Characterization of the Pharmacokinetic and Pharmacodynamic Properties of Pacritinib, a Novel Oral JAK2/FLT3 Inhibitor, in Patients with Myelofibrosis, AML and Lymphoma

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BACKGROUND

- Pacritinib is a novel selective JAK2-FLT3 inhibitor with demonstrated antitumor activity in FLT3- dependent (MV4-11 and MOLM-13) and JAK2^{V617F}-dependent (Ba/F3-JAK2^{V617F} and SET-2) xenograft models.
- To date, a total of 4 clinical trials have been completed in patients with advanced malignancies (n=191).
- Two single-dose pharmacokinetic studies in healthy volunteers (n=42) also have been completed.
- Two Phase 3 studies either are on-going (PERSIST-1) or planned (PERSIST-2).

AIMS

- To characterize the PK/ PD profile of pacritinib for further clinical development.

METHODS

- Population PK of pacritinib was characterized following multiple dose administration of pacritinib in patients with advanced myeloid malignancies (NonMem Software, ICON, Ireland).
- Two single-dose PK studies were conducted in healthy volunteers to assess the effect of food on the PK of pacritinib and the inter- and intra-individual PK variability of pacritinib.
- Pooled efficacy data from completed phase 1/2 studies were utilized to construct the exposure-response relationship for the clinical response of pacritinib in myelofibrosis (i.e., best overall response ≥35% reduction in spleen volume).
- To construct the exposure-response relationship, patients with pharmacokinetic samples from phase 2 studies were divided into quartiles [Q1-Q4] based on their model predicted steady-state AUC and the percentage of patients achieving ≥35% spleen volume reduction was determined for each quartile.

RESULTS

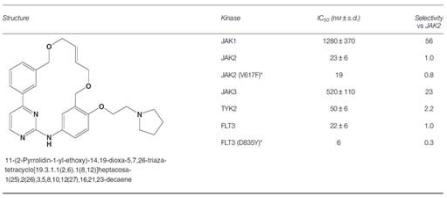
Pharmacodynamics and Clinical Response

- With pacritinib at a 100 mg QD dosing regimen, mean steady-state plasma levels exceeded the in vitro IC_{50} values for inhibition of the targeted kinases (JAK2/FLT3).
- A total of 26 out of 65 (40%) patients who received the 400 mg QD regimen of pacritinib achieved ≥50% reduction in spleen size by physical exam assessed through 24 weeks.

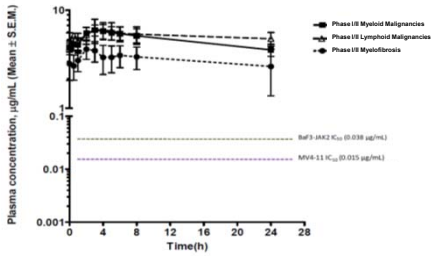
Pharmacokinetics

- The systemic exposure of pacritinib was comparable across the two completed Phase 1/2 studies (SB1518-2007-001 and SB1518-2008-003) in MF patients.
- Pooled analyses of PK assessments from the two completed pacritinib clinical trials in patients treated up to a pacritinib dose of 600 mg QD showed slow absorption (Tmax 4-6 hrs) and dose-related increases in systemic exposure. The results demonstrated a long elimination half-life (mean Day 1 $t_{1/2}$ = 47 hrs), supporting a QD regimen of pacritinib.
- Comparison of drug concentrations on Days 1 and 15 showed a 1.5- to 2-fold increase in exposure at steady-state. There was only minimal increase in systemic exposure at doses beyond 400 mg QD suggesting involvement of a saturable process in oral absorption of pacritinib.
- No additional accumulation of drug was observed after repeated administration over several 28-day cycles. While between-subject variability was relatively high (28-45%), within-subject variability was low (13-15%), highlighting consistent systemic exposure for pacritinib in individual subjects.
- The PK of pacritinib in patients was comparable to that of healthy volunteers.
- Pacritinib is not a PgP substrate and no significant formation (i.e. <10% of parent exposure) of pacritinib metabolites was observed in metabolism studies, indicating limited liability of pacritinib to metabolic and PgP-related drug-drug interactions.
- There is no significant effect of food on pacritinib PK. Pacritinib can be orally administered without regard to timing of meals.

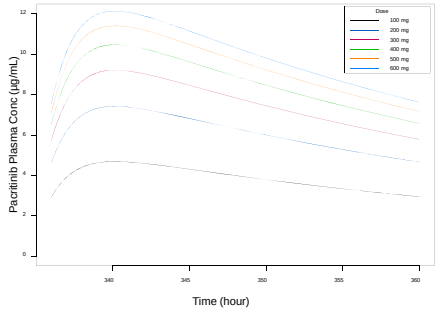
In Vitro Kinase Spectrum of Pacritinib



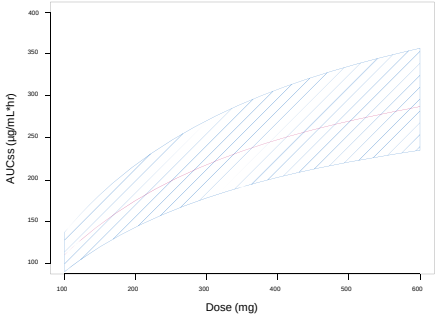
Mean Pacritinib Plasma Concentrations at Steady-State in Patients Receiving 100 mg QD



Simulated Steady-State PK profiles (Pacritinib QD regimen)



AUCss vs. Dose (Mean and 90%C.I.)

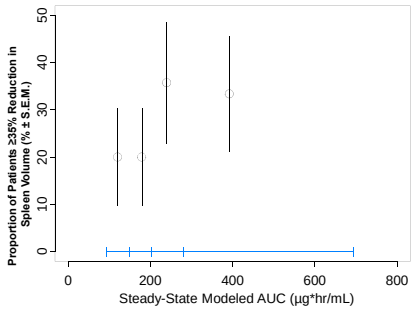


Mean PK Parameters of Pacritinib at Steady-State

QD Dose (mg)		100	150	200	300	400	500	600
	n	3	6	3	6	6	7	6
Cmax (µg/mL)	Mean	6.4	6.7	7.2	6.4	9.8	8.7	9.2
	SD	1.5	3.2	1.0	2.1	4.8	3.8	1.8
$AUC_{0\text{-}24}$ (µg.hr/mL)	Mean	120.3	139.9	148.7	132.9	202.9	178.4	161.3
	SD	31.7	75.2	17.4	50.2	103.9	87.6	72.9
Tmax (hr)	Median	3	2.5	5	4	5	4	4
Ctrough (µg/mL)	Mean	3.9	5.4	5.6	5.0	8.4	6.6	6.4
	SD	1.0	3.0	0.9	2.3	4.8	3.8	2.4

*Data from Study SB1518-2007-001, day 15

Exposure-Response Relationship for Pacritinib by Exposure Quartile



Note: the horizontal blue line indicates the cutpoints of exposure quartiles for binning the data

SUMMARY AND CONCLUSIONS

- The exposure-response relationship for pacritinib supports selection of the 400 mg QD regimen of pacritinib in phase 3 pivotal trials.
- Overall, the efficacy and favorable PK/PD profile of pacritinib along with its relative lack of suppression of platelet and red cell production (See Pacritinib Safety Poster #P278), even in patients with severe cytopenias, support further clinical development of pacritinib in myelofibrosis.
- Ongoing phase 3 studies of pacritinib in myelofibrosis do not restrict study entry due to thrombocytopenia or anemia and allow enrollment of platelet and RBC transfusion dependent patients.

REFERENCES

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