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MEDIA UPDATE

Novartis Leqvio®* (inclisiran) analyses show effective and sustained LDL-C reduction in two sub-populations of patients with ASCVD

- *Separate post hoc analyses of pooled Phase III ORION-9, -10 and -11 data show twice-yearly** Leqvio® (inclisiran) consistently reduced low-density lipoprotein cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease (ASCVD) with established cerebrovascular disease (CeVD)[1] and polyvascular disease (PVD)[2]*

- *Overall, Leqvio was well-tolerated, with a safety profile similar to placebo and consistent with the overall pooled population from the combined trials[1-3]*

- *LDL-C is one of the most readily modifiable risk factors for ASCVD; however, despite widespread statin use, 80% of patients do not reach guideline-recommended LDL-C targets[4,5]*

Basel, August 30, 2021 — Novartis today announced results from two pooled post hoc analyses of Phase III ORION-9, -10 and -11 trials that showed twice-yearly** Leqvio® (inclisiran) provided effective and sustained low-density lipoprotein cholesterol (LDL-C) reduction in two sub-populations of atherosclerotic cardiovascular disease (ASCVD) – established cerebrovascular disease (CeVD) and polyvascular disease (PVD)[1,2]. Results were presented at the ESC Congress 2021, organized by the European Society of Cardiology (ESC).

In the first analysis, patients with established CeVD treated with Leqvio achieved an average 55.2% reduction in LDL-C from baseline to Day 510 compared with placebo (P<.0001)[1]. In the second analysis, patients with PVD treated with Leqvio achieved an average 48.9% reduction in LDL-C from baseline to Day 510 compared with placebo (P<.0001)[2]. Results were similar for patients without PVD, with an average 51.5% reduction in LDL-C from baseline to Day 510 for Leqvio compared with placebo (P<.0001)[2].

“We know that long-term exposure to persistently elevated LDL-C increases the risk of ASCVD, which may lead to cardiovascular events such as heart attack or stroke. These analyses show that twice-yearly** Leqvio provides similar effective and sustained LDL-C reduction in two smaller ASCVD sub-populations – CeVD and PVD – as in the wider Phase III ORION ASCVD population,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development, Novartis. “As the first and only small interfering RNA to provide effective and sustained LDL-C reduction, Leqvio helps manage a critical cardiovascular risk factor for ASCVD. It is a key component of our ambition to bend the curve of life by reducing and stopping premature death from cardiovascular disease.”

Leqvio was well-tolerated in both analyses, with a modest excess of mainly mild treatment-emergent adverse events (TEAEs) at the injection site that were transient in nature, which is consistent with the results from the overall pooled population from the combined trials[1-3]. Treatment-emergent serious adverse events (TESAEs) were reported more frequently in patients with PVD, which was likely due to their more advanced disease[2].

Leqvio is the first and only approved small interfering RNA (siRNA) LDL-C-lowering treatment in Europe[6,7]. It is currently under review by the U.S. Food and Drug Administration (FDA) and other health authorities.

**Product and brand name are currently under FDA review.*
***After an initial dose and one at three months.*

About the pooled post hoc analyses from Phase III ORION-9, -10 and -11 trials in patients with established cerebrovascular disease and patients with polyvascular disease
The pooled analyses include data from the Leqvio ORION-9, -10 and -11 trials, which were multicenter, double-blind, randomized, placebo-controlled,18-month (540-day) studies evaluating Leqvio in 3,655 patients with heterozygous familial hypercholesterolemia (ORION-9), atherosclerotic cardiovascular disease (ASCVD) (ORION-10), and ASCVD or ASCVD risk equivalents (ORION-11) on statin therapy who required additional low-density lipoprotein cholesterol (LDL-C) lowering[1-3]. The primary endpoints for these studies were percentage change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline between Day 90 and up to Day 540[1-3]. The primary endpoints were achieved in all three studies[3]. Safety was assessed over 540 days[1-3].

The established cerebrovascular disease (CeVD) post hoc analysis included 202 patients with established CeVD, of which 110 received Leqvio and 92 received placebo[1]. Patients with established CeVD had prior ischemic stroke, and/or carotid artery narrowing (by angiography or ultrasound) of more than 70%, and/or prior percutaneous or surgical carotid artery revascularization.

The polyvascular disease (PVD) post hoc analysis included 470 patients with PVD, of which 228 received Leqvio and 242 received placebo[2]. Patients with PVD had ASCVD in at least two of the major vascular artery territories: coronary, cerebrovascular and/or peripheral.

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 sodium salt 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose[8], 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[8,9].

ORION-10 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of Leqvio sodium salt 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose[10], 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[9,10].

ORION-11 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of Leqvio sodium salt 300 mg, equivalent to 284 mg of Leqvio, administered subcutaneously by a healthcare professional. Starting with an initial dose[10], 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[9,10].

The Phase III ORION-9, -10 and -11 trials are part of the larger Leqvio VictORION dynamic evidence generation alliance. VictORION has been designed with a purpose to disrupt conventions and assess how Leqvio could bring about a profound transformation for patients living with ASCVD every day.

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[11,12]. ASCVD accounts for over 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)[10,16].

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[8,10,17]. With two doses a year** and effective and sustained LDL-C reduction, Leqvio works as a complement to statins[8,10]. 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[17]. Leqvio is dosed initially, again at three months and then once every six months[8,10]. In three clinical trials, patients taking Leqvio maintained LDL-C reduction throughout each six-month dosing interval[8,10]. Administered in-office as a subcutaneous injection, Leqvio is expected to integrate seamlessly into a patient's healthcare routine[8,10].

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.

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.

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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 109,000 people of more than 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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