Novartis iptacopan meets primary endpoints in Phase II study in rare kidney disease C3 glomerulopathy (C3G)

Nov 04, 2021

- Statistically significant and clinically important reductions in proteinuria were achieved for the primary endpoint for patients with C3G(1)
- Additionally, statistically significant reduction in C3 protein deposits were achieved in the same study in a cohort of patients whose C3G recurred following kidney transplantation(1)
- No current approved treatments exist for C3G - a rare and often progressive disease that often affects adolescents and young adults and frequently progresses to kidney failure(2-4)
- Novartis is rapidly advancing clinical development of iptacopan to potentially address several complement-driven renal diseases (CDRDs) with high unmet need, as part of our wider commitment to cardiovascular, renal and metabolic disease; pivotal Phase III APPEAR-C3G study is actively recruiting

EAST HANOVER, N.J., Nov. 4, 2021 - Novartis today announced that a Phase II study of investigational iptacopan (LNP023) – a first-in-class, oral, selective factor B inhibitor – in patients with C3 glomerulopathy (C3G) met primary endpoints in both patient cohorts[1]. The data were presented at the American Society of Nephrology (ASN) 2021 Annual Meeting.

In the final analysis from the open-label, two-cohort Phase II study (NCT03832114), patients were treated with 200mg of iptacopan twice daily for 12 weeks, in addition to background therapy[1]. Patients in cohort A (16 with C3G, but who have not had a kidney transplant [native C3G]) showed a significant 45% reduction in proteinuria (protein in urine) compared to baseline, as measured by 24-hour urinary protein to creatine ratio (UPCR 24h; P=0.0003)[1]. Patients in cohort B (7* whose C3G had returned following a kidney transplant) showed significantly reduced C3 protein deposits compared to baseline, as measured by C3 deposit score (based on immunofluorescence microscopy) from kidney biopsy (P=0.0313)[1].

"The data presented at ASN provide a detailed picture of the potential of iptacopan for the treatment of patients with C3G and, for the first time, in patients whose C3G had returned following kidney transplantation," said lead study investigator Edwin Wong, Consultant Nephrologist at the National Renal Complement Therapeutics Centre, Newcastle upon Tyne NHS Foundation Trust, Newcastle University, UK. "These results are important for patients with C3G because proteinuria is a key risk predictor for kidney disease progression, and deposits of C3 protein ultimately cause inflammation and kidney damage."

Additionally, both cohorts of this Phase II study showed strong and sustained inhibition of alternative complement pathway activity and normalization of serum C3 levels over 12 weeks[1]. In combined data from both cohorts, kidney function remained stable after 12 weeks, as assessed by estimated glomerular filtration rate (eGFR, average increase of 1.04 mL/min compared to baseline)[1]. Previously presented data from the long-term extension study (NCT03955445) showed kidney function was maintained in the seven patients that were treated for a total of six months at that time, suggesting extended iptacopan treatment may prolong the time to, or even potentially prevent, the development of kidney failure[5,6].

Iptacopan showed a favorable safety and tolerability profile in the Phase II final analysis, with no serious adverse events suspected to be related to iptacopan[1].

"C3G is a devastating disease where people can end up facing life-altering and often exhausting kidney dialysis or transplantation at a time when they might otherwise be focused on building their lives, careers, and families. With currently no approved treatments, there is a major unmet need for therapies that can delay progression to kidney failure," said John Tsai, Head of Global Drug Development and Chief Medical Officer at Novartis. "These data demonstrate the ability of iptacopan to strongly and specifically inhibit the key driver for C3G – the alternative complement pathway. The results also show the potential for iptacopan to provide the first targeted treatment for people living with C3G, and we are actively recruiting for our pivotal Phase III APPEAR-C3G study."

*11 patients were recruited into cohort B, but only 7 patients had data to analyze for the C3 protein deposits primary endpoint.

