Assessment of drug interactions with Iptacopan

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Introduction

Iptacopan (LNP023) is a first-in-class, oral, low molecular weight, Factor B inhibitor being developed for the treatment of diseases associated with activation of the alternative complement pathway. Current Phase III studies of iptacopan include; paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis, IgA nephropathy, and atypical hemolytic uremic syndrome. Preclinical studies identified CYP2C8, OATP and P-gp as three potential sources of drug-drug interaction with iptacopan either as a victim or a perpetrator. Given the complex medical management of patients with these diseases, a drug interaction study of iptacopan with clopidogrel (CYP2C8 inhibitor), cyclosporine (OATP inhibitor), digoxin (P-gp substrate), and rosuvastatin (OATP substrate) was conducted.

Methods

A total of 56 healthy participants where enrolled into three separate cohorts of 17-21 participants per cohort to study the following interactions: iptacopan as a victim of CYP2C8 or OATP inhibition, and iptacopan as a perpetrator of P-gp and OATP inhibition. The probe victim or perpetrator drugs used are shown in the table below. All perpetrator drugs used, including iptacopan 200 mg BID, were dosed to steady-state. Iptacopan 100 mg single dose was used as a victim drug.

Results

Iptacopan treatment was safe and well tolerated. The geometric mean (90%CI) ratio of baseline to on-treatment maximal concentration (Cmax) and area under the concentration curve from time 0 to infinity (AUCinf) is shown below for the four different drug-drug interaction experiments. In all four cases, no or only minimal (mean change of ≤ 50%) level of drug-drug interaction was observed.

			Geo-metric mean ratio (90%CI)	
Iptacopan status	Pathway tested	Probe drug	Cmax	AUCinf
Victim	CYP2C8	Clopidogrel	1.05 (0.97-1.14)	1.36 (1.28-1.45)
Victim	OATP	Cyclosporine	1.41 (1.35-1.47)	1.50 (1.42-1.59)
Perpetrator	P-gp	Digoxin	1.08 (0.94-1.24)	1.02 (0.93-1.12)
Perpetrator	OATP	Rosuvastatin	1.00 (0.87-1.15)	1.01 (0.91-1.12)

Conclusion

These results are consistent with oral iptacopan having no clinically meaningful drug-drug interactions. Given that iptacopan is not a narrow therapeutic index drug, the mean increase in iptacopan exposure of ≤ 50% when iptacopan was studied as a victim drug of CYP2C8 or OATP inhibition is not considered clinically meaningfully. Iptacopan as a perpetrator drug did not result in significant inhibition of other drugs transported by P-gp or OATP. These results provide reassurance that iptacopan can be used in patients on complex drug regimens without resulting in clinically relevant, iptacopan related, drug-drug interactions.