Japanese and Whites share similar iptacopan pharmacokinetics and pharmacodynamics

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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. These studies are enrolling patients across geographical regions and ethnicities, including those from Japan. The aim of this study was to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of iptacopan in Japanese patients.

Methods

CLNP023X1102 was a randomized, subject-blinded, placebo-controlled, single-dose Phase I study conducted in Japan in healthy Japanese male subjects to assess safety, tolerability, PK, and AP blood biomarkers (Wieslab, Bb) in three dose cohorts, 25, 100, and 400 mg (8 active/2 placebo per cohort). Subjects were dosed on day 1 and observed for 96 hours post-dose. PK and PD data from this study was compared to White data from the similarly designed, previous CLNP023X2101 first-in-human study.

Results

Iptacopan was well tolerated in both Japanese and White subjects. White subjects were on average 15.7 years older and 19.5 kg heavier than Japanese subjects. Iptacopan mean(±SD) Cmax and AUC_{inf} as well as mean(±SD) % change from baseline at 12 hours post-dose for Wieslab and Bb by dose are shown in the table below. All three dose groups manifested a general trend of increased systemic exposure and increased AP biomarker inhibition with increasing dose in both Japanese and White subjects.

Table: PK parameters and PD of iptacopan in Japanese and White patients

Dose	Parameter	Japanese Mean (± SD) [N]	White Mean (± SD) [N]
25 mg	Cmax (ng/mL)	1160±254 [8]	994±211[6]
	AUC_{inf} (ng*h/mL)	12500±3300 [8]	12700±2910
	Wieslab (%)	−27.6±11.84 [8]	−50.7±21.617 [6]
	Bb (%)	−29.7±13.78 [8]	−31.5
100 mg	Cmax (ng/mL)	2460±735 [8]	1980±459 [6]
	AUC_{inf} (ng*h/mL)	28700±9170 [8]	25600±8050 [6]
	Wieslab (%)	−66.0±9.97 [7]	−72.5±29.357 [6]
	Bb (%)	−35.3±10.81 [8]	−42.9
400 mg	Cmax (ng/mL)	7990±1360 [8]	5070±1310 [6]
	AUC_{inf} (ng*h/mL)	73500±14300 [8]	61200±15800 [6]
	Wieslab (%)	−83.3±6.32 [8]	−83.8±9.082 [6]
	Bb (%)	−26.5±11.56 [8]	−49.7

Conclusions

Japanese and White healthy subjects had similar PK and PD results at all dose levels. The slightly higher Cmax and AUC_{inf} in Japanese subjects may be explained in part by the lower average weight of these

subjects. This study provides reassurance that there are no clinically meaningful differences in the human pharmacology of iptacopan between these ethnic groups.