Novartis receives FDA accelerated approval for Fabhalta® (iptacopan), the first and only complement inhibitor for the reduction of proteinuria in primary IgA nephropathy (IgAN)

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- *Fabhalta achieved a 44% proteinuria reduction from baseline in Phase III APPLAUSE-IgAN interim analysis, compared with 9% in placebo arm, demonstrating a clinically meaningful reduction of 38% vs. placebo (p<0.0001)[1]*
- *Fabhalta is an inhibitor of the alternative complement pathway, activation of which is thought to contribute to the pathogenesis of IgAN[1-4]*
- *Despite current standard of care, up to 50% of IgAN patients with persistent proteinuria progress to kidney failure within 10 to 20 years of diagnosis[5-11]*
- *This marks the first approval from Novartis' renal pipeline, which also includes atrasentan and zigakibart*

East Hanover, N.J., Aug. 7, 2024 -- Novartis today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for Fabhalta® (iptacopan), a first-in-class complement inhibitor for the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. This is generally defined as a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g[1]. Fabhalta specifically targets the alternative complement pathway of the immune system. When overly activated in the kidneys, the complement system is thought to contribute to the pathogenesis of IgAN[1-4].

This indication is granted under accelerated approval based on the pre-specified interim analysis of the Phase III APPLAUSE-IgAN study measuring reduction in proteinuria at 9 months compared to placebo. It has not been established whether Fabhalta slows kidney function decline in patients with IgAN. The continued approval of Fabhalta may be contingent upon verification and description of clinical benefit from the ongoing Phase III APPLAUSE-IgAN study, evaluating whether Fabhalta slows disease progression as measured by estimated glomerular filtration rate (eGFR) decline over 24 months[1]. The eGFR data are expected at study completion in 2025 and are intended to support traditional FDA approval.

"The heterogeneous and progressive nature of IgA nephropathy has made it challenging to effectively treat this disease. Thankfully, the treatment landscape is rapidly evolving," said Professor Dana Rizk, Investigator and APPLAUSE-IgAN Steering Committee Member and professor in the University of Alabama at Birmingham Division of Nephrology. "Mounting clinical evidence underscores the pivotal role of complement activation in IgA nephropathy. I am thrilled that this advancement is now available to help enable a targeted treatment approach for IgAN patients."

IgAN is a progressive, rare disease in which the immune system attacks the kidneys, often causing glomerular inflammation and proteinuria[12]. Approximately 25 people per million worldwide are newly diagnosed with IgAN each year[13]. Each person's disease journey is unique as IgAN progresses differently and treatment responses vary as well[12,14].

Despite current standard of care, up to 50% of IgAN patients with persistent proteinuria progress to kidney failure

within 10 to 20 years of diagnosis. These patients often require maintenance dialysis and/or kidney transplantation[5-11]. Effective, targeted therapies with different mechanisms of action can help physicians select the most appropriate treatment for patients[12,14].

Data supporting approval

The ongoing Phase III APPLAUSE-IgAN study is evaluating the efficacy and safety of twice-daily oral Fabhalta (200 mg) versus placebo in adult IgAN patients on a stable dose of maximally-tolerated renin-angiotensin system (RAS) inhibitor therapy with or without a stable dose of SGLT2i. The primary endpoint for the interim analysis was the percent reduction of proteinuria, a marker of kidney damage, measured by comparing UPCR at 9 months to baseline[1,4].

Fabhalta achieved a 44% reduction in proteinuria at 9 months relative to baseline, compared with a 9% reduction in the placebo arm, demonstrating a clinically meaningful and statistically significant 38% reduction vs. placebo ($p<0.0001$). The treatment effect on UPCR at 9 months was consistent across all subgroups, including age, sex, race and baseline disease characteristics (such as baseline eGFR and proteinuria levels), and the use of SGLT2i[1]. Fabhalta demonstrated a favorable safety profile, consistent with previously reported data[1,13]. In patients with IgAN, the most common adverse reactions (≥5%) with Fabhalta were upper respiratory tract infection, lipid disorder, and abdominal pain. Fabhalta may cause serious infections caused by encapsulated bacteria and is available only through a Risk Evaluation and Mitigation Strategy (REMS) that requires specific vaccinations[1].

