American Society of Nephrology

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**TITLE:** Efficacy and Safety of Iptacopan in Patients with atypical hemolytic uremic syndrome (aHUS) Naive to Complement Inhibitor Therapy: Design of a Global, Single-arm, Open-Label Phase III Study

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**GROUP OR TEAM (if applicable):**

**DESCRIPTION: Background**:
Iptacopan (LNP023) is an oral, first-in-class, highly potent, selective inhibitor of factor B that has demonstrated targeted inhibition of the alternative pathway (AP) of the complement system in Phase 1 studies in healthy volunteers, and Phase 2 studies in patients with IgA nephropathy (IgAN), C3 glomerulopathy (C3G) and paroxysmal nocturnal hemoglobinuria (PNH). aHUS is an ultra-rare and severe form of thrombotic microangiopathy (TMA) caused by uncontrolled activation of the AP. Iptacopan has the potential to become an effective and safe treatment for aHUS, with a lower treatment burden because of oral administration.

**Aims:**
The APPELHUS (Alternative Pathway Phase III to Evaluate LNP023 in aHUS) study (NCT04889430) will evaluate the efficacy and safety of iptacopan treatment given as 200 mg twice daily in 50 adult aHUS patients who are treatment naive to complement inhibitor therapy.

**Methods:**
APPELHUS is a global, multicenter, single-arm, open label, Phase 3 study with a 26-Wk Core Treatment period followed by a 26-Wk Extension Treatment period. Eligible patients must have evidence of TMA (platelet count $<150 \times 10^9$/L, LDH ≥1.5xULN, hemoglobin ≤LLN, serum creatinine ≥ULN). Key exclusion criteria include treatment with complement inhibitors, ADAMTS13 deficiency (<5% activity), Shiga toxin-related HUS, positive Coombs test and other causes of TMA identified through diagnostic workup. The primary study endpoint is the proportion of patients achieving complete TMA response without the use of plasma exchange/plasma infusion and anti-C5 antibody during 26 weeks of iptacopan treatment. A two-sided 95% confidence interval for the primary endpoint will be calculated based on asymptotic Gaussian approximation with continuity correction. Secondary endpoints include time to complete TMA response; change from baseline in hemoglobin (≥2 g/dL), eGFR, CKD stage, hematologic parameters (platelets, LDH and hemoglobin), dialysis requirement status, and patient-reported fatigue scores; safety; and tolerability.

**Conclusion:**
APPELHUS will determine if iptacopan is safe and efficacious in patients with aHUS.

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**SUBCATEGORY:** None

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