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Safety and efficacy of iptacopan in adolescent patients with idiopathic (primary) immune-complex-mediated membranoproliferative glomerulonephritis (IC-MPGN)

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CONCLUSION

- This study will provide evidence towards the efficacy and safety of iptacopan in adult as well as adolescent patients with idiopathic (primary) forms of IC-MPGN

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INTRODUCTION

- IC-MPGN is an ultra-rare, fast-progressing complement-mediated kidney disease characterized by immunoglobulin deposits in the kidney, which may be idiopathic (primary) or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies[1]
- Primary IC-MPGN has a comparable clinical course to complement 3 glomerulopathy (C3G), also characterized by membranoproliferative histology. C3G is diagnosed based on dominant glomerular C3 deposition with minimal or no immunoglobulin (Ig) accumulation, whereas IC-MPGN is diagnosed when immunofluorescence staining of the kidney biopsy shows more intense glomerular Ig deposition than C3 deposition[1,2]
- Dysregulation of the alternative complement pathway is strongly implicated in the pathogenesis of both glomerulonephritis entities including children and adults,[2] with comparable percentages of patients with C3G and IC-MPGN carrying genetic and/or acquired abnormalities of the alternative pathway (AP)[3]
- Primary IC-MPGN is frequently diagnosed in adolescence (median age at diagnosis of around 21 years) with no approved treatments[3] that target the underlying complement-mediated pathophysiology. Given the fast-progressing nature of the disease, there is a high unmet need for treatment in patients with IC-MPGN[4]
- Iptacopan (LNP023) is an oral, first-in-class, highly potent proximal complement inhibitor that specifically targets Factor B and inhibits the AP[5,6]
- Inhibition of factor B prevents activity of AP-related C3 convertase and the subsequent formation of C5 convertase.[5,7] While iptacopan inhibits amplification of the lectin and classical pathways, it leaves both direct signaling pathways intact[5]
  - Iptacopan does not inhibit the activation of the lectin and classical pathways, nor does it inhibit opsonization, formation of C3/C5 convertase, or membrane attack complex via these two activation pathways[5,7]
- Iptacopan is currently under development for various complement-driven kidney diseases, and was recently FDA approved for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria in the United States[8]
- In a Phase 2 clinical trial, iptacopan has been found to be well tolerated, significantly reduce proteinuria and C3 deposition, stabilize estimated glomerular filtration rate (eGFR) and normalize plasma C3 levels in patients with C3G[9–12]
- A Phase 3 study (APPEAR-C3G: NCT04817618), to demonstrate the clinical benefits of AP inhibition with iptacopan in C3G has met its primary endpoint, demonstrating superiority of iptacopan vs. placebo in proteinuria reduction at six-month analysis[1]; the safety profile of iptacopan was consistent with previously reported data. The data will be shared in 2024[13-16]
- Given the role of AP dysregulation in the pathophysiology of IC-MPGN,[2,3] inhibiting activity of the AP with iptacopan may provide an attractive therapeutic strategy to halt disease progression

Methods[13,15]

Study design

- **APPARENT**, a multicenter, randomized, double-blind, placebo-controlled, pivotal Phase 3 study (ClinicalTrials.gov NCT05755386) is the first to evaluate the efficacy and safety of iptacopan in patients with idiopathic (primary) IC-MPGN
- This study will be conducted according to International Council for Harmonization E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki
- The study treatment phase comprises a 6-month blinded period (either iptacopan 200 mg [dosing for adolescents will be 2 x 100 mg capsules] twice daily [bid] or placebo) followed by a 6-month open-label period (iptacopan 200 mg bid) for all study participants (**Figure 1**)
- A participant who enters the trial as an adolescent will be considered as adolescent (and treated as such) for the duration of the trial even if the participants turns age 18 during the study
- An independent data monitoring committee (DMC) will assess the safety of iptacopan periodically

