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Effect of renal impairment on iptacopan pharmacokinetics

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INTRODUCTION

- Iptacopan (LNP023) is an oral, proximal complement inhibitor that specifically binds to Factor B and inhibits the alternative complement pathway[1,2]
- Current Phase III studies of iptacopan focus on diseases associated with alternative pathway dysregulation, such as paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulopathy (C3G), IgA nephropathy (IgAN), atypical hemolytic uremic syndrome and immune complex-mediated membranoproliferative glomerulonephritis[3–9]
- The liver is the primary route of iptacopan elimination[10]

AIM

- Based on a previous healthy volunteer pharmacokinetic (PK) study, the contribution of the renal route of intact iptacopan elimination was measured to be low, approximately 14%
- A population PK (PopPK) analysis was carried out to further quantify the effect of renal impairment on iptacopan PK

METHOD

- 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 twice daily [bid]) and included 2,439 datapoints in 234 unique patients. Factors (baseline characteristics) that could possibly affect exposure, body weight, age, gender, ethnicity, and estimated glomerular filtration rate (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, body weight and eGFR were included as the significant covariates in the final model.

RESULTS

- The final modeling dataset (doses 100 and 200 mg bid) consisted of 159 (68%) PNH patients, 48 (21%) IgAN patients, and 27 (12%) C3G patients
- More than half of the modeling population presented with mild (27%), moderate (24%) or severe renal impairment (3%), while 46% of the patients had normal eGFR levels
- Mean eGFR (range) was 84.8 (27.45–142.76) mL/min/1.73m^2
- The median eGFR was 87.5 mL/min/1.73 m^2
- As shown in **Table 1**, the PopPK model detected a significant (p=9.9x10^{-13}) but modest effect of eGFR on simulated mean AUC$_{0\text{-}24}$
- At an eGFR of 34.3, AUC$_{0\text{-}24}$ 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
- **Figure 1** provides a visualization of these eGFR effects on PK concentration-time profiles in simulated patients, relating the changes attributed to eGFR (colored lines) to the inter-patient variability of iptacopan exposure (grey shaded area)
- It can therefore be concluded that changes in exposure attributed to eGFR are small compared to the overall variability

Varying covariate	eGFR	Percentile	Relative change in mean AUC$_{0\text{-}24}$
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

Table 1. Simulated AUC$_{0\text{-}24}$ (day*ng/mL) as function of eGFR (mL/min/1.73 m^2) covariate using final model (on 100 and 200 mg bid).

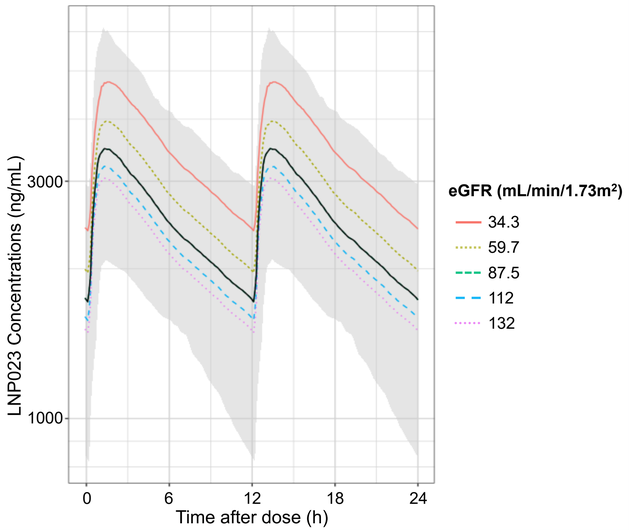

Figure 1. Iptacopan (LNP023)-simulated profiles from final model for a typical patient (shaded area 90% prediction interval and median in black) overlaying with range of eGFR values (h, hours).

CONCLUSIONS

- Consistent with previously observed primarily hepatic clearance of iptacopan in preclinical and clinical studies,[10] 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
- Iptacopan dose adjustment is not required in patients with mild or moderate renal impairment

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