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Title:

A multicenter, randomized, double-blind, placebo-controlled Phase 3 study (APPARENT) to assess the efficacy and safety of iptacopan in idiopathic (primary) immune complex-mediated membranoproliferative glomerulonephritis

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Abstract:

Aims/Purpose: Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) is a rare, fast-progressing kidney disease that may be idiopathic (primary) or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies. Idiopathic IC-MPGN 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, enrolling 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/1.73 m². 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.

The primary objective is to evaluate the efficacy of iptacopan versus placebo on proteinuria reduction measured as 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.