Effect of renal impairment on iptacopan pharmacokinetics

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Background and aims

Iptacopan (LNP023) is a first-in-class, oral, proximal complement inhibitor that specifically binds to Factor B and inhibits the alternative complement pathway (AP). Current Phase III studies of iptacopan focus on diseases associated with AP activation, such as paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis (C3G), IgA nephropathy (IgAN), and atypical hemolytic uremic syndrome. The liver is the primary route of iptacopan elimination. Based on a previous healthy volunteer pharmacokinetic (PK) study, the contribution of the renal route of iptacopan elimination was measured to be low, approximately 14%. A population PK (PopPK) analysis was done to further quantify the effect of renal impairment on iptacopan PK.

Methods

A PopPK dataset pool was created by pooling across 6 Phase II/III studies in PNH, C3G, and IgAN indications. The pool comprised patient data on the two highest dose levels (100 and 200 mg bid) and included 2439 datapoints in 234 unique patients. Factors (baseline characteristics) that could possibly affect exposure, body weight, age, gender, ethnicity, and eGFR (mL/min/1.73m^2) at baseline were investigated. The range of eGFR was 27.4 to 142.8 mL/min/1.73 m^2. Age, ethnicity, and body weight were included as the significant covariates in the final model.

Results

The median eGFR was 87.5 mL/min/1.73 m^2. As shown in the table below, the PopPK model detected a significant ($p=4.3x10^{-11}$) but modest effect of eGFR on simulated mean AUC_{0-24}. At an eGFR of 34.3, AUC_{0-24} is expected to increase by only 38%, compared with median eGFR. Changes of eGFR of ≤15% with respect to median eGFR were observed with eGFR range between 59.7 and 132.0 mL/min /1.73m^2.

Varying covariate	eGFR	Percentile	Relative change in mean AUC_{0-24}
eGFR	34.3	5th	1.38
	59.7	25th	1.14
	87.5	50th	1.00 (Reference)
	112.0	75th	0.92
	132.0	95th	0.87

Conclusions

Consistent with previously observed primarily hepatic clearance of iptacopan in preclinical and clinical studies, renal impairment down to an eGFR of 34.3 did not have a clinically meaningful effect on iptacopan PK. Currently, iptacopan PK in patients with eGFR <30 mL/min/1.73 m^2 is being explored. These results support the use of iptacopan in patients with mild and moderate renal impairment.