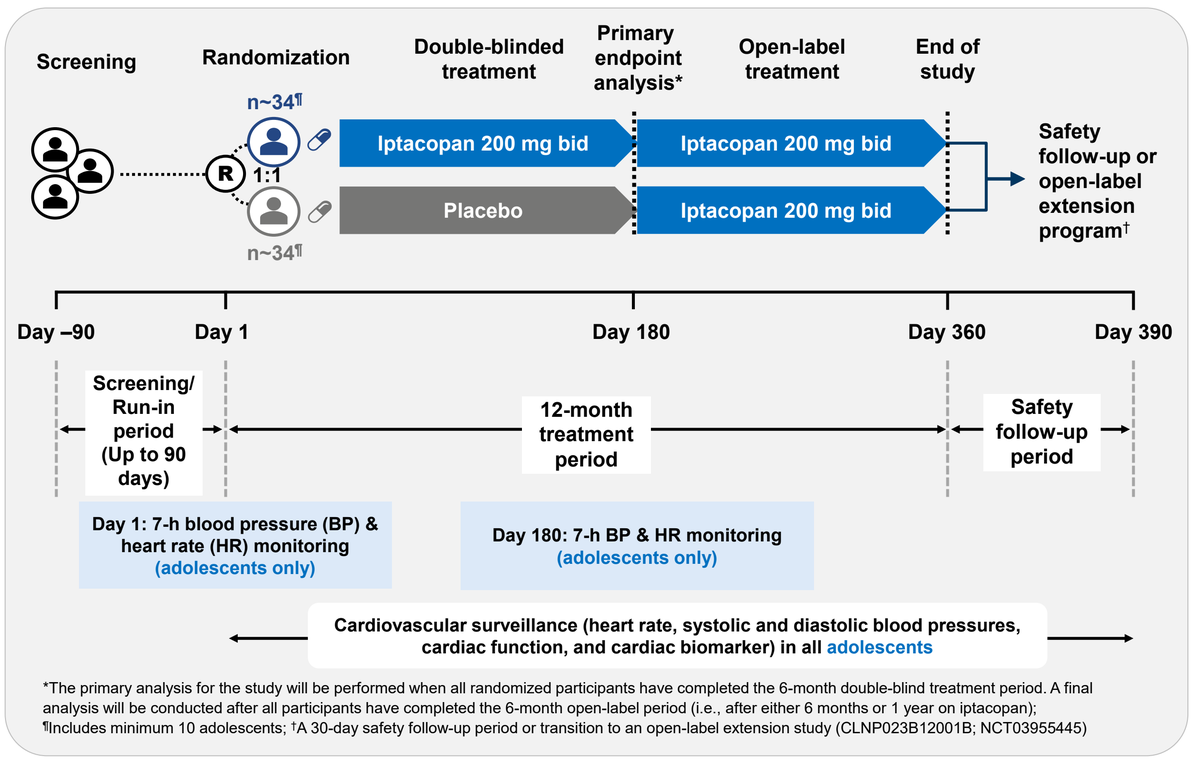
Primary treatment effect and rationale

- The primary treatment effect is the reduction in proteinuria at 6 months for iptacopan versus placebo in patients with biopsy-confirmed idiopathic IC-MPGN without confounding for initiation or intensification of anti-proteinuric (these include any complement pathway modifying agents, corticosteroids or immunosuppressants for a kidney indication) or for kidney replacement therapies administered after randomization
- Patients discontinuing randomized medication will continue to be followed and will contribute to the treatment effect, according to the intention to treat principle

Rationale for inclusion of adolescents

- IC-MPGN disease pathogenesis in adolescents is similar to adults, including a central role of the overactivated AP as well as clinical characteristics of edema, severity of proteinuria, prevalence of nephrotic syndrome, hematuria and histopathology[4]
- The risks and benefits of iptacopan have been evaluated and the potential risks will be closely monitored during the study
- The overall benefit-risk profile of iptacopan in IC-MPGN is considered positive, supporting the start of this study and inclusion of adolescents

Figure 1. Study design



*The primary analysis for the study will be performed when all randomized participants have completed the 6-month double-blind treatment period. A final analysis will be conducted after all participants have completed the 6-month open-label period (i.e., after either 6 months or 1 year on iptacopan);
¶Includes minimum 10 adolescents; †A 30-day safety follow-up period or transition to an open-label extension study (CLNP023B12001B; NCT03955445)

