29th International Complement Workshop (ICW), Newcastle upon Tyne, UK
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APPARENT: A multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of iptacopan in idiopathic (primary) immune complex-mediated membranoproliferative glomerulonephritis

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Background: Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) is a fast-progressing kidney disease that may be idiopathic (primary) or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies. Idiopathic IC-MPGN is rare and has a comparable clinical course to complement 3 glomerulopathy (C3G), which is also characterized by membranoproliferative histology. Dysregulation of the alternative complement pathway is implicated in the pathophysiology of both glomerular diseases. Currently, there are no approved targeted treatments for IC-MPGN. Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically binds to factor B and inhibits the alternative pathway (AP).

Methods: This randomized, double-blind, placebo-controlled, pivotal Phase 3 study (APPARENT; NCT05755386) is the first to evaluate the efficacy and safety of iptacopan in patients with idiopathic IC-MPGN. Approximately 68 patients (including a minimum of 10 adolescents) aged 12–60 years with biopsy-confirmed IC-MPGN, proteinuria ≥1 g/g, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 will be randomized. All patients will have received maximally tolerated angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and vaccination against encapsulated bacteria. Patients with any organ transplant, progressive crescentic glomerulonephritis, or kidney biopsy with >50% interstitial fibrosis/tubular atrophy will be excluded. Patients will be randomized 1:1 to receive either iptacopan 200 mg twice daily (bid) or placebo for 6 months (double-blind period), followed by open-label treatment with iptacopan 200 mg bid for all patients for 6 months. At the end of the study, patients will have the option to transition to an open-label extension study.

The primary objective is to evaluate the efficacy of iptacopan versus placebo on proteinuria reduction as measured by urine protein–creatinine ratio (24-h urine) at 6 months. Key secondary endpoints will assess kidney function measured by eGFR, patients who achieve a proteinuria–eGFR composite renal endpoint, and patient-reported fatigue. The safety objectives are to evaluate the safety and tolerability of iptacopan in all patients and perform cardiovascular surveillance in adolescent patients (blood pressure, heart rate, cardiac function and biomarkers).

Results: The study is expected to start in Q2 2023.

Conclusion: This study will provide evidence towards the efficacy and safety of iptacopan in idiopathic IC-MPGN.

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Keywords

LNP023, iptacopan, IC-MPGN, alternative pathway, APPARENT

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Topic Complement therapeutics (options: Complement activation & control, Complement structure function, Complement genetics, Complement in inflammatory/infectious disease, Complement therapeutics, Complement Animal models in Complement research & Translational Complement, Complement diagnostics & biomarkers, Emerging topics)

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