (**21.8%**)	16 (**29.6%**)
Thrombocytopenia**	11 (**21.2%**)	12 (**21.8%**)	22 (**40.7%**)
Nausea	12 (**23.1%**)	11 (**20.0%**)	15 (**27.8%**)
Fatigue	9 (**17.3%**)	13 (**23.6%**)	13 (**24.1%**)
Abdominal pain	9 (**17.3%**)	6 (**10.9%**)	13 (**24.1%**)
Pyrexia	8 (**15.4%**)	9 (**16.4%**)	7 (**13.0%**)
Anemia	5 (**9.6%**)	6 (**10.9%**)	13 (**24.1%**)
Peripheral edema	7 (**13.5%**)	5 (**9.1%**)	9 (**16.7%**)
Decreased appetite	6 (**11.5%**)	4 (**7.3%**)	10 (**18.5%**)

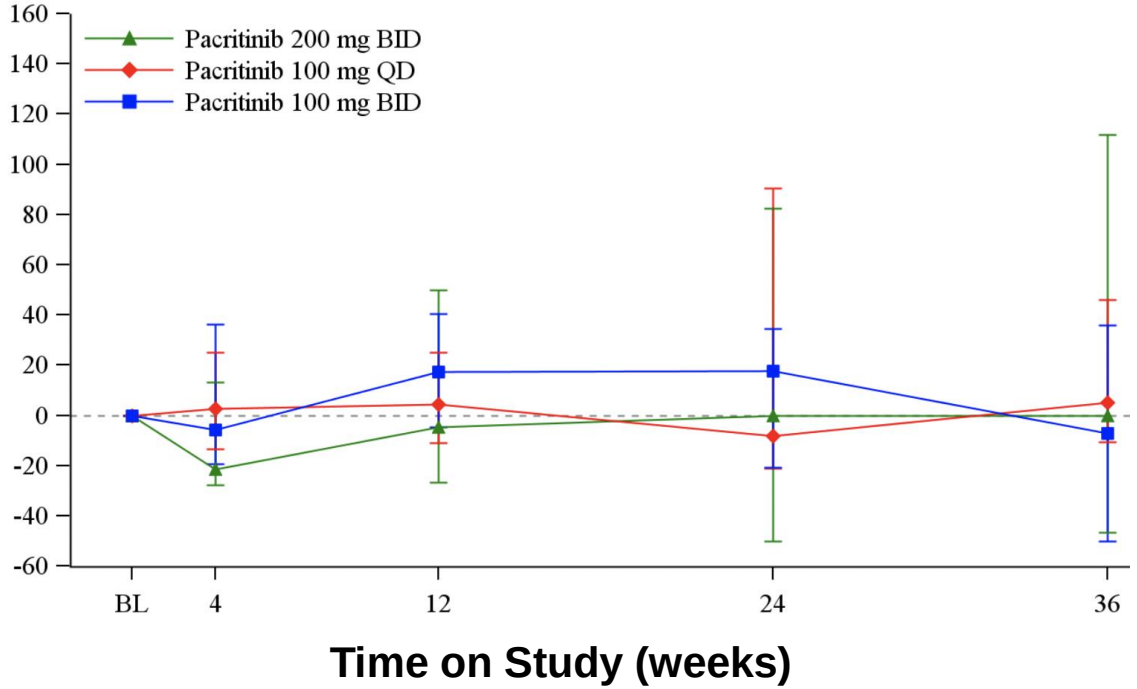
* All events reported regardless of relatedness
** Includes terms '*thrombocytopenia*' and '*platelet count decrease*'

Platelet Count Stability on Study

Overall population



Baseline platelet count <50,000/µL



Dose Arm	Number of subjects									
100mg QD	53	49	38	26	14		24	24	20	13	9
100mg BID	52	44	37	22	11		23	23	16	8	4
200mg BID	55	49	42	24	16		24	23	19	9	6

