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

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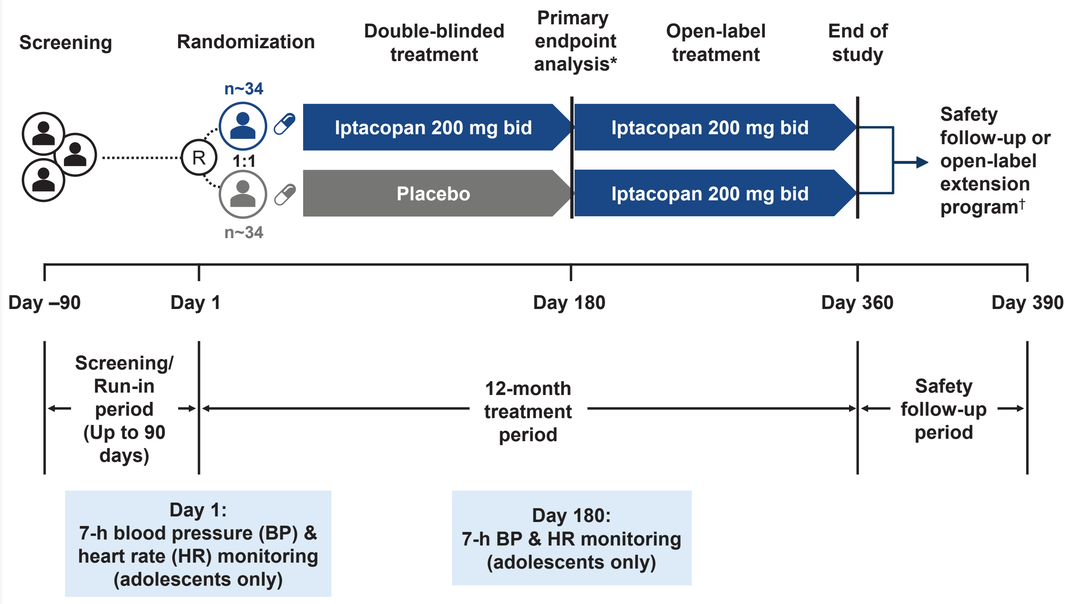
Conclusion

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

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)

†A 30-day safety follow-up period or transition to an open-label extension study (CLNP023B12001B)

Study design

- This multicenter, randomized, double-blind, placebo-controlled, pivotal Phase III study (APPARENT; ClinicalTrials.gov NCT05755386) is the first to evaluate the efficacy and safety of iptacopan in patients with idiopathic 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**)

Key milestones

- Study start date: Q1 2023
- Site initiation visit: May 2023
- First patient first visit: July 2023
- Estimated completion: 2026

Primary treatment effect and study design 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 agent corticosteroid or immunosuppressant for a kidney indication) or 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 intent to treat principle

Introduction

- IC-MPGN is a fast-progressing complement-mediated kidney disease that may be idiopathic (primary) or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies[1]
- Idiopathic IC-MPGN is rare and has a comparable clinical course to complement 3 glomerulopathy (C3G), which is 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 intense glomerular Ig deposition as well as C3[1,2]
- Dysregulation of the alternative complement pathway (AP) is strongly implicated in the pathophysiology of both diseases,[2] with comparable percentages of patients with C3G and IC-MPGN carrying genetic and/or acquired abnormalities of the AP.[3] In IC-MPGN, the deposition of immune complexes initially also trigger the activation of the classical complement pathway. Currently, there are no approved targeted treatments for C3G or 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 AP[4,5]
- Inhibition of factor B prevents activity of AP-related C3 convertase and the subsequent formation of C5 convertase.[4,6] While iptacopan inhibits amplification of the classical and lectin pathways, it leaves both direct signaling pathways intact.[4] Iptacopan does not inhibit the activation of the classical and lectin pathways, nor does it inhibit opsonization, formation of C3/C5 convertase, or membrane attack complex via these two activation pathways[4,6]
- In Phase II clinical trials, 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[7–10]
- Given the role of complement system dysregulation in the pathophysiology of IC-MPGN,[2,3] inhibiting activity of the AP and amplification of the classical and lectin pathways with iptacopan may provide an attractive therapeutic strategy to halt disease progression

Study population

- The study will enroll approximately 68 adult and adolescent patients aged 12–60 years with biopsy-confirmed idiopathic 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

Statistical analysis

- The primary analysis will be performed when all randomized participants have completed the 6-month double-blind treatment period. This analysis will determine the efficacy of iptacopan compared with placebo in decreasing proteinuria, stabilizing eGFR, and inhibiting the overactive AP
- The primary endpoint analysis will use the Bayesian dynamic borrowing approach,[11] which allows for "dynamic borrowing" of prior information from the C3G APPEAR study.[12] Data from the IC-MPGN trial will be analyzed using a Mixed Model for Repeated Measures (MMRM) model. The MMRM estimate will be combined with the prior information to derive posterior distribution for the treatment difference via Bayesian analysis
- 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). This analysis will provide insights on the persistence of efficacy and an assessment of iptacopan's safety profile over a longer period of treatment

Key inclusion criteria

- Age ≥12 and ≤60 years at screening
- Diagnosis of idiopathic IC-MPGN as 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)
- 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 (or as according to local guidelines)
- Doses of other antiproteinuric 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 (non-idiopathic) 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, e.g., *N. meningitidis* and *S. 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

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

- 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 (adolescents only)
- To evaluate the safety and tolerability of iptacopan

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Declaration of funding and interests

David Kavanagh: scientific founder of and holds stocks in Gyroscope Therapeutics. He has received consultancy income from Gyroscope Therapeutics, Alexion Pharmaceuticals, Novartis, Apellis, and Sarepta. His spouse works for GSK.

Marina Vivarelli: honoraria for advisory boards and consulting fees, participation in clinical studies sponsored by the following pharmaceutical companies: Achillion, Alexion, Apellis, Bayer, Catalyst, Novartis, Roche, Retrophin/Travere, GSK, BioCryst Pharmaceuticals, Chinook Therapeutics.

Andrew Bomback: consulting honoraria from Achillion, Alexion, Chemocentryx, Novartis, Silence, Catalyst, and Principio.

Richard JH Smith: research funding from NIH, consultant for Novartis.

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