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MEDIA & INVESTOR RELEASE

New long-term Leqvio® (inclisiran) data from Novartis show sustained efficacy and safety over four years

- *Results from ORION-3 open-label trial show twice-yearly* Leqvio®(inclisiran), as a complement to statin therapy, provides effective and sustained reductions in low-density lipoprotein cholesterol (LDL-C) over four years of treatment*[1,2]
- *At any time throughout the trial, approximately 80% of patients reached an LDL-C level of <70mg/dL*[2]
- *Longest Leqvio safety follow-up study to date demonstrates safety-benefit profile is consistent with findings in previous 18-month Phase III trials*[1-4]
- *LDL-C is one of the most readily modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD)*[5-8]*; however, despite widespread statin use, four in five patients do not reach guideline-recommended LDL-C targets*[9,10]

Basel, November 7, 2022 — Novartis today announced results from the Phase II open-label extension ORION-3 trial, which showed that Leqvio provides effective low-density lipoprotein cholesterol (LDL-C) reduction over a four-year period in patients with either atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk equivalent, and elevated LDL-C despite maximally tolerated statin therapy[1,2]. Leqvio is the first and only small interfering RNA (siRNA) therapy to lower LDL-C and is administered with two doses a year*. Results were presented at the American Heart Association (AHA) Scientific Sessions 2022[1,2].

“The results we’ve seen in patients after four years of treatment demonstrate that inclisiran is well-tolerated and can help patients achieve LDL-C reduction while also maintaining and sustaining their levels,” said Kausik Ray, M.D., Professor of Public Health in the Department of Public Health and Primary Care at Imperial College London and Honorary Consultant Cardiologist at the Imperial College NHS Trust. “Still too many patients are struggling to reach their LDL-C target levels. A therapy that provides sustained LDL-C reduction with a twice-yearly maintenance dosing schedule may be a turning point in the treatment of ASCVD.”

In ORION-3, an open-label extension of the Phase II ORION-1 trial, LDL-C level reduction was sustained over the four-year study period: patients treated with Leqvio achieved an average 47.5% reduction in LDL-C from baseline (Day 1 of ORION-1) to Day 210 (95% CI:-50.69,-44.27) and a time-averaged reduction in LDL-C of 44.2% over the four years through twice-yearly dosing[1,2].

“Patients with ASCVD are a large, high-risk population in the US, and a majority are not achieving their LDL-C target levels,” said Norman Lepor, M.D., a Los Angeles based cardiologist and Director of the National Heart Institute. “The sustained benefit of a twice-yearly treatment is a major advance in meeting the needs of these patients.”

ORION-3 provides the longest safety follow-up in a Leqvio study to date. After four years of therapy, Leqvio was well-tolerated, with a safety profile consistent with previous 18-month Phase III LDL-C lowering studies[1,4]. The most common drug-related treatment-emergent adverse events were general disorders and injection site reactions that were mostly mild-to-moderate, consistent with previous studies[1-4]. In addition to this ORION-3 data presented at the AHA Scientific Sessions, there was a pooled exploratory safety analysis of the Phase III ORION trials entitled, “Inclisiran and cardiovascular events: a patient-level analysis of Phase III trials” published in the *European Heart Journal* on November 4, adding to the growing body of safety evidence for Leqvio[11].

“The ORION-3 results show that Leqvio consistently helped patients lower their LDL-C, and with a well-tolerated safety profile,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development, Novartis. “With two maintenance doses a year, Leqvio is an important option for ASCVD patients who are not reaching recommended LDL-C target levels despite taking other cholesterol-lowering medications.”

Current evidence suggests that elevated LDL-C is the most readily modifiable risk factor of ASCVD[5-8].

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

About Leqvio
Leqvio is approved for the treatment of primary hyperlipidemia (including heterozygous familial hypercholesterolemia) as an adjunct to diet and maximally tolerated statin therapy to reduce LDL-C. Of note, the indication may vary depending on countries. Leqvio is a subcutaneous injection given by a healthcare provider with an initial dose, another at three months, and then every six months. This approach may help those who have trouble sticking to medicines that are self-administered and have greater dosing frequency[3,4]. Leqvio is approved in more than 60 countries worldwide, including the US, and the EU.

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 ORION-3
ORION-3 (NCT03060577) is an open-label, non-randomized, extension of the Phase II ORION-1 trial which evaluated Leqvio the long-term safety and efficacy of Leqvio in 233 patients with ASCVD (~1210 patient years), ASCVD risk equivalents, and elevated LDL-C despite maximally tolerated lipid-lowering therapy[1,2,12]. The primary endpoint of the study was percentage LDL-C change from baseline (Day 1 of ORION-1) to day 210 of ORION-3. LDL-C levels were assessed up to Day 1440 (4 years). Patients received twice-yearly doses of 300 mg inclisiran sodium in this study[1,2].

About VictORION
Novartis envisions a world where ASCVD is eliminated so patients can live longer and healthier lives. ORION-3 is part of VictORION, an innovative and robust clinical program for Leqvio, comprising 27 trials and enrolling 47,000 patients in more than 50 countries worldwide. The program is designed to expand on the foundational evidence of LDL-C reduction with Leqvio in diverse patient populations to include implementation research, real-world evidence, and trials that establish its benefits on cardiovascular outcomes. A growing number of studies are planned to generate a vast array of data with major trials such as

ORION-4, V (VictORION)-2-PREVENT, V-INITIATE, V-INCEPTION, V-REAL, V-DIFFERENCE, and V-PLAQUE. The VictORION program reinforces our commitment to stopping premature death from cardiovascular disease and to leading a generational decline in cardiovascular morbidity and mortality.

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[5]. Events due to ASCVD, including heart attacks and strokes, account for 85% of all cardiovascular disease deaths[13]. 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[14,15]. ASCVD risk-equivalent corresponds to conditions that confer a similar risk for an ASCVD event (e.g., diabetes, heterozygous familial hypercholesterolemia)[3,16].

About Novartis in Cardiovascular
Cardiovascular (CV) disease is a global health crisis[13,17].

CV disease is the number one killer in the world[13,17]. Taking more lives than all cancers combined, it contributes to one in every three deaths globally[13,17]. Of all CV events, 80% can be prevented[18]. 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 how CV disease is managed throughout life. Our efforts include the use of early interventions and the development of pioneering treatments that address the spectrum of CV disease, 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.

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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,” “seek,” “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 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 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 reimagining medicine to improve and extend people's lives. We deliver high-value medicines that alleviate society's greatest disease burdens through technology leadership in R&D and novel access approaches. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. About 108,000 people of more than 140 nationalities work together to bring Novartis products to nearly 800 million people around the world. Find out more at https://www.novartis.com

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