High-Grade / Serious Treatment-Emergent AEs

TEAE Description	100mg QD N=52	100mg BID N=55	200mg BID N=54
≥1 Grade 3/4	31 (**59.6%**)	33 (**60.0%**)	40 (**74.1%**)
≥1 Serious	19 (**36.5%**)	20 (**36.4%**)	25 (**46.3%**)
≥1 leading to discontinuation	7 (**13.5%**)	12 (**21.8%**)	9 (**16.7%**)
Fatal (Grade 5)	4 (**7.7%**) Sepsis Disease progression Tuberculosis General state deterioration	3 (**5.5%**) Myelofibrosis Subdural hemorrhage Heart failure	3 (**5.6%**) Sepsis Respiratory failure Subdural hematoma

SAE, serious adverse event; **TEAE**, treatment-emergent adverse event

Hemorrhagic TEAEs

Hemorrhage (Worst Grade)	100mg QD N=52	100mg BID N=55	200mg BID N=54
≥1 TEAE	19 (**36.5%**)	14 (**25.5%**)	23 (**42.6%**)
Grade 1	12 (**23.1%**)	11 (**20.0%**)	13 (**24.1%**)
Grade 2	3 (**5.8%**)	2 (**3.6%**)	6 (**11.1%**)
Grade 3	4 (**7.7%**)	0	3 (**5.6%**)
Grade 4	0	0	0
Grade 5	0	1 (**1.8%**)	1 (**1.9%**)

Grade 3 events: muscle hemorrhage [1], epistaxis [3], hematuria [1], hematoma [1], gastrointestinal bleed [1]
Grade 5 events: subdural hematoma [2]

Events determined by Standard MedDRA Query (SMQ).

Cardiac TEAEs

Cardiac AE (Worst Grade)	100mg QD N=52	100mg BID N=55	200mg BID N=54
≥1 TEAE	11 (**21.2%**)	12 (**21.8%**)	22 (**40.7%**)
Grade 1	4 (**7.7%**)	5 (**9.1%**)	12 (**22.2%**)
Grade 2	4 (**7.7%**)	3 (**5.5%**)	8 (**14.8%**)
Grade 3	3 (**5.8%**)	3 (**5.5%**)	2 (**3.7%**)
Grade 4	0	0	0
Grade 5	0	1 (**1.8%**)	0

Grade 3 events: ejection fraction decrease [4], syncope [1], heart failure [1], right arm edema [1], splenic infarction [1]
Grade 5 events: heart failure [1]

Events determined by Standard MedDRA Query (SMQ).

Comparison of TEAEs on PAC203 and PERSIST

Hemorrhagic Event Grade	PAC203 200mg BID N=54	PERSIST-2 200mg BID N=106	PERSIST-2 BAT N=98
Grade 3	5.6%	14.2%	7.1%
Grade 4	0	0	1.0%
Grade 5	1.9%	1.9%	0

Cardiac Event Grade	PAC203 200mg BID N=54	PERSIST-2 200mg BID N=106	PERSIST-2 BAT N=98
Grade 3	3.7%	4.7%	5.1%
Grade 4	0	1.9%	2.0%
Grade 5	0	0	4.1%

BAT, Best Available Therapy (included 19% of patients receiving "**watch and wait**" only)

Events determined by Standard MedDRA Query (SMQ).

PAC203 Study Conclusions

- A dose-response relationship was observed, with greatest efficacy at 200mg BID compared to lower doses
- Spleen volume responses at 200mg BID primarily observed in patients with severe thrombocytopenia (platelet counts <50,000/µL)
- Pacritinib 200mg BID is generally well tolerated, with no excess in high-grade cardiac or bleeding AEs compared to lower doses

Moving Forward with Pacritinib 200mg BID

- Risk-benefit profile of pacritinib 200mg BID supports its use in future studies
  - 200mg BID dose selection supported by dose- and exposure-response modeling based on all available data from PAC203 and prior Phase 3 studies
- The Phase 3 PACIFICA study will compare pacritinib vs. Physician's Choice therapy for patients with MF and severe thrombocytopenia (platelet counts <50,000/µL)[1]
- Risk mitigation measures on PAC203 will be carried forward into the PACIFICA trial

[1] Harrison CN, et al. PACIFICA: A Randomized Phase 3 Study of Pacritinib vs. Physician's Choice in Patients with Myelofibrosis and Severe Thrombocytopenia. ASH 2019 Abstract #4175

Questions?