Human pharmacokinetics of multiple, steady-state dosing of iptacopan

Robert Schmouder[1], Guido Junge[2], Prasanna Kumar Nidamarthy[3], and Kenneth Kulmatycki[4]

[1]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [4]Novartis Institutes of BioMedical Research, Cambridge, MA, USA

Background and aims

Iptacopan (LNP023) is a first-in-class, oral, proximal complement inhibitor that specifically binds to Factor B and inhibits the alternative complement pathway (AP). Current Phase III studies of iptacopan focus on diseases associated with AP activation, such as paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis, IgA nephropathy, and atypical hemolytic uremic syndrome. Early modeling efforts suggested that an iptacopan concentration of ~1000 ng/mL would provide near-maximal AP inhibition. The aim of this study was to evaluate the PK of oral iptacopan in healthy subjects to determine the dose that results in a ~1000-ng/mL mean steady-state concentration over the entire 12-h dosing interval.

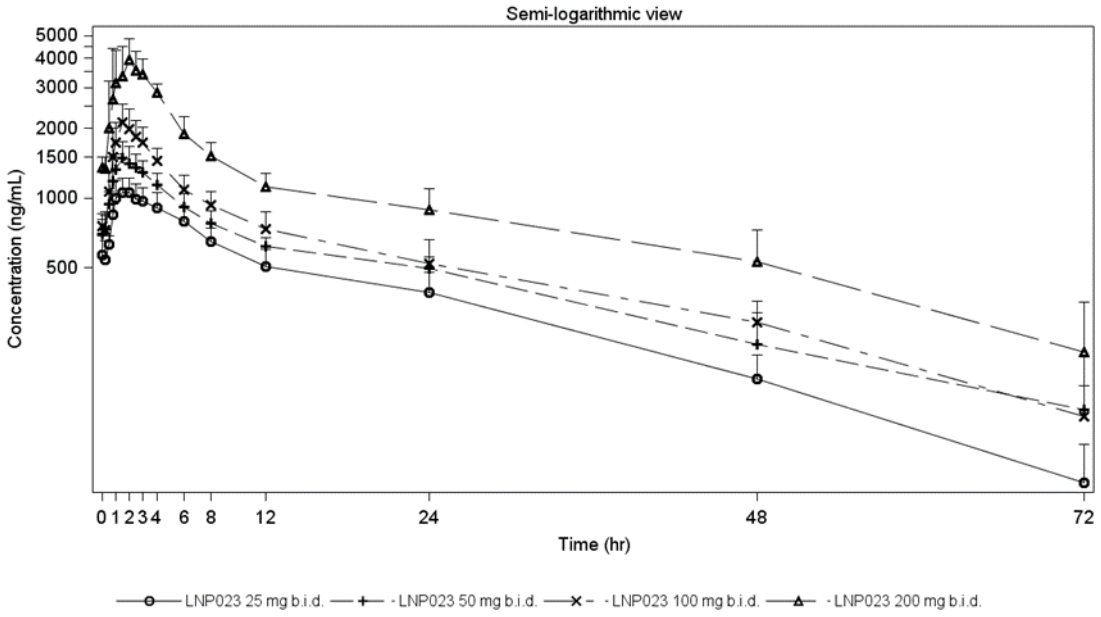
Methods

In this blinded, controlled, randomized study, a total of 32 healthy subjects were enrolled into 5 cohorts receiving twice-daily dosing for 14 days: placebo (n=8) or iptacopan 25, 50, 100, or 200 mg (n=6 per group). Plasma iptacopan concentration was intensively measured for 72 hours post day 14 dose using a validated LC-MS/MS assay (LLOQ=1 ng/mL).

Results

Iptacopan treatment was safe and well tolerated at all dose levels. Iptacopan steady-state concentration-time curves are shown below. Iptacopan was rapidly absorbed, with a median T_{max} of approximately 2 hours (Figure). The mean half-life was moderately long at 18 to 25 hours. The inter-subject variability (CV%) of iptacopan C_{max} and AUC_{inf} was low at approximately 12% to 27%, and both parameters were under-dose proportional with increasing dose. At all time points from 0 to 12 hours, mean iptacopan concentration for the 200-mg dose cohort was >1000 ng/mL.

Figure: Steady-state concentration-time curves of iptacopan



Conclusions

Iptacopan was rapidly absorbed, had low inter-subject variability, and a moderately long half-life. Only the 200-mg b.i.d dose produced mean iptacopan concentrations of ≥1000 ng/mL over the dosing interval, and thus is expected to result in near-complete, continuous AP inhibition. 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.