About the study

NCT03832114 is a Phase II, open-label, two cohort, non-randomized study evaluating the efficacy, safety and pharmacokinetics of iptacopan in patients with C3 glomerulopathy (C3G) (cohort A) and patients who have undergone kidney transplantation and have subsequent C3G recurrence in the transplanted organ (cohort B)[1,7]. The primary endpoint for cohort A was reduction in proteinuria (as measured by UPCR 24h) from baseline to week 12[1,7]. The primary endpoint for cohort B was change in C3 deposit score (based on immunofluorescence microscopy) from kidney biopsy from baseline to week 12[1,7]. On completion of the study, all patients had the option to receive ongoing iptacopan in a long-term extension study (NCT03955445)[1].

About iptacopan

Iptacopan is an investigational, first-in-class, orally administered factor B inhibitor of the alternative complement pathway, targeting one of the key drivers of CDRDs[8-10]. It is the most advanced asset in the Novartis nephrology pipeline and has the potential to become the first targeted therapy to delay progression to dialysis in C3G[9]. Discovered at the Novartis Institutes for BioMedical Research, iptacopan is currently in development for a number of CDRDs where significant unmet needs exist, including C3G, IgA nephropathy (IgAN), atypical hemolytic uremic syndrome (aHUS), and idiopathic membranous nephropathy (iMN), as well as the blood disorder paroxysmal nocturnal hemoglobinuria (PNH).

Phase III studies in IgAN (APPLAUSE-IgAN) and aHUS (APPELHUS), and a Phase II study in iMN, are actively recruiting. Two Phase III studies in PNH (APPLY-PNH and APPOINT-PNH) are also actively recruiting. Based on disease prevalence and positive data from Phase II studies, iptacopan has received EMA PRIME designation for C3G, orphan drug designations from the FDA and EMA in C3G and PNH, EMA orphan drug designation in IgAN, and FDA Breakthrough Therapy Designation in PNH.

While Novartis has a 35-year history in kidney transplantation treatments, iptacopan is the first treatment in the nephrology pipeline addressing CDRDs. Our aim is to transform treatment by targeting one of the key drivers of these rare and often progressive diseases and, in doing so, potentially extend dialysis-free life for people with CDRDs[8-10].

About C3 glomerulopathy (C3G) and complement-driven renal diseases (CDRDs)

In C3G, an overly-active alternative complement pathway – part of the innate 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)[2,4,11-13]. This triggers inflammation and glomerular damage that results in proteinuria (protein in urine), hematuria (blood in urine) and reduced kidney function[2,4,11-13]. Approximately 50% of C3G patients progress to kidney failure within 10 years of diagnosis[2,3,13,14]. Among patients who have undergone kidney transplantation, disease recurrence is not uncommon, with one study seeing an estimated 30% and 70% risk of transplant loss at 5 and 10 years, respectively[2,13,14-16].

Each year, there are approximately 1-2 new cases of C3G per million people worldwide[17]. People with C3G have reported that their symptoms limit their physical and functional ability to perform day-to-day activities and also cause emotional stress[18].

CDRDs, which include C3G, are thought to arise from an overactivation of the alternative complement pathway, which creates inflammation and leads to tissue and kidney damage[9,19-21]. CDRDs mainly affect teenagers and young adults and can progress to kidney failure, which requires dialysis or transplantation and can lead to premature death[2-4,19-21].

There is a need for effective and well-tolerated, targeted therapies for C3G that can delay disease progression.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs nearly 15,000 people in the United States. For more information, please visit https://www.novartis.us.

Novartis and Novartis US is on Twitter. Sign up to follow @Novartis at https://twitter.com/novartisnews and @NovartisUS at https://twitter.com/NovartisUS.

For Novartis multimedia content, please visit https://www.novartis.com/news/media-library.

For questions about the site or required registration, please contact media.relations@novartis.com.

# # #

Novartis Media Relations

E-mail: media.relations@novartis.com

Julie Masow	**Jamie Bennett**
Head, US External Engagement	Director, US External Engagement
+1 862 579 8456	+1 862 217 3976
julie.masow@novartis.com	jamie.bennett@novartis.com