Expanding commitment in IgAN

"Today's approval of Fabhalta as a first-in-class medicine for IgA nephropathy is an important milestone in our journey to evolve rare renal disease care by bringing new treatments to people in urgent need of options," said Victor Bultó, President US, Novartis. "We are deeply committed to those living with rare renal diseases and look forward to continued partnership with this community as we further advance our broad portfolio."

Novartis is advancing the late-stage development of two additional IgAN therapies with highly differentiated mechanisms of action: atrasentan, an investigational oral endothelin A receptor antagonist that received FDA filing acceptance in Q2 2024, and zigakibart, an investigational subcutaneously administered anti-APRIL monoclonal antibody that is currently in Phase III development.

"As a parent of a son living with the disease for 20 years, I understand firsthand the fear and uncertainty that come with an IgAN diagnosis, and the devastating impact it can have on patients and their families," said Bonnie Schneider, Director and Co-Founder, IgAN Foundation. "Today's approval offers new hope for people living with IgA nephropathy as it represents a treatment innovation that provides us with a new way to fight this multifaceted disease."

In addition to developing innovative medicines for people with rare renal diseases, Novartis offers resources to help eligible patients access their treatment. The comprehensive Novartis Patient Support program provides personalized assistance for patients to navigate insurance coverage and identify financial assistance options, and offers educational resources to get started and stay on treatment. Patients or providers can call Novartis Patient Support at 1-833-993-2242 or visit support.fabhalta.com to learn more.

About APPLAUSE-IgAN

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 Fabhalta (200 mg) in 518 adult primary IgAN patients[1,15].

The two primary endpoints of the study for the interim and final analysis, respectively, are proteinuria reduction at 9 months as measured by 24 hour UPCR, and the annualized total eGFR slope over 24 months[1,4]. 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, and change from baseline to 9 months in the fatigue scale as measured by the Functional Assessment Of Chronic Illness Therapy-Fatigue questionnaire[15,16].

The main study population included 250 IgAN patients with an eGFR ≥30 mL/min/1.73 m^2 and UPCR ≥1 g/g at baseline[15,16]. In addition, a smaller cohort of patients with severe renal impairment (eGFR 20–30 mL/min/1.73 m^2 at baseline) was also enrolled to provide additional information but will not contribute to the main efficacy analyses[1].

Indication
FABHALTA is a prescription medicine used to reduce protein in the urine (proteinuria) in adults with primary immunoglobulin A nephropathy (IgAN), who are at risk of their disease progressing quickly. It is not known if FABHALTA is safe and effective in children with IgAN.

FABHALTA has been approved based on a reduction of proteinuria. Continued approval may require results from an ongoing study to determine whether FABHALTA slows decline in kidney function.

Important Safety Information
FABHALTA is a medicine that affects part of the immune system and may lower one's ability to fight infections. FABHALTA increases the chance of getting serious infections caused by encapsulated bacteria, including Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type b. These serious infections may quickly become life-threatening or fatal if not recognized and treated early. Patients must complete or update vaccinations against Streptococcus pneumoniae and Neisseria meningitidis at least 2 weeks before the first dose of FABHALTA. If patients have not completed vaccinations and FABHALTA therapy must be started right away, they should receive the required vaccinations as soon as possible. If patients have not been vaccinated and FABHALTA must be started right away, they should also receive antibiotics to take for as long as their doctor tells them. If patients have been vaccinated against these bacteria in the past, they might need additional vaccinations before starting FABHALTA. Their doctor will decide if they need additional vaccinations. Vaccines do not prevent all infections caused by encapsulated bacteria. Patients should call their doctor or get emergency medical care right away if they have any of these signs and symptoms of a serious infection: fever with or without shivers or chills, fever with chest pain and cough, fever with high heart rate, headache and fever, confusion, clammy skin, fever and a rash, fever with breathlessness or fast breathing, headache with nausea or vomiting, headache with stiff neck or stiff back, body aches with flu-like symptoms, or eyes sensitive to light. Doctors will give their patients a Patient Safety Card about the risk of serious infections. Patients must carry it with them at all times during treatment and for 2 weeks after their last dose of FABHALTA. The risk of serious infections may continue for a few weeks after their last dose of FABHALTA. It is important for patients to show this card to any doctor who treats them. This will help doctors diagnose and treat patients quickly.

