

## MEDIA UPDATE

# Novartis receives EU approval for Leqvio<sup>®\*</sup> (inclisiran), a first-in-class siRNA to lower cholesterol with two doses a year<sup>\*\*</sup>

- *Leqvio<sup>®</sup> (inclisiran) is the first and only approved small-interfering RNA (siRNA) low-density lipoprotein cholesterol (LDL-C) lowering treatment in Europe<sup>1-3</sup>*
- *Cardiovascular disease causes 3.9 million deaths annually in Europe, and 80% of high-risk patients do not reach guideline-recommended LDL-C targets despite the widespread use of statins<sup>4-7</sup>*
- *Approval is based on a robust clinical development program demonstrating effective and sustained LDL-C reduction of up to 52% in patients with elevated LDL-C despite maximally tolerated statin therapy<sup>1,2</sup>*
- *Novartis is committed to improving population health outcomes in CVD by partnering with European healthcare systems to identify new ways of bringing transformative innovations to patients with atherosclerotic cardiovascular disease who are struggling to reach their LDL-C goals*
- *Leqvio is currently under review by the U.S. Food and Drug Administration and other health authorities*

**Basel, December 11, 2020** — Novartis announced today that the European Commission (EC) has approved Leqvio<sup>®</sup> (inclisiran) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia. This approval is based on the results of the robust ORION clinical development program, where Leqvio provided an effective and sustained low-density lipoprotein cholesterol (LDL-C) reduction of up to 52% in patients with elevated LDL-C, despite maximally tolerated statin therapy. With two doses a year, after an initial dose and one at 3 months, Leqvio is expected to support long-term adherence<sup>1-3</sup>.

Leqvio is a first-in-class small interfering RNA (siRNA) providing effective and sustained LDL-C reduction for patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalent and heterozygous familial hypercholesterolemia (HeFH), which are major drivers of heart attacks, strokes and may ultimately lead to death<sup>1-3</sup>.

“Long-term exposure to persistently elevated LDL-C increases the risk of ASCVD<sup>8</sup>, which may lead to a cardiovascular event such as a heart attack or a stroke. As the first and only siRNA providing effective and sustained LDL-C reduction, Leqvio will give an opportunity to change how elevated LDL-C is treated, a highly important modifiable risk factor for ASCVD,” said Professor Ulf Landmesser, M.D., Director of Charité Center for Cardiovascular Diseases, Berlin. “With only two doses a year administered by a healthcare professional, Leqvio is

expected to circumvent the challenges of treatment adherence by improving therapeutic coverage and persistence.”

“Cardiovascular disease remains the leading cause of mortality in Europe<sup>4</sup>, which demonstrates the urgent need for innovative treatments for patients struggling to reach their LDL-C goals. With Leqvio, we’re proud to bring a first-in-class treatment delivering effective and sustained LDL-C reduction that has the potential to improve outcomes for people living with ASCVD,” said Marie-France Tschudin, President, Novartis Pharmaceuticals. “At Novartis, we’re committed to reimagining care for cardiovascular disease by working together with healthcare systems and other stakeholders to explore innovative access models and bend the curve of life for patients.”

Leqvio is approved for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximally tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The EC marketing authorization is valid in the 27 countries that are members of the EU. Norway, Iceland and Liechtenstein, as members of the European Economic Area (EEA), will take corresponding decisions based on the EC’s recommendation.

Leqvio is also under review by the U.S. Food and Drug Administration for adults who have elevated LDL-C while being on a maximally tolerated dose of statin therapy.

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

*\*\*After an initial dose and one at 3 months.*

### **About the ORION Phase III 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 inclisiran sodium salt 300 mg, equivalent to 284 mg of inclisiran, administered subcutaneously by a healthcare professional. Starting with an initial dose<sup>1</sup>, inclisiran was then administered again at 3 months and then every 6 months thereafter in 482 participants with clinical or genetic evidence of heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (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, inclisiran delivered mean placebo-adjusted percentage change in LDL-C reductions of 48% ( $P<.0001$ ) at 17 months and demonstrated time-adjusted percentage change in LDL-C reductions of 44% ( $P<.0001$ ) from 3 through 18 months. The international study was conducted at 46 sites in eight countries<sup>1,9</sup>.

ORION-10 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium salt 300 mg, equivalent to 284 mg of inclisiran, administered subcutaneously by a healthcare professional. Starting with an initial dose<sup>2</sup>, inclisiran was then administered again at 3 months and then every 6 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, inclisiran delivered mean placebo-adjusted percentage change in LDL-C reductions of 52% ( $P<.0001$ ) at 17 months and demonstrated time-adjusted percentage change in LDL-C reductions of 54% ( $P<.0001$ ) from 3 through 18 months. The study was conducted at 145 sites in the United States<sup>2,9</sup>.

ORION-11 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium salt 300 mg, equivalent to 284 mg of inclisiran, administered subcutaneously by a healthcare professional. Starting with an initial dose<sup>2</sup>, inclisiran was then administered again at 3 months and then every 6 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, inclisiran delivered placebo-adjusted change in LDL-C reductions of 50% ( $P < .0001$ ) at 17 months and demonstrated time-adjusted LDL-C reductions of 49% ( $P < .0001$ ) from 3 through 18 months. The international study was conducted at 70 sites in seven countries<sup>2,9</sup>.