Novartis Investor Relations

E-mail: investor.relations@novartis.com

North America

Sloan Simpson
North America
+1 862 778 5052

SOURCE Novartis Pharmaceuticals Corporation

References

1. Wong E, Nester C, Cavero T, et al. Iptacopan, a novel oral complement alternative pathway Factor B inhibitor, significantly reduces urinary protein excretion and C3 Deposit Scores in native and transplanted kidneys in patients with C3 glomerulopathy. Presented at the American Society of Nephrology (ASN) 2021 Annual Meeting.
2. Smith RJH, Appel GB, Blom AM, et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat Rev Nephrol. 2019;15(3):129-143.
3. Nester CM, Smith RJ. Treatment options for C3 glomerulopathy. Curr Opin Nephrol Hypertens. 2013;22(2):231–237.
4. Ravindran A, et al. C3 glomerulopathy associated with monoclonal Ig is a distinct subtype. Kidney Int. 2018;94:178–86.
5. Wong E, Praga M, Nester C, et al. Iptacopan (LNP023): a novel oral complement alternative pathway factor B inhibitor safely and effectively stabilises eGFR in C3 glomerulopathy. Presented at the ERA-EDTA 2021 congress.
6. Wong, E et al. LNP023, a novel, oral complement alternative pathway Factor B inhibitor, safely and effectively reduces proteinuria in C3 glomerulopathy. Presented at the American Society of Nephrology Annual Meeting 2020.
7. Clinicaltrials.gov. Study on Efficacy and Safety of LNP023 in C3 Glomerulopathy Patients Transplanted and Not Transplanted. Available at: https://clinicaltrials.gov/ct2/show/NCT03832114. Accessed October 2021.
8. Merle NS, et al. Complement System Part II: Role in Immunity. Front Immunol. 2015;6:257.
9. Schubart A, et al. Small-molecule factor B inhibitor for the treatment of complement-mediated diseases. Proc Natl Acad Sci U S A. 2019;116(16):7926–7931.
10. Harris CL. Expanding horizons in complement drug discovery: challenges and emerging strategies. Semin Immunopathol. 2018;40(1):125–140.
11. Caravaca-Fontán F, et al. Update on C3 Glomerulopathy: A Complement-Mediated Disease. Nephron. 2020;144:272–80.
12. Schena F, et al. A Narrative Review on C3 Glomerulopathy: A Rare Renal Disease. Int J Mol Sci. 2020;21:525.
13. Medjeral-Thomas N, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. Clin J Am Soc Nephrol. 2014;9:46–53.
14. Goodship THJ, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017;91(3):539-551.
15. Regunathan-Shenk R, et al. Kidney transplantation in C3 glomerulopathy: a case series. Am J Kidney Dis. 2018:73:316–23.
16. Zand L, et al. Clinical Findings, Pathology, and Outcomes of C3GN after Kidney Transplantation. J Am Soc Nephrol 2014;25:1110–7.
17. Estimated by Decision Resources Group Epidemiology.
18. National Kidney Foundation. Voice of patient C3G report. August 2019.
19. Łukawska E, Polcyn-Adamczak M, Niemir ZI. The role of the alternative pathway of complement activation in glomerular diseases. Clin Exp Med. 2018;18(3):297–318.
20. Koscielska-Kasprzak K, Bartoszek D, Myszka M, Zabinska M, Klinger M. The complement cascade and

renal disease. Arch Immunol Ther Exp (Warsz). 2014;62(1):47–57.
21. De Vriese AS, Sethi S, Van Praet J, Nath KA, Fervenza FC. Kidney disease caused by dysregulation of the complement alternative pathway: An etiologic approach. J Am Soc Nephrol. 2015;26(12):2917–2929.

Source URL: *https://qa1.novartis.us/us-en/news/media-releases/novartis-iptacopan-meets-primary-endpoints-phase-ii-study-rare-kidney-disease-c3-glomerulopathy-c3g*

List of links present in page

1. https://qa1.novartis.us/us-en/us-en/news/media-releases/novartis-iptacopan-meets-primary-endpoints-phase-ii-study-rare-kidney-disease-c3-glomerulopathy-c3g
2. https://qa1.novartis.us/us-en/us-en/home
3. https://twitter.com/novartisnews
4. https://twitter.com/NovartisUS
5. https://www.novartis.com/news/media-library
6. mailto:media.relations@novartis.com
7. mailto:media.relations@novartis.com
8. mailto:julie.masow@novartis.com
9. mailto:jamie.bennett@novartis.com
10. mailto:investor.relations@novartis.com
11. https://clinicaltrials.gov/ct2/show/NCT03832114