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MEDIA & INVESTOR RELEASE

Novartis atrasentan Phase III data show clinically meaningful proteinuria reduction further advancing company's IgA nephropathy (IgAN) portfolio

- *In the ALIGN study, atrasentan, in addition to supportive care with a renin-angiotensin system (RAS) inhibitor, demonstrated a statistically significant 36.1% proteinuria (protein in urine) reduction vs. placebo + supportive care at 36 weeks*[1]
- *Endothelin A (ETA) receptor activation contributes to elevated proteinuria in IgAN*[2-5]*; atrasentan is a potent, selective ETA receptor antagonist with potential to reduce persistent proteinuria and preserve kidney function for a broad patient population*[1]
- *IgAN is a heterogeneous, progressive, rare kidney disease with a need for effective, targeted therapies*[6,7]*; up to 30% of patients with persistent proteinuria (≥1 g/day) progress to kidney failure within 10 years*[8]
- *Through its rare kidney disease portfolio, Novartis is committed to exploring a range of treatment options with different modes of action to slow IgAN progression*

Basel, May 25, 2024 – Novartis today presented results from a pre-specified interim analysis of the Phase III ALIGN study of atrasentan, an investigational oral selective endothelin A (ETA) receptor antagonist, in patients with IgA nephropathy (IgAN)[1]. Patients treated with atrasentan, in addition to supportive care (maximally tolerated and stable dose of a renin-angiotensin system [RAS] inhibitor), achieved a 36.1% ($p<0.0001$) reduction in proteinuria (as measured by 24-hour urine protein to creatinine ratio [UPCR]) at 36 weeks when compared to placebo on top of supportive care[1]. The results were presented during a late-breaking clinical trials session at the European Renal Association (ERA) Congress[1]. The study also showed atrasentan has a favorable safety profile consistent with previously reported data[1,9].

Proteinuria reduction is a recognized surrogate marker correlating with delaying progression to kidney failure and has been used as an endpoint in IgAN clinical trials to support accelerated regulatory approvals[10]. US FDA submission for atrasentan in IgAN is on track for the first half of 2024.

“For those living with IgAN and their families, the disease can have a significant impact not only physically, but also mentally. When my son Eddie was diagnosed with IgAN 20 years ago, there were no FDA-approved medicines developed to treat IgAN. That was as devastating as the diagnosis itself because we felt completely in the dark about how to manage the condition,” said Bonnie Schneider, Director and Co-Founder, IgAN Foundation. “It’s a disease that affects people differently, and what works for one person may not work for

another. We're pleased to see ongoing research into different treatments and are excited for a future where the community will have options to meet their individual needs."

The ALIGN study continues in a blinded manner, and therefore only limited interim analysis results can be presented[11,12]. The final analysis, including the key secondary endpoint of change from baseline in estimated glomerular filtration rate (eGFR) at 136 weeks, and the results in participants receiving a sodium-glucose co-transporter-2 (SGLT2) inhibitor as background care in an exploratory cohort, is expected in 2026[11,12].

"ETA receptor activation causes proteinuria, which is usually one of the first clinical signs of IgAN. Patients with persistent proteinuria have a poorer prognosis and are more likely to progress to kidney failure," said Professor Hiddo Heerspink, Professor of Clinical Trials and Personalized Medicine at the Department of Clinical Pharmacy and Pharmacology at the University Medical Center Groningen and ALIGN blinded Steering Committee Chair. "We need targeted treatment options that can support patients with IgAN across the care pathway. These data from the ALIGN study further demonstrate the ability of atrasentan to significantly reduce proteinuria and, if approved, its potential to become a new foundational treatment for people living with IgAN that can be seamlessly added to current supportive therapy."

"Atrasentan has the potential to help transform how IgAN is managed for many people living with this complex illness," said David Soergel, M.D., Global Head, Cardiovascular, Renal and Metabolism Development Unit, Novartis. "Our multi-product IgAN portfolio aims to address the needs of a broad, heterogenous patient population with different modes of action to target distinct drivers of the disease, with the ultimate goal of improving patient care in this therapeutic area."

At ERA, Novartis is also presenting new data across its rare disease portfolio, including 6-month data for Fabhalta® (iptacopan) in C3 glomerulopathy (C3G) from the Phase III APPEAR-C3G study, long-term 33-month efficacy and safety data for Fabhalta in C3G from the Phase II extension study, additional data for Fabhalta in IgAN from the 9-month interim analysis of the Phase III APPLAUSE-IgAN 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)[13-16].

About ALIGN
The ALIGN study (NCT04573478) is a global, randomized, multicenter, double-blind, placebo-controlled Phase III clinical trial comparing the efficacy and safety of atrasentan versus placebo in patients with IgAN at risk of progressive loss of kidney function[11,12]. In total, 340 patients with biopsy-proven IgAN with baseline total proteinuria ≥1 g/day despite optimized RAS inhibitor treatment were randomized to receive once-daily oral doses of atrasentan (0.75 mg) or placebo for approximately 2.5 years (132 weeks)[11,12]. Patients continue receiving a maximally tolerated and stable dose of a RAS inhibitor as supportive care (unless they are unable to tolerate RAS inhibitor therapy)[11,12]. An additional group of 64 patients receiving a stable dose of SGLT2 inhibitor for at least 12 weeks have also been enrolled[11,12].

The primary efficacy endpoint of the study is change in proteinuria as measured by 24-hour UPCR from baseline to 36 weeks[11,12]. Secondary and exploratory objectives include evaluating the change in kidney function from baseline to 136 weeks as measured by eGFR, as well as safety and tolerability[11,12].

About atrasentan
Atrasentan is an investigational potent and selective oral ETA receptor antagonist, currently in Phase III development for IgAN and early-stage development for other rare kidney diseases[1,11,12,17]. Activation of the ETA receptor contributes to elevated proteinuria, which is associated with kidney damage, fibrosis and loss of kidney function in IgAN[2-5]. Atrasentan has potential to be added to current supportive therapy to reduce persistent proteinuria and preserve kidney function for a broad patient population[1]. Preclinical models have also suggested that atrasentan may reduce inflammation and fibrosis in IgAN[18-21].

About IgA nephropathy (IgAN)
IgAN is a heterogeneous, progressive, rare kidney disease[6]. Each year, approximately 25 people per million worldwide are newly diagnosed with IgAN[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 years[8]. There is a need for effective, targeted therapies for IgAN that can help slow or prevent progression to kidney failure[6,7,23].

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, immune complex membranoproliferative glomerulonephritis (IC-MPGN) and lupus nephritis (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.

IgAN is a heterogeneous disease presenting with a variety of clinical manifestations, phenotypes, and variable speeds of progression[6]. In addition to atrasentan, Novartis is advancing the development of two other therapies in IgAN with highly differentiated mechanisms of action: Fabhalta, an investigational oral Factor B inhibitor of the alternative complement pathway, and zigakibart, an investigational subcutaneously administered anti-APRIL monoclonal antibody, which are both in Phase III development[24-26]. Through our IgAN pipeline, we are committed to creating a portfolio of innovative medicines that improve and extend the lives of people living with kidney disease.

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About Novartis
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