A First in man study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of RP7214, a Dihydroorotate Dehydrogenase (DHODH) inhibitor in Healthy Subjects

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Abstract

RP7214 is a potent and selective inhibitor of human mitochondrial enzyme dihydroorotate dehydrogenase (DHODH). This paper describes the results from a Phase 1 study that evaluated safety and pharmacokinetics of single and multiple ascending doses (SAD and MAD) and the food effect of RP7214 in healthy subjects. Target engagement of DHODH was also evaluated. A randomized, double-blind, placebo-controlled trial of single-dose (100, 200, and 400 mg QD) and multiple doses (200 and 400 mg BID for 7 days) followed by food effect at a single dose of 200 mg was conducted. A total of 18 healthy volunteers (HVs) (6 subjects in each of three cohorts) in the SAD part, 12 (6 subjects each in two cohorts) in the MAD part, and 12 in the food effect study were enrolled. RP7214 was well tolerated at all dose levels. None of the subjects reported any RP7214-related adverse events. RP7214 showed dose-proportional pharmacokinetics after single and multiple dosing. Steady-state concentrations were reached within about 3–6 days. The mean plasma half-life of RP724 at steady-state was approximately 13h. RP7214 showed accumulation on multiple dosing.. Food did not impact the absorption of RP7214. RP7214 showed dose-dependent inhibition of DHODH as measured by analyzing accumulating DHO levels, confirming target engagement. The rapid absorption and high systemic exposure of RP724 with a favorable safety profile shows the potential for the development of RP7214 in SARS-CoV-2 infection and acute myeloid leukemia. (NCT04680429). Keywords: RP7214, dihydroorotate dehydrogenase, SAD, MAD, HV

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