

MEDIA UPDATE

Leqvio^{®*} (inclisiran) reduced LDL-C in people who are overweight or obese

- *Regardless of body mass index (BMI), Leqvio provided sustained and effective LDL-C reduction of ~50% with two doses a year**, according to pooled analysis of three Phase III studies¹*
- *Being overweight or obese is often associated with elevated LDL-C levels, or “bad” cholesterol, and may contribute to an increased risk for a cardiovascular event, such as a heart attack or stroke²*
- *LDL-C is one of the most readily modifiable risk factors for ASCVD; however, despite widespread statin use, up to 80% of patients do not reach guideline-recommended LDL-C targets^{3,4}*

Basel, November 8, 2021 — Novartis today announced results from a pooled post-hoc analysis of Phase III ORION-9, -10 and -11 trials, exploring the impact of body mass index (BMI) levels on the efficacy and safety of twice-yearly** Leqvio[®] (inclisiran). At month 17, Leqvio was well-tolerated and provided effective and sustained reduction of approximately 50%, difference from placebo, in low-density lipoprotein cholesterol (LDL-C) when used in addition to other lipid-lowering therapies across all BMI types¹. Results were presented at the American Heart Association Scientific Sessions 2021.

“For patients with vascular disease who have a high BMI, physicians generally recommend weight loss in addition to cholesterol-lowering medication,” said Lawrence A. Leiter, MD, Director of the Lipid Clinic, Associate Director of the Clinical Nutrition and Risk Factor Modification Centre and Associate Scientist in the Li Ka Shing Knowledge Institute of St. Michael’s Hospital, Toronto, Canada. “Despite our best efforts, however, weight loss isn’t always achievable. The BMI analysis sheds new light on the potential of inclisiran (Leqvio) in helping patients reduce their LDL-C by up to half with only twice-yearly dosing no matter what their weight.”

Regardless of BMI, Leqvio showed effective and sustained lipid lowering compared to placebo across a range of atherogenic lipids demonstrating that its pharmacology does not appear to be impacted by excessive body weight. In addition to lowering LDL-C levels by approximately 50%, reductions were also seen across triglycerides (~10%), total cholesterol (~33%), non-HDL-C (~45%) and ApolipoproteinB (~40%). The trials included adults with ASCVD, HeFH and ASCVD risk equivalent¹. Leqvio had a tolerability profile similar to placebo. Serious adverse events increased with BMI levels in both placebo and Leqvio treatment arms. Treatment emergent adverse events (TEAEs) at the injection site were more frequent with

Leqvio, but all were mild or moderate¹. The effect of Leqvio on cardiovascular morbidity and mortality has not been determined.

**Product and brand name are currently under FDA review.*

***After an initial dose and one at three months.*

About the ORION Phase III low-density lipoprotein cholesterol (LDL-C)-lowering studies

ORION-9 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of Leqvio 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose⁵, Leqvio was then administered again at three months and then every six months thereafter in 482 participants with clinical or genetic evidence of heterozygous familial hypercholesterolemia and elevated LDL-C, despite a maximally tolerated dose of LDL-C-lowering therapies (e.g., a statin or ezetimibe). For the primary endpoints of ORION-9, Leqvio delivered mean placebo-adjusted percentage change in LDL-C reductions of 48% ($P<.0001$) at 510 days and demonstrated time-adjusted percentage change in LDL-C reductions of 44% ($P<.0001$) from 90 through 540 days. The international study was conducted at 46 sites in eight countries^{5,6}.

ORION-10 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of Leqvio 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose⁷, Leqvio was then administered again at three months and then every six months thereafter in 1,561 participants with atherosclerotic cardiovascular disease (ASCVD) and elevated LDL-C, despite a maximally tolerated dose of LDL-C-lowering therapies (e.g., a statin and/or ezetimibe). For the primary endpoints of ORION-10, Leqvio delivered mean placebo-adjusted percentage change in LDL-C reductions of 52% ($P<.0001$) at 510 days and demonstrated time-adjusted percentage change in LDL-C reductions of 54% ($P<.0001$) from 90 through 540 days. The study was conducted at 145 sites in the United States^{6,7}.

