Absorption and disposition of a first-in-class alternative complement pathway Factor B inhibitor: Iptacopan

Robert Schmouder[1], Bharti Shah[1], Melissa Hackling[1], Alexander David James[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

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 glomerulopathy, IgA nephropathy, and atypical hemolytic uremic syndrome. This study was conducted to characterize the absorption and disposition characteristics of iptacopan in humans.

Methods

A single 100 mg dose of [^{14}C]iptacopan was given orally to six healthy male participants. Post dose, participants were domiciled and urine, feces and blood were collected for 10 days. Mass balance was measured by total radioactivity in urine and feces in addition to urine parent iptacopan concentration. Plasma concentration of iptacopan and its key metabolites, in addition to total radioactivity in blood and plasma, were also measured. Quantitative metabolite profiling in plasma and excreta samples was also performed.

Results

Iptacopan was safe and well tolerated. Iptacopan 100 mg was rapidly absorbed with a median Tmax of 1.51 hours. The maximal plasma concentration of iptacopan (Cmax) ranged from 1710 to 2360 ng/mL and the area under the concentration curve from time 0 to infinity ($AUC_{0-\infty}$) ranged from 17487 to 29493 h*ng/mL. The mean plasma elimination half-life of iptacopan and total radioactivity were comparable (12.5 and 14.9 hr), respectively. Mean plasma iptacopan $AUC_{0-\infty}$ was approximately 83% of mean plasma total radioactivity $AUC_{0-\infty}$, indicating limited exposure to metabolites. Total radioactivity exposure was higher in plasma than in blood, indicating preferential distribution of iptacopan and metabolites towards plasma rather than blood cells.

On average 24.7% of radioactivity was recovered in the urine within 72 h post dose and 71.1% of radioactivity was recovered from feces within 120 h post dose. Mean total recovery was 96.4% of the dose. Two acyl glucuronide metabolites were detected in plasma at levels <10% of total circulating drug related material. Metabolite profiling in excreta showed metabolites formed by oxidative pathways accounted for approximately 50% of the administered dose. Mean oral absorption was estimated to be 70.6% of dose (24.8% of urinary excreted radioactivity plus 45.8% of dose in feces attributable to metabolites).

Conclusion

These results are consistent with oral iptacopan being rapidly and highly (>70%) absorbed in humans. The variability of systemic iptacopan exposure between subjects was low providing evidence of predictable drug exposure. The half-life is moderately long allowing a dosing interval of approximately 12 hours. Systemic exposure to short lived metabolites of iptacopan was low. Metabolism of iptacopan was mainly oxidative, with a likely smaller contribution from direct acyl glucuronidation. These results support favorable absorption and disposition characteristics of iptacopan that promise consistent and predictable systemic exposure in patients receiving this novel therapy.