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Japanese and Whites share similar iptacopan pharmacokinetics and pharmacodynamics

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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 (AP) dysregulation, such as paroxysmal nocturnal hemoglobinuria, C3 glomerulopathy, IgA nephropathy, atypical hemolytic uremic syndrome and immune complex-mediated membranoproliferative glomerulonephritis[3–9]
- These studies are enrolling patients across geographical regions and ethnicities, including Japan

AIM

- To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of iptacopan in Japanese patients

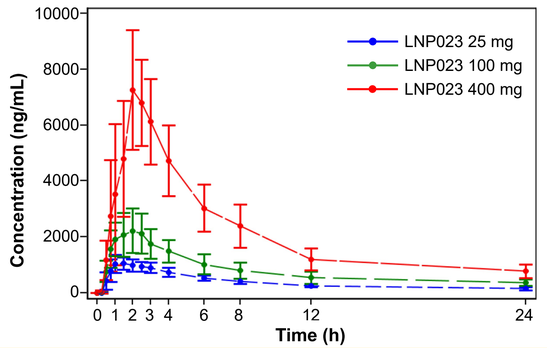
METHOD

- A randomized, subject-blinded, placebo-controlled, single-dose Phase I study (CLNP023X1102) was 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 iptacopan (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 were compared with data from White participants in the similarly designed first-in-human study (CLNP023X2101)[10,11]

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
- Following a single oral dose (25, 100 and 400 mg) of iptacopan, plasma concentrations increased with dose with a median T_{max} from 1.50 to 2.25 h post-dose (**Figure 1**), indicating rapid absorption. The systemic exposure (C_{max} and AUC) to iptacopan increased with dose. After T_{max}, plasma concentrations decreased with a mean apparent T1/2 of 13.2 to 24.7 hours (h)

Figure 1. Mean (SD) plasma concentration–time profile (0–24 h)



- Following iptacopan administration, a sharp reduction (>80%) in AP activity was observed from baseline to 2 h post-dose for all Japanese dose groups (**Figure 2**)
- Iptacopan mean C_{max} and AUC_{inf} as well as mean percentage change from baseline at 12 h post-dose for Wieslab and Bb by dose are shown in **Table 1**
  - All three dose groups demonstrated a general trend of increased systemic exposure and increased AP biomarker inhibition with increasing dose in both Japanese and White subjects (**Table 1**)

Figure 2. Mean (SD) % change from baseline in Wieslab assay over time

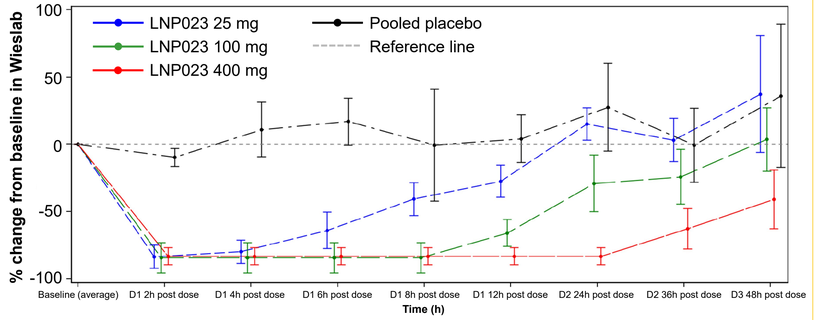


Table 1. Iptacopan PK and PD parameters in Japanese and White patients

Dose	Parameter	Japanese Mean (± SD) [N]	White Mean (± SD) [N]
25 mg	C_{max} (ng/mL)	1160±254 [8]	994±211 [6]
	AUC_{inf} (ng*h/mL)	12500±3300 [8]	12700±2910 [6]
	Wieslab (%)	−27.6±11.84 [8]	−50.7±21.617 [6]
	Bb (%)	−29.7±13.78 [8]	−31.5 [6]
100 mg	C_{max} (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* [6]
400 mg	C_{max} (ng/mL)	7990±1360 [8]	5070±1310 [6]
	AUC_{inf} (ng*h/mL)	73500±14300 [7]	61200±15800 [6]
	Wieslab (%)	−83.3±6.32 [8]	−83.8±9.082 [6]
	Bb (%)	−26.5±11.56 [8]	−49.7 [6]

AUC_{inf}, area under the curve from time zero extrapolated to infinity; Bb, fragment of factor B; C_{max}, maximum concentration.

CONCLUSIONS

- Japanese and White healthy subjects had similar PK and PD results at all dose levels
  - The slightly higher mean C_{max} and AUC_{inf} in Japanese subjects is well within the inter-patient variability
- This study provides reassurance that there are no clinically meaningful differences in the human pharmacology of iptacopan between these ethnic groups

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