

Novartis presents latest Phase III Fabhalta® (iptacopan) data in C3 glomerulopathy (C3G) showing clinically meaningful and statistically significant 35.1% proteinuria reduction vs. placebo

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- Secondary endpoint data for estimated glomerular filtration rate (eGFR) showed numerical improvement over 6 months vs. placebo¹; additional 6-month open-label data to be presented at a future medical meeting^{2,3}
- Fabhalta showed a favorable safety profile with no new safety signals¹
- C3G, an ultra-rare kidney disease caused by alternative complement pathway overactivation, progresses to kidney failure in ~50% of patients within 10 years⁴⁻⁷; currently there are no treatments approved for C3G⁷⁻⁹
- Fabhalta, an oral Factor B inhibitor of the alternative complement pathway, selectively targets the underlying cause of C3G¹; late-stage development program ongoing across several other rare diseases¹⁰⁻¹³

EAST HANOVER, N.J., May 25, 2024 – Novartis today presented results from the 6-month, double-blind period of the Phase III APPEAR-C3G study of Fabhalta® (iptacopan) at the late-breaking clinical trials session of the European Renal Association (ERA) Congress¹. Patients treated with Fabhalta in addition to supportive care achieved a 35.1% (p=0.0014) reduction in proteinuria (as measured by 24-hour urine protein to creatinine ratio [UPCR]) at 6 months when compared to placebo on top of supportive care¹. In many kidney diseases, proteinuria reduction is an increasingly recognized surrogate marker correlating with delaying progression to kidney failure^{14,15}.

Fabhalta is an oral Factor B inhibitor of the alternative complement pathway being investigated in adult patients with C3 glomerulopathy (C3G)¹⁻³. Regulatory submissions, including to the FDA and EMA, for the adult C3G indication are planned for the second half of 2024.

"C3G is an overlooked and devastating illness that often strikes when people are young. The prognosis for patients with C3G is poor, and around half of the affected patients progress to kidney failure requiring dialysis or transplant within 10 years of being diagnosed," said Marianne Silkjær Nielsen, Founder of CompCure, a Danish non-profit association committed to improving outcomes for individuals with C3G and immune complex membranoproliferative glomerulonephritis (IC-MPGN). "Currently there are no therapies approved for C3G, but research into potential new treatments developed specifically for this disease gives us hope that we can improve outcomes for patients and blunt its emotional, physical and social effects."

Additional data on the secondary endpoint of estimated glomerular filtration rate (eGFR), a measure of kidney

function, showed a numerical improvement of +2.2 mL/min/1.73 m² (p=0.1945) over 6 months with Fabhalta compared to placebo¹. The study also showed Fabhalta has a favorable safety profile with no new safety signals¹.

"This is an exciting milestone for patients and the potential future management of C3G. The hallmark of C3G is overactivation of part of the immune system called the alternative complement pathway, which damages the kidneys and leads to severe loss of kidney function in many patients. Currently used treatments don't address the underlying biology of C3G and often come with significant side effects that add to the burden of the illness," said Professor David Kavanagh, Professor of Complement Therapeutics & Honorary Consultant Nephrologist at the Faculty of Medical Sciences at Newcastle University and APPEAR-C3G Steering Committee Member. "Fabhalta is the first potential treatment that targets the alternative complement pathway in C3G, and its impact on measures of kidney damage and kidney function in this study, in addition to its safety profile, is encouraging for patients and the clinical community."

The APPEAR-C3G study continues with an additional 6-month, open-label period following the 6-month double-blind period, in which all patients receive Fabhalta, including those previously receiving placebo^{2,3}. These data will be presented at an upcoming medical meeting when available.

At ERA, Novartis is also presenting new data across its rare disease portfolio, including results for investigational atrasentan in IgA nephropathy (IgAN) from the 36-week interim analysis of the Phase III ALIGN study, additional data for Fabhalta in IgAN from the 9-month interim analysis of the Phase III APPLAUSE-IgAN study, long-term 33-month efficacy and safety data for Fabhalta in C3G from the Phase II extension study, 1-year Phase I/II data for investigational zigakibart in IgAN, and data from real-world studies in C3G and atypical hemolytic uremic syndrome (aHUS)¹⁶⁻¹⁹.

