

MEDIA & INVESTOR RELEASE

Novartis investigational atrasentan Phase III study demonstrates clinically meaningful and highly statistically significant proteinuria reduction in patients with IgA nephropathy (IgAN)

Ad hoc announcement pursuant to Art. 53 LR

- *Phase III ALIGN study met its primary endpoint, demonstrating superiority of atrasentan vs. placebo in proteinuria reduction at 36-week interim analysis¹; the safety profile of atrasentan was consistent with previously reported data^{1,2-4}*
- *IgAN is a progressive kidney disease, affecting mostly young adults, and is a major cause of chronic kidney disease and kidney failure worldwide⁵*
- *Novartis plans to review interim results with FDA to enable a potential regulatory submission for accelerated approval; study continues with final readout expected in the first quarter of 2026*
- *Novartis is advancing the development of three highly differentiated therapies in IgAN, with the potential to address unmet needs for people living with the disease*

Basel, October 30, 2023 — Novartis today announced positive topline results from the interim analysis of the ongoing pivotal Phase III ALIGN study (NCT04573478) of atrasentan, an oral endothelin A receptor antagonist (ERA), in patients with IgA nephropathy (IgAN)¹. The study met its primary efficacy endpoint at the 36-week interim analysis, with atrasentan demonstrating superiority versus placebo with a clinically meaningful and highly statistically significant reduction in proteinuria (protein in urine) in patients with IgAN receiving supportive care (maximally tolerated and stable dose of a renin-angiotensin system [RAS] inhibitor)¹. In the study, the safety profile of atrasentan was consistent with previously reported data from the Phase II AFFINITY study IgAN cohort^{1,2-4}. Based on the results from this interim proteinuria endpoint analysis, Novartis plans to submit an application in 2024 for possible accelerated approval in the US.

“These positive topline Phase III data showcase the potential of atrasentan to improve outcomes for patients with IgAN by demonstrating clinically meaningful proteinuria reduction,” said Shreeram Aradhya, M.D., President, Development and Chief Medical Officer, Novartis. “Along with investigational iptacopan, which recently also showed positive topline Phase III results, and investigational zigakibart, our development portfolio of three highly differentiated late-stage therapies in IgAN has the potential to provide much-needed treatment options for people living with this debilitating disease.”

IgAN is a major cause of chronic kidney disease and kidney failure, and mostly affects young adults⁵. Up to 30% of people who have IgAN with persistent higher levels of proteinuria (≥ 1 g/day) progress to kidney failure within 10 years⁶. There is a need for effective therapies for IgAN that can help slow progression to kidney failure^{5,7,8}.

Atrasentan, an investigational oral endothelin A receptor antagonist in development for IgAN and other rare kidney diseases, was added to the Novartis portfolio through the recent acquisition of Chinook Therapeutics along with investigational zigakibart (BION-1301), a subcutaneously administered anti-APRIL monoclonal antibody in Phase III development for IgAN⁹. The addition of these two late-stage medicines, as well as an early-stage pipeline, expands the Novartis renal portfolio, which also includes iptacopan, an investigational factor B inhibitor that recently achieved positive Phase III interim results in IgAN¹⁰. Novartis is advancing the development of these three potential therapeutic options, with different mechanisms of action, to address unmet needs in IgAN and other rare kidney diseases.

The ALIGN study continues in a blinded manner to evaluate the change in kidney function over 136 weeks as measured by estimated glomerular filtration rate (eGFR), with topline results from the confirmatory endpoint analysis expected in the first quarter of 2026^{11,12}.

About the study

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}. Approximately 340 patients with biopsy-proven IgAN with baseline total proteinuria over one gram per 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 (renin-angiotensin system) inhibitor as supportive care (unless they are unable to tolerate RAS inhibitor therapy)^{11,12}. An additional group of up to 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 urine protein to creatinine ratio (UPCR) from baseline to 36 weeks^{11,12}. Secondary and exploratory objectives include evaluating the change in kidney function from baseline to week 136 as measured by eGFR, as well as safety and tolerability^{11,12}. Topline results from the confirmatory endpoint analysis are expected in the first quarter of 2026^{11,12}.

About atrasentan

Atrasentan is an investigational oral endothelin A receptor antagonist (ERA), currently in Phase III development for IgAN and early-stage development for other rare kidney diseases^{2-4,9,11,12}. Atrasentan has shown significant reductions in proteinuria versus baseline in a Phase II trial for IgAN²⁻⁴.

About IgA nephropathy (IgAN)

IgAN is a progressive, rare kidney disease that mostly affects young adults⁵. It is estimated that approximately 110,000 people in the US and 47,000 people across 10 European countries live with IgAN, with approximately 25 people per million newly diagnosed with IgAN each year globally^{5,13-16}.

In IgAN, autoimmune reaction to an abnormal form of IgA results in formation of immune complexes that deposit in the kidney^{5,7,17-19}. These immune complexes trigger an inflammatory response leading to progressive kidney damage and loss of kidney function^{5,7,17-19}. Up to 30% of people who have IgAN with persistent higher levels of proteinuria (≥ 1 g/day) progress to kidney failure within 10 years⁶.

There is a need for effective therapies for IgAN that can help slow progression to kidney failure^{5,7,8}.

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 "plans," "accelerated," "continues," "advancing," "potential," "to address," "ongoing," "to submit," "transform," "investigational," "advancing," "will," "to evaluate," "can," "expected," "progressive," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for atrasentan or the other investigational or approved products described in this press release, or regarding potential future revenues from such products. 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 atrasentan 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 atrasentan or the other investigational or approved products described in this press release 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 a focused 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](#).

