Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

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MEDIA & INVESTOR RELEASE

Novartis new analysis shows high consistency in lowering LDL-C in individual response with investigational inclisiran

- *Pooled data from Phase III ORION-10 and -11 showed highly consistent efficacy, tolerability and safety profile over 17 months on twice-yearly subcutaneous dosing in 2,300 patients (of which 1,164 were on inclisiran)* [1]

- *New post-hoc analysis demonstrates 99% of patients treated with inclisiran showed placebo-adjusted reduction in low-density lipoprotein cholesterol (LDL-C) of ≥30% with a mean reduction of 54.1% from baseline (observed values)*[2]

- *88% of inclisiran-treated patients achieved LDL-C placebo-adjusted reduction of at least 50% at any time point during the study (observed values)*[2]

- *Inclisiran is currently under review by the FDA and the EMA 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, August 30, 2020 — Novartis today announced results from a post-hoc analysis of pooled data from the Phase III ORION-10 and -11 trials evaluating the individual responses of patients on low-density lipoprotein cholesterol (LDL-C) reduction with inclisiran, a first-in-class investigational treatment for hyperlipidemia in adults. This new analysis of inclisiran showed a highly consistent effect, with a safety and tolerability profile similar to placebo, on a twice-yearly dosing schedule after an initial dose and one 3 months later, across individual patients with atherosclerotic cardiovascular disease (ASCVD) or risk equivalents over 17 months of treatment.

Presented at the ESC Congress 2020, the annual meeting of the European Society of Cardiology, the analysis evaluated the efficacy and tolerability of inclisiran on top of a maximally tolerated dose of statins, in two studies of more than 2,300 patients (of which 1,164 were on inclisiran) from the Phase III trials. Results demonstrated a low inter-individual variability, with 99% of inclisiran-treated patients showing a placebo-adjusted ≥30% reduction of their LDL-C levels with a mean reduction of 54.1% from baseline (observed values)[2] .

“This analysis confirms that as a small interfering RNA (siRNA), inclisiran provides a remarkably consistent treatment profile. Nearly all patients from these trials achieved clinically meaningful reductions of their LDL-C levels over the 17 month period, and inclisiran had a safety and tolerability profile similar to placebo,” said ORION-11 principal investigator Kausik Ray, M.D., Professor of Public Health, Consultant Cardiologist, Imperial College London. “These efficacy and safety results showcase the promise of inclisiran as a therapy for those ASCVD patients who cannot reach their LDL-C goals.”

An LDL-C reduction of at least 50% was reached by 88.4% of patients at any time point in the study (observed values). After 17 months, 66.4% of the inclisiran group had a reduction in LDL-C of at least 50% as compared to 2.5% from the placebo group (observed values) [2]. Overall, inclisiran was well-tolerated with a safety profile similar to placebo. All patients were on twice-yearly dosing, following an initial dose and one 3 months later.

“There remains an urgent need for innovative LDL-C-lowering therapies for patients not reaching their LDL-C target goals with current standard of care. This analysis reinforced our view of inclisiran’s therapeutic value and its potential as the first cholesterol-lowering siRNA,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development, Novartis. “With a unique twice-yearly dosing, if approved, inclisiran may fit seamlessly into patients’ regular healthcare visits and help us reimagine treatment for ASCVD.”

Inclisiran is currently under review by the U.S. Food and Drug Administration and the European Medicines Agency 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.

About the ORION-10 and -11 Phase III LDL-C Lowering Studies
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 in an initial dose, again at 3 months, and then every 6 months thereafter in 1,561 participants with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C), despite a maximum tolerated dose of LDL-C-lowering therapies (e.g. a statin 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 (observed values). The study was conducted at 145 sites in the United States[1].

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 in an initial dose, 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 maximum 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 (observed values). The international study was conducted at 70 sites in seven countries[1].

About ASCVD
Atherosclerosis corresponds to the accumulation of lipids over time – mainly 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[3]. Atherosclerotic Cardiovascular Disease (ASCVD) accounts for over 85% of all cardiovascular disease deaths[4]. ASCVD is the primary cause of death in the EU and its burden in the US is greater than that from any other chronic diseases[5,6].

About Inclisiran
Inclisiran, an investigational cholesterol-lowering treatment, was added to the pipeline from the Novartis acquisition of The Medicines Company. Inclisiran will potentially be the first and only LDL-C-lowering small-interfering RNA (siRNA) treatment. It is intended to be administered by a healthcare professional by subcutaneous injection with an initial dose, again at 3 months and then every 6 months thereafter. Its twice-yearly dosing by subcutaneous injection may integrate seamlessly into a patient’s healthcare routine. As a

siRNA, inclisiran is thought to harness the body's natural process of clearing LDL-C from the bloodstream. Inclisiran is a double-stranded siRNA, conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake by hepatocytes and lowering LDL-C levels in the circulation. Data from each of the Phase III studies was recently published online, ahead of print, in The New England Journal of Medicine. A cardiovascular outcomes trial, ORION-4, is ongoing.

In the Phase III trials, inclisiran was reported to be well-tolerated with a safety profile similar to placebo. 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[1,7].

Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals.

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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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)
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
Pierre-Michel Bringer	+41 61 324 1065	Cory Twining	+1 862 778 3258
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		