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MEDIA & INVESTOR RELEASE

Novartis investigational iptacopan Phase III study demonstrates clinically meaningful and statistically significant proteinuria reduction in patients with C3 glomerulopathy (C3G)

Ad hoc announcement pursuant to Art. 53 LR

- *Phase III APPEAR-C3G study met its primary endpoint, demonstrating superiority of iptacopan vs. placebo in proteinuria reduction at six-month analysis[1]; the safety profile of iptacopan was consistent with previously reported data[1-3]*

- *C3 glomerulopathy (C3G) is an ultra-rare complement-mediated kidney disease, with approximately 50% of patients progressing to kidney failure within 10 years of diagnosis[4-7]; currently no treatments address the underlying cause of C3G[7-9]*

- *Novartis plans to review results with global health authorities to enable potential submissions in 2024; data will be submitted for presentation at an upcoming medical meeting*

- *Iptacopan demonstrated positive Phase III results in IgA nephropathy (IgAN) at the interim analysis and a late-stage development program is ongoing across four investigational indications[10-14]*

Basel, December 11, 2023 — Novartis today announced positive topline results from the six-month, double-blind period of the Phase III APPEAR-C3G study of iptacopan for the treatment of patients with C3 glomerulopathy (C3G)[1]. The study met its primary endpoint, with iptacopan (200 mg twice daily) demonstrating superiority compared to placebo in providing clinically meaningful and statistically significant proteinuria (protein in urine) reduction on top of background therapy at six months[1]. The safety profile of iptacopan was consistent with previously reported data[1-3].

The data will be submitted for presentation at an upcoming medical meeting and discussed with global health authorities anticipating potential regulatory submissions in 2024. The APPEAR-C3G study continues for a six-month, open-label period, in which all patients receive iptacopan, including those previously receiving placebo[12,15]. In addition, enrollment is ongoing in a separate cohort of adolescent patients with C3G[12,15].

“People living with C3 glomerulopathy have no approved treatment options indicated for this progressive disease, posing many challenges and uncertainty for these mostly young patients,” said Shreeram Aradhye, M.D., President, Development and Chief Medical Officer,

Novartis. “These positive results demonstrate the potential of iptacopan to provide clinically meaningful benefit in C3G and add to our growing body of evidence that supports its use across multiple complement-mediated diseases.”

Iptacopan, which is also being investigated in other complement-mediated diseases, recently achieved positive interim results in IgA nephropathy (IgAN)[10]. On December 5, 2023, the FDA approved iptacopan, under the brand name Fabhalta®, as the first oral monotherapy for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH), and it is currently being reviewed by the EMA for the same indication[16-17].

About the study
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 iptacopan (200 mg) in C3G patients[12,15]. In addition to the announced topline results for adult patients with C3G, enrollment is ongoing in a separate cohort of adolescent patients with C3G[12,15]. The study comprises a six-month double-blind period where patients were randomized 1:1 to receive iptacopan or placebo on top of background therapy, followed by a six-month open-label period where all patients receive iptacopan (including those who were previously on placebo) on top of background therapy[12,15].

The primary endpoint for the six-month double-blind period was proteinuria reduction at six months as measured by urine protein to creatinine ratio (UPCR)[12,15]. The primary endpoint for the open-label period is proteinuria reduction at 12 months (both treatment arms) and a comparison between proteinuria reduction at 6 and 12 months (placebo arm)[12,15]. Secondary endpoints include change in estimated glomerular filtration rate (eGFR), proportion of participants meeting composite renal endpoint criteria (≤15% reduction in eGFR and ≥50% reduction in UPCR), change in glomerular inflammation (as measured by disease total activity score in a renal biopsy), change in patient reported fatigue (as measured by FACIT-Fatigue score), and safety and tolerability[12,15].

About C3G
C3 glomerulopathy (C3G) is an ultra-rare, progressive complement-mediated kidney disease that initially presents in mostly children and young adults[4-6,18]. 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)[4,7,18-20]. This triggers inflammation and glomerular damage that results in proteinuria (protein in urine), hematuria (blood in urine) and reduced kidney function[4,7,18-20]. 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-transplant[21-24].

About iptacopan
Iptacopan is an oral, Factor B inhibitor of the alternative complement pathway[17].

Discovered at Novartis, iptacopan recently demonstrated clinically meaningful and highly statistically significant proteinuria reduction in patients with IgA nephropathy (IgAN) at the interim analysis in the Phase III APPLAUSE-IgAN study (NCT04578834)[10]. Iptacopan is also being investigated in Phase III studies for atypical hemolytic uremic syndrome (aHUS) (APPELHUS [NCT04889430]) and immune complex membranoproliferative glomerulonephritis (IC-MPGN) (APPARENT [NCT05755386])[13-14]. On December 5, 2023, the FDA approved iptacopan, under the brand name Fabhalta®, as the first oral monotherapy for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH), and it is currently being reviewed by the EMA for the same indication[16-17].

Based on disease prevalence, unmet needs and data from Phase II studies, iptacopan has received FDA Breakthrough Therapy Designation in C3G and PNH, orphan drug designations

from the FDA and EMA in PNH and C3G, EMA PRIME designation for C3G, and EMA orphan drug designation in IgAN[25-28].

Novartis and renal
Chronic kidney disease (CKD) affects 1 in 10 people worldwide[29]. People living with CKD may ultimately progress to kidney failure, requiring maintenance dialysis and/or kidney transplantation[30-31].

At Novartis, our mission in nephrology began 40 years ago with transplantation and immunosuppression. Our commitment continues today through our aim to transform the lives of people living with kidney diseases by investigating new options that may slow kidney disease progression and extend dialysis-free life.

We are committed to advancing the development of our renal portfolio, exploring potential therapeutic options to address the current unmet need for people living with C3G, IgAN, IC-MPGN, lupus nephritis and aHUS.

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This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plans,” “may,” “could,” “investigational,” “progressing,” “development,” “upcoming,” “ongoing,” “aim,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for iptacopan, or regarding potential future revenues from iptacopan. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that iptacopan will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that iptacopan will be commercially successful in the future. In particular, our expectations regarding iptacopan could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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.

Reimagine medicine with us: Visit us at **https://www.novartis.com** and connect with us on **LinkedIn, Facebook, X/Twitter** and **Instagram.**

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