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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

A First-in-Human, Phase 1 Study to Assess the Pharmacodynamic Properties of Single-Dose Iptacopan (CLNP023X2101)

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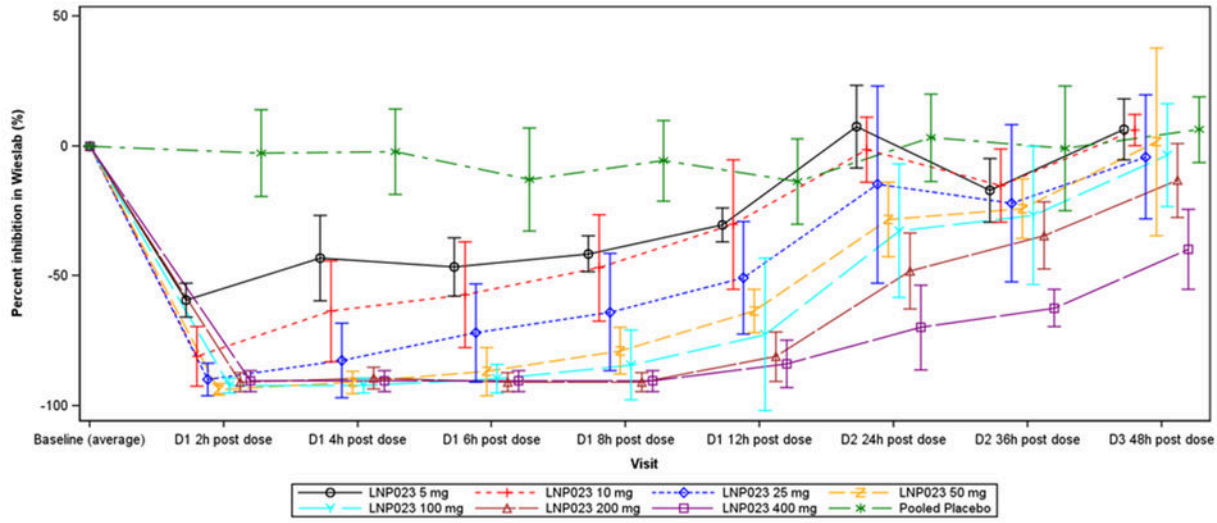
Introduction: Iptacopan is a first-in-class, oral, selective inhibitor of factor B, a key component of the complement system alternative pathway (AP). Inhibition of the complement system represents a potential mechanism for treatment of several diseases including paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Here, we report the exploratory pharmacodynamics of single doses of iptacopan from part 1 of the phase 1 study (CLNP023X2101) in healthy participants.
Methods: CLNP023X2101 was a randomized, non-confirmatory, first-in-human assessment of iptacopan in healthy participants. Part 1 was a participant-blinded, placebo-controlled, single-ascending dose (SAD) study. SADs ranged from 5 mg to 400 mg in 56 participants across 7 cohorts. Eight participants per cohort were randomized to receive a single oral dose of iptacopan or placebo in a 3:1 ratio. Inhibition of terminal complex activity of the complement system was assessed using the Wieslab assay which was based on the in vitro formation of the C5b-9 complex, triggered by AP activation. Other soluble biomarkers measured were plasma fragment Bb, a biomarker of AP activation generated by the cleavage of Factor B, and plasma sC5b-9.
Results: Demographic data were similar across the treatment groups. Most participants were men with a median age of 45 years. Iptacopan led to dose-dependent suppression of the AP activity as measured by the Wieslab assay (**Figure 1**). Following administration, >81% reduction of the AP activity (compared with baseline) was observed at 2 hours post-dose for all dose groups except the 5-mg dose group. Duration of sustained inhibition of AP activity was dose-dependent. Greater than 80% inhibition of the AP activity compared with baseline was maintained beyond 12 hours after 200-mg and 400-mg doses. Wieslab values returned to baseline levels after 48 hours post dose except for the 200-mg and 400-mg cohorts. The decrease in Bb levels from baseline was observed at 2 hours post-dose in all groups and was sustained until 12 hours post-dose before returning to baseline levels by 48 hours (**Figure 2**). In the 200-mg and 400-mg cohorts, Bb levels plateaued until 24 hours post-dose and similarly returned to baseline by 48 hours. In contrast, no significant change in Bb level was seen in participants receiving placebo. A trend to decreased sC5b-9 levels was observed until 6 hours post-dose in most cohorts (≥25 mg).
Conclusions: Iptacopan achieved rapid, substantial, and sustained dose-dependent suppression of AP activity at 2 hours post-dose for all doses >5 mg. Further validating this result, the decrease in Bb levels at 2 hours post-dose was maintained until 12 hours post-dose, with doses ≥100 mg showing sustained inhibition beyond 12 hours. These pharmacodynamic findings of single-dose iptacopan were part of the rationale for dose selection in clinical Phase 2 and 3 studies contributing to the evidence of 200 mg twice daily being the appropriate dose.

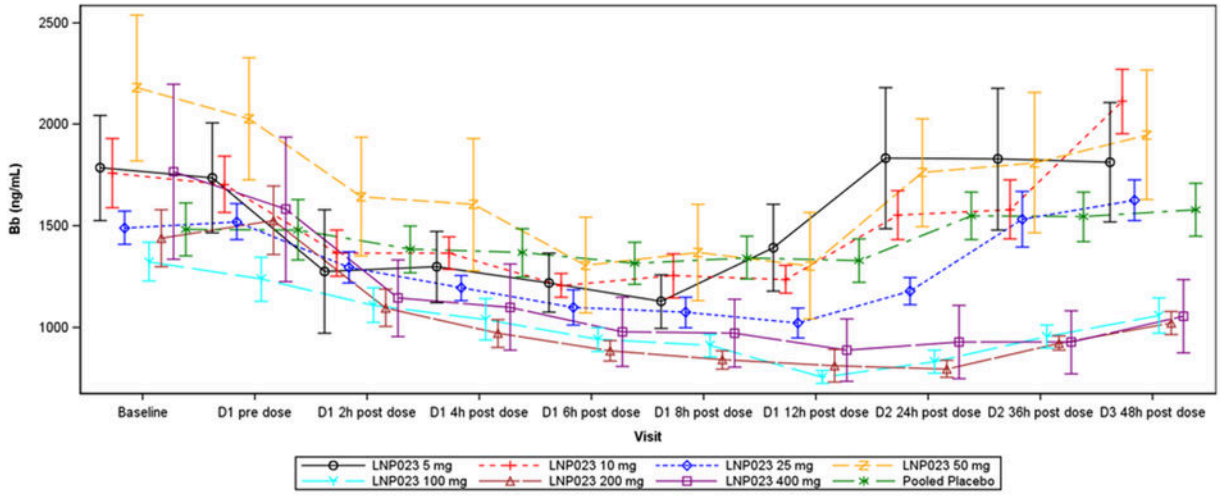
Disclosures Schmouder: *Novartis Pharmaceuticals Corporation:* Current Employment, Current holder of *stock options* in a privately-held company. **Junge:** *Novartis Institutes of Biomedical Research:* Current Employment, Current equity holder in publicly-traded company. **Nidamarthy:** *Novartis Healthcare Pvt Ltd:* Current Employment. **Kulmatycki:** *Novartis Institutes of Biomedical Research:* Current Employment.

Figure 1. Mean (SD) Percentage Inhibition in Wieslab Assay Following Single Iptacopan Doses



D, day; h, hour.

Figure 2. Mean (SE) Concentration of Plasma Bb Following Single Iptacopan Doses (ng/mL)



D, day; h, hour.

Figure 1

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