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PRESS RELEASE

Novartis Leqvio® shows statistically significant and clinically meaningful early LDL-C goal achievement with less muscle pain

- *V-DIFFERENCE is first study to show that Leqvio prioritized after statins helps more patients achieve guideline low-density lipoprotein cholesterol (LDL-C) goals early with reduced muscle pain*[1]

- *85% of patients on Leqvio plus individually optimized lipid-lowering therapy (LLT) achieved LDL-C targets within 90 days vs. 31% of patients on placebo plus LLT*[1]

- *Patients on Leqvio plus LLT were 43% less likely to experience muscle-related adverse events compared to those on placebo plus LLT*[1]

Basel, August 30, 2025 – Novartis today announced positive results from V-DIFFERENCE, a Phase IV study evaluating Leqvio® (inclisiran) compared to placebo, both administered on top of individually optimized lipid-lowering therapy (LLT), in patients with high cholesterol (hypercholesterolemia) who have not achieved guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals[1]. These data will be presented in one of the Hot Line sessions of the 2025 European Society of Cardiology (ESC) Congress, held in Madrid, Spain, from August 29 to September 1, 2025.

After 90 days of treatment with Leqvio on top of LLT, 85% of patients achieved their guideline-recommended LDL-C target compared to 31% of those receiving placebo on top of LLT ($p<0.0001$)[1]. Significant benefits were observed as early as 30 days with 81% of patients achieving LDL-C targets[1]. Results were consistent regardless of age, sex, or cardiovascular risk of trial participants.The results of the V-DIFFERENCE study add to the growing body of evidence for Leqvio within the VictORION clinical program, which encompasses more than 60,000 patients from 50 countries worldwide.

“V-DIFFERENCE is the largest LDL-C lowering study with Leqvio to read out to date, and the first to focus on patient-centered outcomes," said Ulf Landmesser, M.D., Chairman of the Department of Cardiology, Angiology and Intensive Care Medicine at German Heart Center of Charité and Charité University Medicine Berlin. "These findings are significant as they demonstrate effective options for lipid management improvement in patients at risk, a majority of whom continue to remain above recommended LDL-C levels."

V-DIFFERENCE is the first study to evaluate the effect of Leqvio on muscle symptoms and pain, which are common amongst patients receiving statins and other LLT[1,2]. Patients who received Leqvio plus LLT were 43% less likely to experience muscle-related adverse events (MRAE) compared to patients who received placebo plus LLT ($p<0.0001$), with numerical improvement in pain-related quality-of-life scores also reported [1]. Furthermore, Leqvio on top

of LLT reduced LDL-C levels on average by 59% after 360 days of treatment, outperforming placebo plus LLT by 35% ($p<0.0001$), with clinically significant differences observed as early as 60 days into treatment [1].

“Novartis is dedicated to tackling the most challenging problems in cardiovascular disease,” said Ruchira Glaser, M.D., Global Head, Cardiovascular, Renal and Metabolic Development Unit, Novartis. “These results highlight the potential of Leqvio to transform cardiovascular care by improving meaningful patient outcomes. V-DIFFERENCE has provided evidence that early use of Leqvio is an effective way to help patients reach their LDL-C goals faster without the need to add other therapies or maximize statin doses.”

About Leqvio
Leqvio® (inclisiran) is the first and only small interfering RNA (siRNA) therapy to lower low-density lipoprotein cholesterol (LDL-C). It is a subcutaneous injection given by a healthcare provider (HCP) with an initial dose, another at three months, and then every six months[3,4]. As a twice-yearly, HCP-administered treatment, Leqvio may help to circumvent the challenges of treatment adherence, a common issue in cholesterol management.

Leqvio is approved in more than 100 countries, including the US, EU, Japan and China[3-6]. Novartis obtained global rights to develop, manufacture and commercialize Leqvio under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNA interference (RNAi) therapeutics.

About V-DIFFERENCE
V-DIFFERENCE (NCT05192941) is a randomized, double-blind, placebo-controlled Phase IV study to evaluate the efficacy, safety, and quality-of-life (QoL) outcomes of Leqvio compared to placebo, on top of individually optimized lipid-lowering therapy (LLT), in individuals with high cholesterol (hypercholesterolemia) at high and very high cardiovascular risk who have not achieved guideline-recommended LDL-C goals[2]. A total of 1,770 individuals were randomized in a 1:1 ratio to receive Leqvio plus LLT (n=898) or placebo plus LLT (n=872)[1].

The primary endpoint was the proportion of patients achieving their individual LDL-C target (<55 mg/dL or <70 mg/dL, depending on the cardiovascular risk category) after 90 days of treatment[7]. Key secondary endpoints included the percentage change from baseline in mean LDL-C level, and the proportion of patients experiencing at least one muscle-related adverse event (MRAE) after 360 days of treatment[7]. Other secondary endpoints included the proportion of patients experiencing self-reported pain, and pain-related QoL measures using the Short-Form Brief Pain Inventory (SF-BPI) after 360 days of treatment[7].

About VictORION
The V-DIFFERENCE study is part of VictORION, a clinical trial program to expand the foundational evidence of LDL-C reduction with Leqvio in diverse patient populations through randomized clinical trials, implementation research, real-world evidence, and primary and secondary prevention trials assessing the potential benefits of Leqvio on cardiovascular outcomes. The VictORION program is one of the largest clinical trial programs of its kind, enrolling over 60,000 patients in more than 50 countries worldwide across more than 30 trials, including ORION-4 (secondary prevention), V-2-PREVENT (secondary prevention), V-1-PREVENT (high-risk primary prevention), V-INTERVENTION, V-PLAQUE, and V-RIDES.

About Atherosclerotic Cardiovascular Disease (ASCVD)
Cardiovascular disease (CVD) affects hundreds of millions of people and claims more lives globally than cancer, chronic lung disease and diabetes combined[8]. Around 80% of premature cardiovascular deaths can be prevented by addressing factors that cause or worsen CVD[9].

ASCVD accounts for 85% of all cardiovascular deaths[10-13]. It is the primary cause of mortality in the European Union and its burden in the US is greater than that of any other chronic diseases[10-13]. ASCVD is caused by the development and growth of plaques in the inner lining

of the arteries[14]. The atherosclerotic plaque is mainly composed of LDL-C that accumulates over time[15]. Cumulative exposure to LDL-C can increase one's risk of cardiovascular events such as a heart attack or stroke[14,15].

About Novartis in Cardiovascular Disease
At Novartis, our mission is to ensure no heart is lost too soon. We envision a world where preventable cardiovascular deaths are no longer part of our lives. We're proud of the positive impact we've made over the past 40 years and remain dedicated to tackling the most challenging problems in CVD. Through cutting-edge science and technology, we are focusing on areas of high unmet need, including scaling our xRNA platform across multiple risk factors and pioneering breakthroughs for genetically driven CVD risk factors and common heart conditions, including atrial fibrillation.

We also work with patients, healthcare professionals, and organizations around the world to improve cardiovascular care beyond medicine alone. Together, we can help people with CVD enjoy longer, healthier lives and more time with their loved ones.

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," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the 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 the 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 nearly 300 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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