FABHALTA is only available through a program called the FABHALTA Risk Evaluation and Mitigation Strategy (REMS). Before patients can take FABHALTA, their doctor must enroll in the FABHALTA REMS program, counsel patients about the risk of serious infections caused by certain bacteria, give patients information about the symptoms of serious infections, make sure that patients are vaccinated against serious infections caused by encapsulated bacteria and that they receive antibiotics if they need to start FABHALTA right away and are not up to date on vaccinations, as well as give patients a Patient Safety Card about the risk of serious infections.

Patients should not take FABHALTA if they are allergic to FABHALTA or any of the ingredients in FABHALTA. Patients should not take FABHALTA if they have a serious infection caused by encapsulated bacteria, including Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae type b when starting FABHALTA.

Before taking FABHALTA, patients should tell their doctor about all their medical conditions, including if they have an infection or fever, have liver problems, are pregnant or plan to become pregnant (it is not known if FABHALTA

will harm an unborn baby), or are breastfeeding or plan to breastfeed as it is not known if FABHALTA passes into breast milk. Patients should not breastfeed during treatment and for 5 days after the final dose of FABHALTA.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking FABHALTA with certain other medicines may affect the way FABHALTA works and may cause side effects. Patients should know the medicines they take and the vaccines they receive. Patients should keep a list of them to show their doctor and pharmacist when they get a new medicine.

FABHALTA may cause serious side effects, including those mentioned above as well as increased cholesterol and triglyceride (lipid) levels in the blood. Doctors will do blood tests to check patients' cholesterol and triglycerides during treatment with FABHALTA. Doctors may start patients on medicine to lower cholesterol if needed.

The most common side effects of FABHALTA in adults include headache; nasal congestion, runny nose, cough, sneezing, and sore throat (nasopharyngitis); diarrhea; pain in the stomach (abdomen); infections (bacterial and viral); nausea; and rash.

Please see full Prescribing Information, including Boxed WARNING and Medication Guide.

Novartis 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 a broad renal R&D portfolio targeting the underlying causes of disease to preserve kidney function. We aim to help transform the lives of people living with kidney diseases enabling them to live longer without the need for dialysis or transplantation.

Discovered at Novartis, Fabhalta (iptacopan) is the first of our renal pipeline to receive FDA approval. Novartis is also studying the investigational agents atrasentan and zigakibart for IgAN.

Beyond IgAN, Fabhalta is in development for a range of additional rare diseases, including C3 glomerulopathy (C3G), atypical hemolytic uremic syndrome (aHUS), immune complex membranoproliferative glomerulonephritis (IC-MPGN) and lupus nephritis (LN). Studies are ongoing to evaluate the safety and efficacy profiles in these investigational indications and support potential regulatory submissions. Fabhalta submissions to the FDA and EMA for the treatment of C3G are planned by year-end.

Disclaimer
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," "plan," "may," "could," "would," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," "progress," "accelerated," "targets," "continued," "contingent," "progressive," "evolving," "enable," "innovation," "ongoing," "evaluating," "evolve," "committed," "advance," "advancing," "commitment," "to developing," "to provide, "development," "to address," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Fabhalta or the other investigational or approved products described in this press release, or regarding potential future revenues from such product. 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 Fabhalta or the other investigational or approved products described in this press release 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 such products will be commercially successful in the future. In particular, our expectations regarding such products 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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