The World Congress of Nephrology (WCN) 2023
Bangkok, Thailand, March 30 – April 2, 2023

Abstract title:

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

Abstract text:

Introduction: IC-MPGN is a fast-progressing kidney disease that may be idiopathic or secondary to chronic infection, autoimmune disorders, or monoclonal gammopathies. Idiopathic IC-MPGN is ultra-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. Dysregulation of the alternative complement pathway (AP) is strongly implicated in the pathogenesis 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 AP.

Methods: This randomized, double-blind, placebo-controlled, pivotal Phase 3 study is the first to evaluate the efficacy and safety of iptacopan in patients with idiopathic IC-MPGN (see **Figure**). Approximately 68 patients aged ≥12 to ≤60 years with biopsy-confirmed IC-MPGN, proteinuria ≥1 g/g, and eGFR ≥30 mL/min/1.73 m^2 will be randomized. All patients will have received maximally tolerated ACEi/ARBs and vaccination against encapsulated bacteria. Patients with any organ transplant, secondary IC-MPGN, rapidly progressive crescentic glomerulonephritis, and kidney biopsy with >50% interstitial fibrosis/tubular atrophy will be excluded. Patients receiving immunosuppressants (except mycophenolic acids) or systemic prednisone >7.5 mg/day (or equivalent for a similar medication) within 90 days of study drug administration, or other complement inhibitors within 6 months prior to the screening visit, and those

participating in any other investigational drug trial at the time of enrolment will also 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 demonstrate the superiority of iptacopan versus placebo on proteinuria reduction as measured by UPCR (24h urine collection) at 6 months. Key secondary endpoints will assess improvement in eGFR, the proportion of patients who achieve a proteinuria–eGFR composite endpoint, and improvement in 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). The effect of iptacopan on functional and complement biomarkers will also be explored. This study aims to demonstrate clinical benefits of AP inhibition with iptacopan in IC-MPGN.

Results: The study is expected to start in 2023.

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

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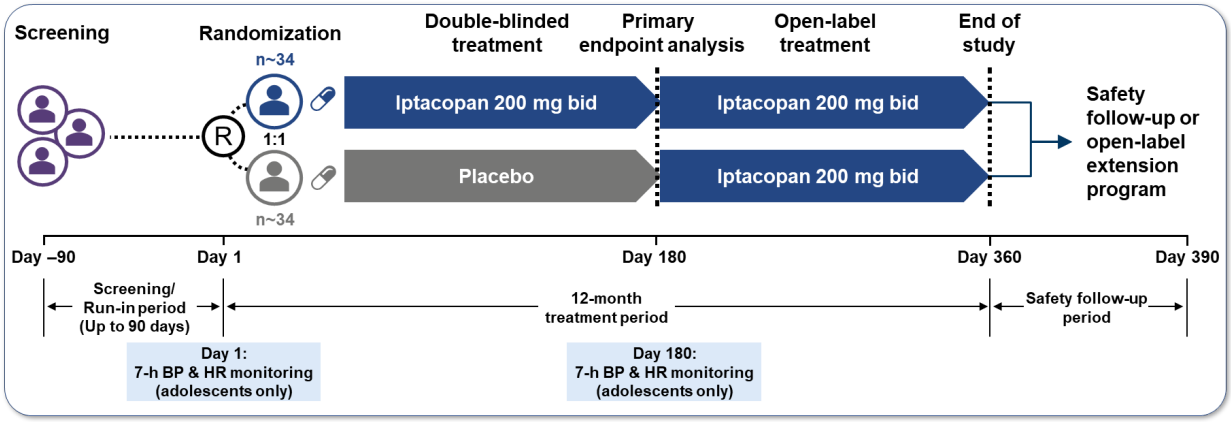
Figure: Study design and endpoints



Participants	Adults and adolescents aged 12–60 years with biopsy-confirmed native kidney IC-MPGN, UPCR ≥1 g/g, and eGFR ≥30 mL/min/1.73 m^2
Primary objective	To demonstrate the superiority of iptacopan vs. placebo in reducing proteinuria at 6 months
Secondary objectives	• To demonstrate the superiority of iptacopan vs. placebo in improving – eGFR – the proportion of participants 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 safety and tolerability

bid, twice daily; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; UPCR, urine protein-to-creatinine ratio

Key words (up to 5): iptacopan, immune complex-mediated membranoproliferative glomerulonephritis, IC-MPGN, clinical trial, Phase 3

Authors:

Uday Kiran Veldandi,[1] David Kavanagh,[2] Marina Vivarelli,[3] Andrew Bomback,[4] Yaqin Wang,[5] Karolina Bogdanowicz,[6] Nicholas Webb,[7] Matthias Meier,[7] Richard JH Smith[8]

Institutions:

[1]Global Drug Development, Novartis HC Pvt Ltd, Hyderabad, India;
[2]National Renal Complement Therapeutics Centre, Newcastle upon Tyne Hospitals, National Health Service Foundation Trust, Newcastle upon Tyne, UK;
[3]Division of Nephrology and Dialysis, Department of Pediatric Subspecialties, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy;
[4]Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, US;
[5]Global Drug Development, Novartis Pharmaceuticals, US;
[6]Global Drug Development, Novartis Pharmaceuticals, London, UK;
[7]Global Drug Development, Novartis Pharma AG, Basel, Switzerland;
[8]Molecular Otolaryngology and Renal Research Laboratories and the Departments of Internal Medicine and Pediatrics (Divisions of Nephrology), Carver College of Medicine, University of Iowa, Iowa City, IA, US

Abstract topic: Chronic Kidney Disease, Hypertension, Diabetes and CVD - Other CKD

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Transparency declaration and ethics statement:

This study was conducted according to International Council for Harmonization E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki.

Declaration of funding and interests:

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

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Uday Kiran Veldandi, Yaqin Wang, Karolina Bogdanowicz, Nicholas Webb, and Matthias Meier are employees and stockholders of Novartis.