Assessment of drug interactions with iptacopan

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Introduction

Iptacopan (LNP023) is an oral, first-in-class, low molecular weight inhibitor of Factor B in clinical development for the treatment of diseases associated with activation of the alternative complement pathway. Phase 3 studies of iptacopan are ongoing in paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis, IgA nephropathy, and atypical hemolytic uremic syndrome. Preclinical studies identified CYP2C8, OATP and P-gp as potential sources of drug–drug interactions with iptacopan that warranted clinical investigation.

Methods

In total, 56 healthy participants were enrolled into three separate cohorts (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 or OATP inhibition. Test compounds used are shown (Table). All perpetrator drugs, including iptacopan 200 mg twice daily, were dosed to steady state. A single dose of iptacopan 100 mg was used as a victim drug.

Results

Treatment with iptacopan treatment was well tolerated. Mean (standard deviation [SD]) oral drug clearance (CL/F) and volume of distribution (Vz/F) are shown for the four different drug–drug interactions (Table). In all cases, there was no significant change in how the drug was cleared from the body (CL/F) or distributed (Vz/F).

			PK Parameter, mean (SD)	
Iptacopan Status	Pathway Tested	Probe Drug	CL/F (L/hr)	Vz/F (L)
Victim	CYP2C8	Iptacopan alone	3.72 (0.934)	89.5 (31.6)
		Iptacopan + Clopidogrel	2.72 (0.755)	82.6 (13.8)
	OATP	Iptacopan alone	3.87 (1.03)	87.5 (19.7)
		Iptacopan + Cyclosporine	2.75 (0.851)	91.8 (15.3)
Perpetrator	P-gp	Digoxin alone	16.5 (3.86)	997 (281)
		Digoxin + Iptacopan	16.3 (3.97)	970 (230)
	OATP	Rosuvastatin	166 (86.8)	3270 (2190)
		Rosuvastatin + Iptacopan	164 (76.0)	2910 (1160)

Conclusion

These data show that iptacopan has no relevant effect on the systemic exposure of P-gp or OATP transported drugs, and CYP2C8 or OATP inhibition have a ≤50% effect on systemic exposure of iptacopan. This finding provides reassurance that iptacopan can be used in patients on complex drug regimens without clinically relevant, iptacopan-related drug–drug interactions.

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Theme

The Kidney Losing Function: Dialysis, CKD-MBD, Anemia and Interventional Nephrology

Topic

CKD, experimental models, biomarkers, precision medicine

Key words (5 maximum)

complement, iptacopan, C3G, IgAN, DDI

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