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Human pharmacokinetics of multiple, steady-state dosing of iptacopan

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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]
- Early modeling efforts suggest that an iptacopan concentration of ~1000 ng/mL would provide near-maximal AP inhibition

AIM

- The aim of this first-in human study was to evaluate the safety, tolerability, and pharmacokinetics (PK) of ascending single and multiple oral doses of iptacopan in healthy participants
- Data from this study will support further clinical development of iptacopan

METHOD

- This was a blinded, controlled, randomized study
- Safety assessments included collecting all adverse events (AEs), serious AEs, monitoring of kidney and liver safety, assessment of pregnancy and fertility and vital signs
- PK samples were collected at defined timepoints
- Iptacopan in plasma was determined by a validated LC-MS/MS method; the Lower Limit of Quantification (LLOQ) was 1 ng/mL

RESULTS

- In total, 32 healthy subjects were enrolled into 5 cohorts receiving placebo (n=8) or iptacopan 25, 50, 100, or 200 mg bid (n=6 per group) for 14 days
- Demographic data were similar across treatment groups. Most (95%) subjects were white, predominantly male, with a median (range) age of 47 (21-55) years and a mean (SD) BMI of 2.53 (2.37) kg/m^2
- Iptacopan treatment showed a good safety profile and was well tolerated at all dose levels, with no serious or significant adverse events
- After multiple oral dose administration iptacopan, plasma concentrations increased rapidly and dose-dependently (**Figure 1**)
- Median, steady state T_{max} ranged from 0.88 to 1.75 h indicating rapid absorption
- With the 8-fold increase in iptacopan dose from 25 to 200 mg, C_{max} and AUC_{tau} increased by a factor of 3.7 and 2.8, respectively
- C_{max} at steady state was 1.10 to 1.49 times greater than that observed after the initial dose on Day 1. The calculated, mean accumulation ratio based on AUC_{tau} ranged from 1.35 to 1.61
- $T_{1/2}$ at steady state ranged from 18.4 to 25.0 h
- The AUC_{tau} steady state CV% was < 17%
- At all time points from 0 to 12 h, iptacopan concentration with the 200 mg bid dose was >1000 ng/mL (**Figure 2**)

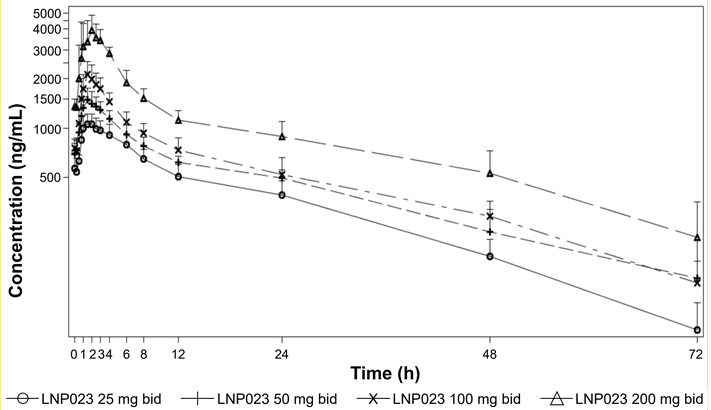

Figure 1. Steady-state concentration-time curves of iptacopan at multiple oral doses (25, 50, 100 and 200 mg bid) on Day 14 (h, hours).

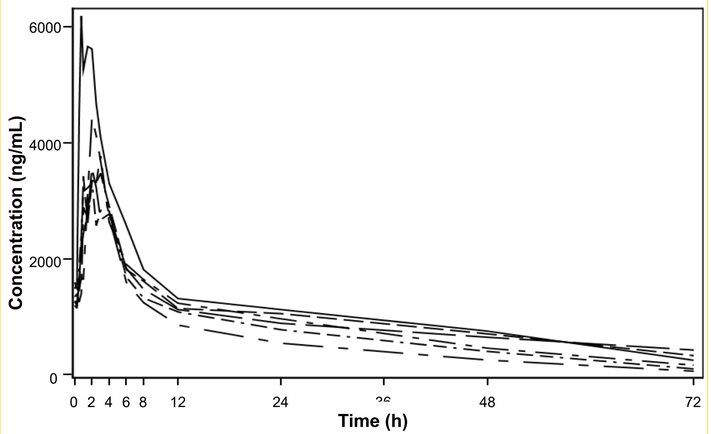

Figure 2. Overlaying individual concentration-time profiles in participants treated with iptacopan 200 mg bid on Day 14.

CONCLUSIONS

- Iptacopan was rapidly absorbed with low inter-subject variability, and a moderately long half-life
- Only the 200 mg bid dose produced mean iptacopan concentrations of ≥1000 ng/mL over the 12 hr dosing intervals, and thus is expected to result in near-complete, continuous AP inhibition with 200 mg bid dosing
- These results support the rationale for use of iptacopan 200 mg twice daily as the therapeutic dose in ongoing clinical trials and provide evidence of durable AP inhibition in patients administered oral iptacopan therapy

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