"Our ambition is to transform the care of patients living with rare kidney diseases by discovering, developing and delivering innovative treatment options," said David Soergel, M.D., Global Head, Cardiovascular, Renal and Metabolism Development Unit, Novartis. "The APPEAR-C3G results add to the growing body of evidence demonstrating Fabhalta's potential to target the underlying pathophysiological drivers and to provide clinically meaningful outcomes in a range of rare conditions."

About APPEAR-C3G

APPEAR-C3G (NCT04817618) is a Phase III multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of twice-daily oral Fabhalta (200 mg) in C3G patients^{2,3}. In addition to the results from adult patients with C3G, enrollment is ongoing in a separate cohort of adolescent patients with C3G^{2,3}. The study comprises a 6-month double-blind period where adult patients were randomized 1:1 to receive Fabhalta or placebo on top of supportive care, followed by a 6-month open-label period where all patients receive Fabhalta (including those who were previously on placebo)^{2,3}.

The primary endpoint for the double-blind period was proteinuria reduction from baseline at 6 months for Fabhalta compared to placebo as measured by 24-hour UPCR^{2,3}. The primary endpoint for the open-label period is proteinuria reduction from baseline at 12 months for both treatment arms and proteinuria reduction from 6 to 12 months for the placebo arm^{2,3}. Secondary endpoints for the double-blind period include change in eGFR, proportion of participants meeting composite renal endpoint criteria ($\leq 15\%$ reduction in eGFR and $\geq 50\%$ reduction in UPCR), change in glomerular inflammation (as measured by disease total activity score in renal biopsy), change in patient reported fatigue (as measured by FACIT-Fatigue score), and safety and tolerability^{2,3}.

Fabhalta (iptacopan) is an oral, Factor B inhibitor of the alternative complement pathway¹.

Discovered at Novartis, Fabhalta is currently in development for a range of rare diseases including IgAN, C3G, aHUS, IC-MPGN and lupus nephritis (LN), and, as such, the safety and efficacy profile have not been established in these indications^{2,11-13,20}. There is no guarantee that Fabhalta will become commercially available for these indications.

Fabhalta was approved by the FDA in December 2023 and the EMA in May 2024 for the treatment of adults with the rare blood disorder paroxysmal nocturnal hemoglobinuria (PNH)^{21,22}.

About C3 glomerulopathy (C3G)

C3G is an ultra-rare, progressive kidney disease that initially presents in mostly children and young adults^{4-6,23}. Each year, approximately 1-2 people per million worldwide are newly diagnosed with C3G, a form of membranoproliferative glomerulonephritis (MPGN)⁴.

In C3G, overactivation of the alternative complement pathway – part of the immune system – causes deposits of C3 protein to build up in kidney glomeruli (a network of blood vessels that filter waste and remove extra fluids from the blood)^{4,7,23-25}. This triggers inflammation and glomerular damage that results in proteinuria (protein in urine), hematuria (blood in urine) and reduced kidney function^{4,7,23-25}. Approximately 50% of C3G patients progress to kidney failure within 10 years of diagnosis, at which point they will require dialysis and/or kidney transplantation^{6,7}, with over 55% of patients with C3G experiencing disease recurrence post-transplant²⁶⁻²⁹.

Novartis commitment in rare kidney diseases

At Novartis, our journey in nephrology began more than 40 years ago when the development and introduction of cyclosporine helped reimagine the field of transplantation and immunosuppression. We continue today with the same bold ambition to transform the lives of people living with kidney diseases.

Through our portfolio, we are exploring potential therapeutic options to address the current unmet needs of people living with rare diseases, including IgAN, C3G, aHUS, IC-MPGN and LN. Innovative treatment options that target the underlying causes of these diseases may preserve kidney function and help people live longer without the need for dialysis or transplantation.

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About Novartis

Novartis is an innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

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