ORION-11 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of Leqvio 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose⁷, Leqvio was then administered again at three months and then every six months thereafter in 1,617 patients with ASCVD or ASCVD-risk equivalents and elevated LDL-C despite a maximally tolerated dose of statin therapy (with or without ezetimibe). For the primary endpoints of ORION-11, Leqvio delivered placebo-adjusted change in LDL-C reductions of 50% ($P<.0001$) at 510 days and demonstrated time-adjusted LDL-C reductions of 49% ($P<.0001$) from 90 through 540 days. The international study was conducted at 70 sites in seven countries^{6,7}.

The Phase III ORION-9, -10 and -11 trials are part of the larger Leqvio VictORION dynamic evidence generation program.

About atherosclerotic cardiovascular disease (ASCVD)

Atherosclerosis corresponds to the accumulation of lipids over time mainly low-density lipoprotein cholesterol (LDL-C) in the inner lining of the arteries. Unexpected rupture of the atherosclerotic plaque can cause an atherosclerotic cardiovascular event such as a heart attack or stroke^{8,9}. ASCVD accounts for over 85% of all cardiovascular disease deaths¹⁰. ASCVD is the primary cause of death in the European Union and its burden in the United States is greater than that from any other chronic diseases^{11,12}. ASCVD risk-equivalent corresponds to conditions that confer a similar risk for an ASCVD event (e.g., diabetes, heterozygous familial hypercholesterolemia)^{7,13}.

About Leqvio® (inclisiran)

Leqvio (inclisiran, KJX839) is the first and only small interfering RNA (siRNA) therapy to reduce low-density lipoprotein cholesterol (LDL-C) levels via an RNA interference (RNAi) mechanism of action and could help improve outcomes for patients with atherosclerotic cardiovascular disease (ASCVD), a deadly form of cardiovascular disease^{5,7,14}. With two doses a year** and effective and sustained LDL-C reduction, Leqvio works as a complement to statins^{5,7}. Leqvio works differently from other therapies by preventing the production of the target protein in the liver, increasing hepatic uptake of LDL-C and clearing it from the bloodstream¹⁴. Leqvio is dosed initially, again at three months and then once every six months^{5,7}. In three clinical trials, patients taking Leqvio maintained LDL-C reduction throughout each six-month dosing interval^{7,9}. Administered in-office as a subcutaneous injection, Leqvio is expected to integrate seamlessly into a patient's healthcare routine^{5,7}.

In the Phase III trials, Leqvio was well-tolerated. The most common adverse events reported (≥3% of patients treated with Leqvio and occurring more frequently than placebo) were injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity and dyspnea. Among those, injection site reactions were the most frequent ones. Those were generally mild, and none were severe or persistent.

Novartis has obtained global rights to develop, manufacture and commercialize Leqvio under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics.

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This media update 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 media update, 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 media update 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 such as COVID-19; 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 media update as of this date and does not undertake any obligation to update any forward-looking statements contained in this media update as a result of new information, future events or otherwise.

About Novartis in Cardiovascular-Renal-Metabolism

Cardiovascular (CV), renal and metabolic diseases are a global health crisis^{10,15-17}.

These chronic, complex and often hereditary diseases are frequently inter-related, and come with healthcare and treatment barriers and a lack of transformative medicines and almost always lead to the same outcome: death due to CV disease^{10,15-17}.

CV disease is the number one killer in the world¹⁰. Taking more lives than all cancers combined, it contributes to one in every three deaths globally^{10,18}. Of all CV events, 80% can be prevented¹⁹. Patients and their families deserve better, and our society deserves more.

Thanks to a combination of our legacy, global footprint and leading science, Novartis is uniquely positioned to help change this landscape. We are transforming the way we think about the relationship between these diseases and how they are managed throughout life. Our efforts include the use of early interventions and the development of pioneering treatments that address the spectrum of CV, renal and metabolic diseases, from prevention to management, as well as the creation of innovative access models. By re-writing the way we work with society, we will lead a worldwide effort to improve health outcomes and roll back the crisis of CV death.

Our goal is to bend the curve of life by reducing and stopping premature death from CV disease.

About Novartis

Novartis is reimaging medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 108,000 people of more than 140 nationalities work at Novartis around the world. Find out more at <https://www.novartis.com>.

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