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Pharmacokinetics and Safety of Pacritinib in Patients with Hepatic Impairment and Healthy Volunteers

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Abstract : Pacritinib is an oral kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R. In clinical studies, pacritinib was well tolerated with clinical activity in patients with myelofibrosis. The most frequent adverse events (AEs) observed with pacritinib are gastrointestinal (diarrhea, nausea, and vomiting; mostly grade 1-2 in severity) and typically resolve within 2 weeks. A human ADME mass balance study demonstrated that pacritinib is predominantly cleared via hepatic metabolism and biliary excretion (>85% of administered dose). The major hepatic metabolite identified, M1, is not thought to materially contribute to the pharmacological activity of pacritinib. Hepatic diseases are known to impair hepatic blood flow, drug-metabolizing enzymes, and biliary transport systems and may affect drug absorption, disposition, efficacy, and toxicity. This phase 1 study evaluated the pharmacokinetics (PK) and safety of pacritinib and the M1 metabolite in study subjects with mild, moderate, or severe hepatic impairment (HI) and matched healthy subjects with normal liver function to determine if pacritinib dosage adjustments are necessary for patients with varying degrees of hepatic insufficiency. Study participants (aged 18-85 y) were enrolled into 4 groups based on their degree of HI as defined by Child-Pugh Clinical Assessment Score: mild (n=8), moderate (n=8), severe (n=4), and healthy volunteers (n=8) matched for age, BMI, and sex. Individuals with concomitant renal dysfunction or progressive liver disease were excluded. A single 400 mg dose of pacritinib was administered to all participants. Blood samples were obtained for PK evaluation predose and at multiple time points postdose through 168 h. Key PK parameters evaluated included maximum plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration time curve (AUC) from hour zero to last measurable concentration (AUC0-t), AUC extrapolated to infinity (AUC0-∞), and apparent terminal elimination half-life (t1/2). Following treatment, pacritinib was quantifiable for all study participants at 1 h through 168 h postdose. Systemic pacritinib exposure was similar between healthy volunteers and individuals with mild HI. However, there was a significant difference between those with moderate and severe HI and healthy volunteers with respect to peak concentration (Cmax) and plasma exposure (AUC0-t, AUC0-∞). Mean Cmax decreased by 47% and 57% respectively in participants with moderate and severe HI vs matched healthy volunteers. Similarly, mean AUC0-t decreased by 36% and 45% and mean AUC0-∞ decreased by 46% and 48%, respectively in individuals with moderate and severe HI vs healthy volunteers. Mean t1/2 ranged from 51.5 to 74.9 h across all groups. The variability on exposure ranged from 17.8% to 51.8% across all groups. Systemic exposure of M1 was also significantly decreased in study participants with moderate or severe HI vs. healthy participants and individuals with mild HI. These changes were not significantly dissimilar from the inter-patient variability in these parameters observed in healthy volunteers. All AEs were grade 1-2 in severity. Diarrhea and headache were the only AEs reported in >1 participant (n=4 each). Based on these observations, it is unlikely that dosage adjustments would be warranted in patients with mild, moderate, or severe HI treated with pacritinib.

Keywords : pacritinib, myelofibrosis, hepatic impairment, pharmacokinetics
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