

MEDIA & INVESTOR RELEASE

Novartis investigational iptacopan Phase III study demonstrates clinically meaningful and highly statistically significant proteinuria reduction in patients with IgA nephropathy (IgAN)

Ad hoc announcement pursuant to Art. 53 LR

- *Phase III APPLAUSE-IgAN study met its pre-specified interim analysis primary endpoint, demonstrating superiority of iptacopan vs placebo in proteinuria reduction¹*
- *Iptacopan is an investigational, first-in-class, oral factor B inhibitor targeting the alternative pathway of the complement system²⁻⁴*
- *IgAN is a complement-mediated kidney disease, affects mostly young adults, and is a major cause of chronic kidney disease and kidney failure worldwide⁵⁻⁹*
- *Novartis plans to review interim results with FDA to enable a potential regulatory submission for accelerated approval; study continues with final readout (24 months) in 2025⁴*
- *APPLAUSE-IgAN is the third positive Phase III trial for iptacopan and development program is ongoing across five indications; regulatory review is underway for paroxysmal nocturnal hemoglobinuria (PNH) in the US and EU^{10,11}*

Basel, October 2, 2023 — Novartis today announced positive top-line results from the pre-specified interim analysis of the Phase III APPLAUSE-IgAN study (NCT04578834) at 9 months¹. Iptacopan, an investigational factor B inhibitor targeting the alternative complement pathway, demonstrated superiority versus placebo in proteinuria (protein in urine) reduction and provided a clinically meaningful and highly statistically significant proteinuria reduction on top of supportive care in patients with IgA nephropathy (IgAN), a complement-mediated disease¹⁻⁴. In the study, the safety profile of iptacopan (200 mg twice daily) was consistent with previously reported data^{1,3,4}. The study continues in a double-blind fashion to evaluate iptacopan's ability to slow IgAN progression by measuring estimated glomerular filtration rate (eGFR) slope over 24 months – the primary endpoint at the study end with topline results expected in 2025⁴.

“These positive data from the Phase III APPLAUSE study reinforce the potential of iptacopan to provide clinically meaningful benefit to patients with IgAN, a debilitating disease that affects

mostly young adults,” said Shreeram Aradhye, M.D., President, Development and Chief Medical Officer, Novartis. “We are excited about this milestone in the development of our factor B inhibitor of the alternative complement pathway and remain focused on further advancing our portfolio of renal programs through pivotal trials.”

It is estimated that approximately 25 people per million worldwide are newly diagnosed with IgAN each year⁸. Up to 30% of people who have IgAN with persistent higher levels of proteinuria (≥ 1 g/day) may progress to kidney failure within 10 years¹².

There is a need for effective, targeted therapies for IgAN that slow or prevent progression to kidney failure^{6,13–15}. Although current supportive care and treatment can help, they don’t address a key pathogenic step in the progression of IgAN: activation of the complement system¹⁶.

Discovered and developed by Novartis, iptacopan aims to address IgAN and other complement-mediated diseases by inhibiting factor B, a protease essential to the alternative complement pathway².

Iptacopan is under review by regulators following positive Phase III results in paroxysmal nocturnal hemoglobinuria (APPLY-PNH [NCT04558918] and APPOINT-PNH [NCT04558918])^{10,11}. Iptacopan is also being investigated in Phase III studies for C3 glomerulopathy (APPEAR-C3G [NCT04817618]), atypical hemolytic uremic syndrome (APPELHUS [NCT04889430]) and immune complex membranoproliferative glomerulonephritis (APPARENT [NCT05755386]). With the recent acquisition of Chinook Therapeutics, the Novartis renal portfolio expands with two additional late-stage medicines in development for IgAN, complementing the existing pipeline¹⁷.

Novartis intends to submit for possible accelerated approval with the FDA in 2024.

About the study

APPLAUSE-IgAN (NCT04578834) is a Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of twice-daily oral iptacopan (200mg) in 470 adult primary IgAN patients^{4,18}.

The two primary endpoints of the study for the interim and final analysis, respectively, are proteinuria reduction at 9 months as measured by urine protein to creatinine ratio (UPCR), and the annualized total estimated glomerular filtration rate (eGFR) slope over 24 months^{4,18}. At the time of final analysis, the following secondary endpoints will also be assessed: proportion of participants reaching (UPCR) < 1 g/g without receiving corticosteroids/immunosuppressants or other newly approved drugs or initiating new background therapy for treatment of IgAN or initiating kidney replacement therapy (KRT), time from randomization to first occurrence of composite kidney failure endpoint event (reaching either sustained $\geq 30\%$ decline in eGFR relative to baseline or sustained eGFR < 15 mL/min/1.73m² or maintenance dialysis or receipt of kidney transplant or death from kidney failure), change from baseline to 9 months in the fatigue scale measured by the Functional Assessment Of Chronic Illness Therapy-Fatigue questionnaire^{4,18}.

About IgA nephropathy (IgAN)

IgAN is a progressive, rare, complement-mediated kidney disease that mostly affects young adults^{2–4,7}. Each year, approximately 25 people per million worldwide are newly diagnosed with IgAN⁸.

In IgAN, autoimmune reaction to an abnormal form of IgA results in formation of immune complexes that deposit in the kidney^{6,13,19–22}. These immune complexes trigger an inflammatory response leading to progressive kidney damage and loss of kidney function^{6,13,19–22}. Up to 30% of people who have IgAN with persistent higher levels of proteinuria (≥ 1 g/day) may progress to kidney failure within 10 years¹².

There is a need for effective, targeted therapies for IgAN that slow or prevent progression to kidney failure^{6,13-15}.

About iptacopan

Iptacopan is an oral, proximal complement inhibitor that binds factor B and inhibits the alternative complement pathway²⁻⁴.

Discovered at the Novartis Biomedical Research, iptacopan is currently in development for a range of complement-mediated diseases including paroxysmal nocturnal hemoglobinuria (PNH), immunoglobulin A nephropathy (IgAN), C3 glomerulopathy (C3G), immune complex membranoproliferative glomerulonephritis (IC-MPGN) and atypical hemolytic uremic syndrome (aHUS).

Based on disease prevalence, unmet needs and data from Phase II studies, iptacopan has received FDA Breakthrough Therapy Designation in PNH, FDA Breakthrough Therapy Designation in C3G, orphan drug designations from the FDA and EMA in PNH and C3G, EMA PRIME designation for C3G, and EMA orphan drug designation in IgAN²³⁻²⁶.

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About Novartis

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