Pharmacokinetics of single doses of 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. The pharmacokinetics (PK) of oral iptacopan were measured in healthy subjects to determine its capacity to deliver therapeutic (~1000 ng/mL) systemic exposure.

Methods

In this randomized, blinded study, a total of 56 healthy participants were enrolled into seven iptacopan single-dose treatment groups (5–400 mg, n=6 per group) or a placebo group (n=14). Plasma iptacopan concentration was measured at 17 timepoints over 4 days using a validated LC-MS/MS assay (LLOQ=1 ng/mL).

Results

Iptacopan treatment was well tolerated at all dose levels. Iptacopan was rapidly absorbed, with a median T_{max} of approximately 1 hour. The mean half-life was moderately long at 14–18 hours. The intersubject variability (CV%) of iptacopan C_{max} and AUC_{inf} were low, at approximately 11–33%, and both parameters were slightly under dose proportional with increasing dose.

	5 mg N=6	10 mg N=6	25 mg N=6	50 mg N=6	100 mg N=6	200 mg N=6	400 mg N=6
AUCinf (hr*ng/mL)	5300 (24.2%)	8440 (24.6%)	12700 (23.0%)	17500 (21.3%)	25600 (31.5%)	36500 (33.2%)	61200 (25.9%)
CL/F (mL/hr)	999 (27.4%)	1240 (23.3%)	2050 (20.7%)	2950 (18.0%)	4170 (24.0%)	6040 (34.0%)	6970 (29.3%)
Cmax (ng/mL)	466 (15.1%)	714 (19.0%)]	994 (21.2%)	1370 (11.4%)	1980 (23.2%)	3230 (26.2%)	5070 (25.9%)
T1/2 (hr)	14.0 (17.0%)	15.2 (14.6%)	15.5 (33.5%)	18.4 (27.9%)	13.5 (19.0%)	18.0 (55.7%)	17.3 (17.6%)
Tmax (hr)	1.01	1.00	1.13	1.26	1.00	1.13	1.25
Vz/F (mL)	20100 (34.8%)	26900 (20.3%)	46400 (49.1%)	78800 (37.5%)	79900 (26.1%)	138000 (27.6%)	170000 (22.3%)

Conclusion

Iptacopan PK manifested a rapid absorption phase, low intersubject variability and moderately long half-life. A 200 mg twice daily (BID) dose would be expected to result in an iptacopan concentration of ≥1000 ng/mL over the dosing interval, and thus near maximal alternative complement pathway inhibition over this time. These results support the iptacopan clinical dose of 200 mg BID and provide the promise of durable, orally-dosed alternative complement pathway inhibition in patients on iptacopan therapy.

This abstract was also submitted for the NKF'23 congress. By submitting the abstract to WCN'24, abstract authors declare that re-submitting the abstract is permitted by the organizers of the previous meeting.

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, Factor B, IgAN, C3G

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