### **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<sup>10,11</sup>. ASCVD accounts for over 85% of all cardiovascular disease deaths<sup>12</sup>. 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<sup>13,14</sup>. ASCVD risk equivalent corresponds to conditions that confer a similar risk for an ASCVD event (e.g. diabetes, heterozygous familial hypercholesterolemia)<sup>2,15</sup>.

### **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<sup>1-3</sup>. With two doses a year and effective and sustained LDL-C reduction, Leqvio works as a complement to statins<sup>1,2</sup>. 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 bloodstream<sup>3</sup>. Leqvio is dosed initially, again at 3 months and then once every 6 months<sup>1,2</sup>. In three clinical trials, patients taking Leqvio maintained LDL-C reduction throughout each 6-month dosing interval<sup>1,2</sup>. Administered in-office as a subcutaneous injection, Leqvio is expected to integrate seamlessly into a patient's healthcare routine<sup>1,2</sup>.

In the Phase III trials, inclisiran was well-tolerated. The most common adverse events reported ( $\geq 3\%$  of patients treated with inclisiran 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.

### **About Novartis in Cardiovascular-Renal-Metabolism**

Bending the curve of life requires addressing some of society's biggest public health concerns. Novartis has an established and expanding presence in diseases covering the heart, kidney and metabolic system. In addition to essential treatment Entresto® (sacubitril/valsartan), Novartis has a growing pipeline of potentially first-in-class molecules addressing cardiovascular, metabolic and renal diseases.

### **Disclaimer**

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**

Novartis is reimagining 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 110,000 people of more than 140 nationalities work at Novartis around the world. Find out more at <https://www.novartis.com>.

Novartis is on Twitter. Sign up to follow @Novartis at <https://twitter.com/novartisnews>  
For Novartis multimedia content, please visit <https://www.novartis.com/news/media-library>  
For questions about the site or required registration, please contact [media.relations@novartis.com](mailto:media.relations@novartis.com)

### **References**

1. Raal F, Kallend D, Ray K, et al. Inclisiran for Heterozygous Familial Hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520–1530.
2. Ray K, Wright R, Kallend D, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med.* 2020;382(16):1507–1519.
3. Stoekenbroek RM, Kallend D, Wijngaard PL, et al. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. *Future Cardiol.* 2018;14(6):433–442.
4. European Heart Network. European Cardiovascular Disease Statistics 2017 edition. Available from: <http://www.ehnheart.org/cvd-statistics/cvd-statistics-2017> [Last accessed: November 2020].
5. Bruckert E, Parhofer KG, Gonzalez-Juanatey JR, et al. Proportion of High-Risk/Very High-Risk Patients in Europe with Low-Density Lipoprotein Cholesterol at Target According to European Guidelines: A Systematic Review. *Adv Ther.* 2020;37(5):1724–1736.
6. Lansberg P, Lee A, Lee ZV, et al. Nonadherence to statins: individualized intervention strategies outside the pill box. *Vasc Health Risk Manag.* 2018;14:91–102.
7. Wong ND, Young D, Zhao Y, et al. Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US adults using the National Health and Nutrition Examination Survey 2011–2012. *J Clin Lipidol.* 2016;10(5):1109–1118.
8. Ference BA, Graham I, Tokgozoglul L, Catapano AL. Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series. *J Am Coll Cardiol.* 2018;72(10):1141–1156.
9. Clinicaltrials.gov. ORION -9, -10, -11. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03397121>; <https://www.clinicaltrials.gov/ct2/show/NCT03399370>; <https://www.clinicaltrials.gov/ct2/show/NCT03400800> [Last accessed: November 2020].

10. Mayo Clinic. Arteriosclerosis / atherosclerosis. Available from: <https://www.mayoclinic.org/diseases-conditions/arteriosclerosis-atherosclerosis/symptoms-causes/> [Last accessed: November 2020].
11. Goldstein J, Brown M. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell*. 2015;161(1):161–172.
12. World Health Organization. Cardiovascular diseases (CVDs). Available from: [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) [Last accessed: September 2020].
13. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke Statistics–2012 update: A report from the American Heart Association. *Circulation*. 2012;125(1):e2–e220.
14. Kim H, Kim S, Han S, et al. Prevalence and incidence of atherosclerotic cardiovascular disease and its risk factors in Korea: a nationwide population-based study. *BMC Public Health*. 2019;19(1):1112.
15. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143–3421.

###

### **Novartis Media Relations**

E-mail: [media.relations@novartis.com](mailto:media.relations@novartis.com)

Anja von Treskow  
 Novartis External Communications  
 +41 61 324 2279 (direct)  
 E-mail: [anja.von\\_treskow@novartis.com](mailto:anja.von_treskow@novartis.com)

Phil McNamara  
 Global Head, Cardio-Renal-Metabolism  
 Communications  
 +41 79 510 8756 (mobile)  
 E-mail: [phil.mcnamara@novartis.com](mailto:phil.mcnamara@novartis.com)

Eric Althoff  
 Novartis US External Communications  
 +1 646 438 4335  
 E-mail: [eric.althoff@novartis.com](mailto:eric.althoff@novartis.com)

### **Novartis Investor Relations**

Central investor relations line: +41 61 324 7944

E-mail: [investor.relations@novartis.com](mailto:investor.relations@novartis.com)

Central  
 Samir Shah +41 61 324 7944  
 Thomas Hungerbuehler +41 61 324 8425  
 Isabella Zinck +41 61 324 7188

North America  
 Sloan Simpson +1 862 778 5052