Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

https://www.novartis.com
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MEDIA & INVESTOR RELEASE

Novartis receives positive CHMP opinion for Leqvio®* (inclisiran), a potential first-in-class siRNA for the treatment of high cholesterol

- *If approved, inclisiran will be the first and only small interfering RNA (siRNA) in Europe for patients with hypercholesterolemia or mixed dyslipidemia*[1]
- *Cardiovascular disease (CVD) claims 3.9 million lives annually in Europe*[2]*, and 80% of high-risk patients do not reach guideline-recommended low-density lipoprotein cholesterol (LDL-C) targets despite the widespread use of statins*[3–5]
- *Inclisiran provides effective and sustained reduction of LDL-C of up to 52%, with a safety profile similar to placebo, in patients with elevated LDL-C despite maximally tolerated lipid-lowering therapy*[6,7]
- *With only two doses a year administered by healthcare professionals, inclisiran is expected to support long-term adherence*[6,7]
- *Inclisiran is also under review by the U.S. FDA and other health authorities for the treatment of primary hyperlipidemia (including heterozygous familial hypercholesterolemia) in adults who have elevated LDL-C while being on a maximally tolerated dose of statin therapy*

Basel, October 16, 2020 — Novartis announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion and recommended granting marketing authorization of Leqvio®* (inclisiran) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, marking an important milestone towards it becoming available in the EU.

Inclisiran is a potential first-in-class small interfering RNA (siRNA) with a new mechanism of action which delivers effective and sustained low-density lipoprotein cholesterol (LDL-C) reduction for patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalent and heterozygous familial hypercholesterolemia (HeFH) a major driver of heart attacks, strokes and deaths[1].

“This investigational medicine could significantly change how high LDL-C is treated[6,7],” said Professor Ulf Landmesser, M.D., Director of Charité Center for Cardiovascular Diseases, Berlin. “Many patients struggle to keep their LDL-C at recommended levels, and long-term exposure to high LDL-C is a major driver of ASCVD[4,8,9]. The unique mechanism of action of inclisiran provides effective and sustained LDL-C reduction, a causal factor of atherosclerotic disease progression. With only two doses a year, and as an injection administered by healthcare professionals, it is anticipated to remove adherence challenges commonly encountered with self-administered treatments[1,6,7,10-13].”

“LDL-C reduction remains a major public health issue, with 80% of high-risk patients in Europe not achieving guideline-recommended LDL-C targets despite available current standard of care treatments. These patients remain at risk of ASCVD events, such as strokes or heart attacks[3-5]”, said John Tsai, Head Global Drug Development and Chief Medical Officer, Novartis. “This encouraging positive CHMP opinion is a significant step in our journey of reimagining medicine with this transformational treatment, which has the potential to bring new hope to the millions of people in Europe currently unable to reach their LDL-C goals[3-5].”

This CHMP opinion is based on results from the ORION clinical research program including Phase III trials, which involved more than 3,600 patients on a maximally tolerated statin dose and assessed the safety, efficacy and tolerability of inclisiran[6,7]. Inclisiran demonstrated effective and sustained LDL-C reduction of up to 52% (*P*<0.0001) with two doses per year, after an initial dose and one at 3 months, in adults with ASCVD, ASCVD risk equivalent and/or HeFH[6,7]. Further, the reduction in LDL-C achieved with inclisiran was sustained through 17 months, with a safety and tolerability profile similar to placebo[6,7]. Additional post hoc analysis showed low variability among the patients treated with inclisiran: 88% of them reached guideline recommended targets at any timepoint during the study (observed values)[14].

The CHMP recommended granting inclisiran marketing authorization 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 European Commission (EC) – which has the authority to approve medicines for the European Union (EU) – will review the CHMP opinion and is expected to grant a centralized marketing authorization that will be 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. Following EC approval, Novartis will continue to explore innovative collaborations with health agencies and others throughout Europe designed to ensure that people with ASCVD and elevated LDL-C have access to the treatments they need to achieve beneficial health outcomes. Further, Novartis looks forward to the completion of the ongoing cardiovascular outcomes ORION-4 study, which will expand on the scientific evidence associating lower LDL-C levels with improved cardiovascular outcomes.

Inclisiran is also under review by the U.S. Food and Drug Administration for the treatment of primary hyperlipidemia (including HeFH) in adults who have elevated LDL-C while being on a maximally tolerated dose of statin therapy.

**Product and brand name are not FDA approved. Currently under FDA review.*

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 300 mg administered subcutaneously by a healthcare professional starting it at an initial dose[6]. 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[6].

ORION-10 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium 300 mg administered subcutaneously by a healthcare professional starting it at an initial dose[7]. 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[7].

ORION-11 was a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium 300 mg administered subcutaneously by a healthcare professional starting it at an initial dose[7]. 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[7].

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[15,16]. ASCVD accounts for over 85% of all cardiovascular disease deaths[17]. 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[18,19]. ASCVD risk equivalent corresponds to conditions that confer a similar risk for a ASCVD event (e.g. diabetes, HeFH)[7,20].

About Inclisiran
If approved, inclisiran (KJX839) would be the first and only therapy to use the small interfering RNA (siRNA mechanism) of action to lower low-density lipoprotein cholesterol (LDL-C), which could help improve outcomes for patients with ASCVD, a deadly form of cardiovascular disease[1,6,7]. With two doses a year and effective and sustained LDL-C reduction, inclisiran works as a complement to statins. Inclisiran 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[1]. Inclisiran is dosed initially, again at 3 months, and then once every 6 months. In three clinical trials, patients taking inclisiran maintained LDL-C reduction throughout each 6-month dosing interval[6,7]. Administered in-office as a subcutaneous injection, inclisiran integrates seamlessly into a patient's healthcare routine[6,7].

No significant safety or tolerability concerns have been identified with the long-term administration of inclisiran. In the Phase III trials, inclisiran was reported to be well-tolerated with a safety profile similar to placebo[6,7]. The most common adverse reactions reported (≥3% of patients treated with inclisiran and occurring more frequently than placebo) were diabetes mellitus, hypertension, nasopharyngitis, arthralgia, back pain, dyspnea, bronchitis and upper respiratory tract infection. Adverse events at the injection site were more frequent with inclisiran than placebo and were generally mild and none were severe or persistent[6,7].

Novartis has obtained global rights to develop, manufacture and commercialize inclisiran 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 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,” “potentially,” “can,” “will,” “could,” “would,” “expected,” “anticipated,” “looks forward,” “investigational,” “pipeline,” “under review,” “remains,” “advancing,” “to explore,” “to ensure,” “to achieve,” “expanding” “to evaluate,” “to support,” “remains,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for inclisiran, Entresto or the other investigational and 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 inclisiran, Entresto or such other products 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 inclisiran, Entresto or such other 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. 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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Novartis Media Relations
E-mail: media.relations@novartis.com

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

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

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

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Thomas Hungerbuehler	+41 61 324 8425		

Isabella Zinck +41 61 324 7188