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 JAK2V617F-dependent (Ba/F3-JAK2V617F and SET-2) xenograft models.
- To date, a total of 4 clinical trials have been completed in patients with advanced malignancies (n=193).
- Two single-dose pharmacokinetic studies in healthy volunteers (n=42) also have been completed.
- Two Phase 3 studies either are on-going (PERCIST-1) or planned (PERCIST-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 plasma levels exceeded the in vitro IC50 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 ≥35% spleen volume reduction 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 IC50 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 ≥35% 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 t1/2 = 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 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.

REFERENCES


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 PKPD 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.