Study population

- The study will enroll approximately 68 adults and adolescents aged 12–60 years with biopsy-confirmed primary IC-MPGN. The study population will consist of a minimum of 10 adolescents (12–17 years) enrolled in countries and sites as per local requirements
- Adolescents will be enrolled in cohorts of ~5 participants and cardiovascular surveillance data from each cohort will be reviewed by the DMC before the next cohort is allowed to undergo randomization

Primary objective and endpoint

Double-blind period

- *Primary objective:* To demonstrate the superiority of iptacopan versus placebo on reducing proteinuria at 6 months
- *Primary endpoint:* Log-transformed ratio to baseline in UPCR (sampled from a 24-h urine collection) at 6 months

Open-label period

- *Primary objective:* To assess the effect of iptacopan on proteinuria at 12 months
- *Primary endpoints:*
  - Log-transformed ratio to baseline in UPCR at the 12-month visit (both study treatment arms)
  - Log-transformed ratio to 6-month visit in UPCR at the 12-month visit in the placebo arm (iptacopan treatment period)

Secondary objectives for both double-blind (at 6 months) and open-label period (at 12 months)

- To demonstrate the superiority of iptacopan versus placebo in improving:
  - eGFR
  - The proportion of patients achieving a composite renal endpoint (a stable or improved eGFR [≤15% reduction in eGFR] and a ≥50% reduction in UPCR compared with the baseline visit)
  - Patient-reported fatigue
- To perform cardiovascular surveillance for assessing the potential effect of iptacopan on blood pressure, heart rate, cardiac function and biomarkers of cardiac injury at study visits (adolescents only)
- To evaluate the safety and tolerability of iptacopan

Key inclusion criteria

- Age ≥12 and ≤60 years at screening
- Body weight of ≥35 kg (both adolescents and adults) at screening and randomization
- Diagnosis of idiopathic IC-MPGN confirmed by kidney biopsy within 12 months (adults) or within 3 years (adolescents) prior to enrollment (a biopsy report, review and confirmation by the investigator is required; if this confirmation is not available for an adult, it should be obtained by kidney biopsy at screening)
- Urine protein creatinine ratio (UPCR) ≥1.0 g/g sampled from the first morning void (FMV) urine sample at both Day –75 and –15
- eGFR (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula for patients aged ≥18 years and modified Schwartz formula for patients aged 12–17 years) or measured GFR ≥30 mL/min/1.73m^2 at Screening and Day –15
- Maximally recommended or tolerated dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for ≥90 days (according to local guidelines)
- Doses of other anti-proteinuric medications including mycophenolic acids, corticosteroids, sodium-glucose co-transporter-2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists should be stable for ≥90 days prior to randomization
- Vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* infections

Key exclusion criteria

- Patients who have received any cell or solid organ transplantation, including kidney transplantation
- Patients diagnosed with secondary IC-MPGN due to, for example: viral, bacterial, and protozoa/other infections; autoimmune diseases; monoclonal gammopathy; fibrillary glomerulonephritis
- Rapidly progressive crescentic glomerulonephritis (defined as a 50% decline in the eGFR within 3 months) with kidney biopsy findings of glomerular crescent formation seen in ≥50% of glomeruli
- Patients with acute post-infectious glomerulonephritis
- Kidney biopsy showing interstitial fibrosis/tubular atrophy >50%
- A history of recurrent invasive infections caused by encapsulated organisms, for example, *Neisseria meningitidis* and *Streptococcus pneumoniae*
- Human immunodeficiency virus infection, liver disease, such as active hepatitis B or hepatitis C virus infection, or liver injury as indicated by abnormal liver function tests at screening
- Use of immunosuppressants (except mycophenolic acids [the use of mycophenolic acids {mycophenolate mofetil or mycophenolate sodium} is not permitted within 90 days prior to randomization in India and is an exclusion criterion for India]), cyclophosphamide or systemic prednisone at doses >7.5 mg/day (or equivalent) within 90 days of study drug administration
- Use of complement inhibitors (e.g., Factor B, Factor D, and C3 inhibitors; anti-C5 antibodies; C5a receptor antagonists) within 6 months prior to the screening visit

Key milestones[17]

- Study start date: **October 2, 2023**
- Recruitment Status: **Currently recruiting**
- Estimated primary completion date: **June 30, 2026**
- Estimated study completion: **June 30, 2026**

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Disclosures

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