References

1. Novartis data on file.
2. Chinook Therapeutics Presents Updated Data from Atrasentan Phase 2 AFFINITY IgA Nephropathy (IgAN) Patient Cohort, Preclinical Atrasentan Research and Ongoing Clinical Trials at the American Society of Nephrology (ASN) Kidney Week 2022. Chinook Therapeutics, Inc. Accessed October 18, 2023. <https://investors.chinooktx.com/news-releases/news-release-details/chinook-therapeutics-presents-updated-data-atrasentan-phase-2>
3. Kim SG, Akinfolarin AA, Inker LA, et al. WCN23-1117 ATRASENTAN IN PATIENTS WITH PROTEINURIC GLOMERULAR DISEASES – THE AFFINITY STUDY. *Kidney Int Rep.* 2023;8(9):1902. doi:10.1016/j.ekir.2023.02.1089.
4. Kim SG, Inker LA, Packham DK, et al. WCN23-1126 ATRASENTAN FOR THE TREATMENT OF IGA NEPHROPATHY: INTERIM RESULTS OF THE AFFINITY STUDY. *Kidney Int Rep.* 2023;8(9):1902. doi:10.1016/j.ekir.2023.02.1088.
5. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4):S1-S276. doi:10.1016/j.kint.2021.05.021.
6. Reich HN, Troyanov SAA, Scholey JW, Cattran DC. Remission of Proteinuria Improves Prognosis in IgA Nephropathy. *J Am Soc Nephrol.* 2007;18(12):3177-3183. doi:10.1681/ASN.2007050526.

7. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. *Kidney Int.* 2012;81(9):833-843. doi:10.1038/ki.2011.501.
8. Xie J, Kiryluk K, Wang W, et al. Predicting Progression of IgA Nephropathy: New Clinical Progression Risk Score. Moura IC, ed. *PLoS ONE.* 2012;7(6):e38904. doi:10.1371/journal.pone.0038904.
9. Novartis completes acquisition of Chinook Therapeutics. Novartis. Accessed October 18, 2023. <https://www.novartis.com/news/media-releases/novartis-completes-acquisition-chinook-therapeutics>
10. Novartis investigational iptacopan Phase III study demonstrates clinically meaningful and highly statistically significant proteinuria reduction in patients with IgA nephropathy (IgAN). Novartis. Accessed October 18, 2023. <https://www.novartis.com/news/media-releases/novartis-investigational-iptacopan-phase-iii-study-demonstrates-clinically-meaningful-and-highly-statistically-significant-proteinuria-reduction-patients-iga-nephropathy-igan>
11. ClinicalTrials.gov. Atrasentan in Patients With IgA Nephropathy (ALIGN). NCT04573478. Accessed October 18, 2023. <https://clinicaltrials.gov/study/NCT04573478>
12. Lambers Heerspink H, Jardine M, Kohan DE, et al. WCN23-1085 A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATRASENTAN IN PATIENTS WITH IGA NEPHROPATY- THE ALIGN STUDY. *Kidney Int Rep.* 2023;8(3):S279-S280. doi:10.1016/j.ekir.2023.02.630.
13. McGrogan A, Franssen CFM, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrol Dial Transplant.* 2011;26(2):414-430. doi:10.1093/ndt/gfq665.
14. Lerma EV, Bensink ME, Thakker KM, et al. Impact of Proteinuria and Kidney Function Decline on Health Care Costs and Resource Utilization in Adults With IgA Nephropathy in the United States: A Retrospective Analysis. *Kidney Med.* 2023;5(9). doi:10.1016/j.xkme.2023.100693.
15. U.S. Census Bureau. QuickFacts: United States. Accessed October 26, 2023. <https://www.census.gov/quickfacts/fact/table/US/PST045222>
16. Willey CJ, Coppo R, Schaefer F, Mizerska-Wasiak M, Mathur M, Schultz MJ. The incidence and prevalence of IgA nephropathy in Europe. *Nephrol Dial Transplant.* 2023;38(10):2340-2349. doi:10.1093/ndt/gfad082.
17. Lafayette RA, Kelepouris E. Immunoglobulin A Nephropathy: Advances in Understanding of Pathogenesis and Treatment. *Am J Nephrol.* 2018;47(Suppl. 1):43-52. doi:10.1159/000481636.
18. Lai KN, Tang SCW, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primer.* 2016;2(1):16001. doi:10.1038/nrdp.2016.1.
19. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. *Clin J Am Soc Nephrol.* 2017;12(4):677-686. doi:10.2215/CJN.07420716.

###

Novartis Media Relations

E-mail: media.relations@novartis.com

Central

Richard Jarvis +41 79 584 2326
 Anja von Treskow +41 79 392 9697
 Anna Schäfers +41 79 801 7267

North America

Julie Masow +1 862 579 8456
 Michael Meo +1 862 274 5414
 Marlena Abdinoor +1 617 335 9525

Switzerland

Satoshi Sugimoto +41 79 619 2035

Novartis Investor Relations

Central investor relations line: +41 61 324 7944

E-mail: investor.relations@novartis.com

Central

Samir Shah +41 61 324 7944
 Nicole Zinsli-Somm +41 61 324 3809
 Isabella Zinck +41 61 324 7188
 Imke Kappes +41 61 324 82 69
 Zain Iqbal +41 61 324 03 90

North America

Sloan Simpson +1 862 345 4440
 Parag Mahanti +1 973 876 4912
 Jonathan Graham +1 201 602 9921