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MEDIA & INVESTOR RELEASE

New Novartis analyses for investigational inclisiran demonstrate consistently effective and sustained LDL-C reduction at month 17 regardless of age and gender

- *Pooled data analyses from Phase III ORION-9, -10 and -11 showed that inclisiran consistently reduced low-density lipoprotein cholesterol (LDL-C) by approximately 51% in both male and female adult patients and in three age categories*[1,2]

- *Sustained LDL-C reduction with inclisiran was observed regardless of age or gender differences*[1,2] *with two doses a year, after an initial dose and then again at three months; the overall trial dosing schedule was at months 1, 3 and then every 6 months up to month 17*

- *LDL-C is the most readily modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), yet despite widespread statin use 80% of high-risk patients do not reach guideline-recommended LDL-C targets*[3,4]

- *Inclisiran recently received a positive CHMP opinion and recommendation for marketing authorization in Europe and is under review by the U.S. Food and Drug Administration*

Basel, November 13, 2020 — Novartis today announced results from two pooled post-hoc analyses of Phase III ORION-9, -10 and -11 trials, evaluating the impact of age and gender on the efficacy and safety of inclisiran, an investigational and potential first-in-class small interfering RNA (siRNA) for hyperlipidemia in adults with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH). The data showed that at month 17, inclisiran was well-tolerated and provided effective and sustained reduction in low-density lipoprotein cholesterol (LDL-C) when used in addition to other lipid lowering therapies regardless of patients' age and gender[1,2]. During the trials, inclisiran was administered at months 1, 3 and then every 6 months up to month 17. Results were presented at the virtual American Heart Association Scientific Sessions 2020.

"High LDL-C and other risk factors for ASCVD, as well as the potential for treatment side effects, may increase with age and differ by gender," said Kausik Ray, MD, ORION-11 trial principal investigator, Professor of Public Health at Imperial College London and Honorary Consultant Cardiologist at the Imperial College NHS Trust. "These data are important as they show that inclisiran, as a siRNA, has the potential to provide consistent efficacy and

tolerability despite the cholesterol-lowering treatment challenges posed by age and gender with two doses a year after the initial dosing regimen on day 1 and month 3."

In post-hoc analyses of the pooled results from the ORION Phase III trials in more than 3,600 patients, treatment with inclisiran delivered similar LDL-C reductions of approximately 51% from baseline for both women and men (50.6% vs 50.6% respectively) compared to placebo[1]. Results from a second pooled analysis showed that inclisiran-treated patients in three age categories all achieved similar LDL-C reductions of approximately 51% (−51.3% <65 years; −49.9% ≥65 years to <75 years; −51.0% ≥75 years)[2]. In both analyses, inclisiran was well-tolerated[1,2].

"Whether you look at it from an age or a gender perspective, inclisiran analyses continue to show consistency with effective and sustained LDL-C reduction lasting over the dosing interval," said David Soergel, MD, Global Head of Cardiovascular, Renal and Metabolic Drug Development, Novartis. "As we move forward in our journey to reimagine treatment for ASCVD, these data analyses reinforce the potential of inclisiran as a first-in-class siRNA treatment to transform LDL-C management with two doses a year, following the initial dose and another dose at three months, and a positive tolerability profile."

On Friday, October 16, 2020, the Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion and recommended granting marketing authorization for inclisiran. Novartis is anticipating a final regulatory decision in Europe in December 2020 and is under review by the US Food and Drug Administration.

About the Pooled Post-Hoc Analyses from Phase III ORION-9, -10 and -11 trials: Age and Gender

The pooled analyses include data from inclisiran's ORION-9, -10 and -11 trials, which were multicenter, double-blind, randomized, placebo-controlled,18-month studies evaluating inclisiran in patients with heterozygous familial hypercholesterolemia (ORION-9), ASCVD (ORION-10) and ASCVD or ASCVD risk equivalents (ORION-11) on statin therapy who required additional LDL-C lowering. The primary endpoints for these studies were percentage change in LDL-C from baseline to 17 months and time-adjusted percentage change in LDL-C from baseline between 3 months and up to 18 months. The primary endpoints were achieved in all three studies[5-7].

The pooled analyses assessed inclisiran's efficacy for lowering LDL-C, as well as safety and tolerability, across age ranges and by gender[1,2].

Impact of age on the efficacy of inclisiran versus placebo (<65 years; ≥65 years to <75 years; ≥75 years)[2]:

- Percentage change between inclisiran and placebo in LDL-C at month 17 was similar across all ages: −51.3% (<65 years), −49.9% (≥65 years to <75 years), −51.0% (≥75 years)
- Time-adjusted percentage LDL-C change between inclisiran and placebo at month 18 was similar across all ages: −49.6% (<65 years), −51.5% (≥65 years to <75 years), −50.8% (≥75 years)

Impact of gender on the efficacy of inclisiran versus placebo[1]:

- Percentage change between inclisiran and placebo in LDL-C at month 17 was consistent across women and men at -50.6% and -50.6% respectively
- Time-adjusted LDL-C change between inclisiran and placebo at month 18 was consistent across women and men at -50.5% and -50.6%

Across both analyses, inclisiran was reported to be well-tolerated irrespective of age or gender. Injection site reactions (ISR) were more frequent in female versus male patients and in the <65 population versus elder patients, all ISRs were transient and mild or moderate in terms of severity.

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 inclisiran sodium salt 300 mg, equivalent to 284 mg of inclisiran, administered subcutaneously by a healthcare professional starting it at an initial dose[5]. 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 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, 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[5].

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 it at an initial dose[6]. 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[6,7].

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 it at an initial dose[6]. 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[6,7].

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[8,9]. ASCVD accounts for over 85% of all cardiovascular disease deaths[10]. 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[11,12]. ASCVD risk equivalent corresponds to conditions that confer a similar risk for a ASCVD event (e.g. diabetes, heterozygous familial hypercholesterolemia)[6,13].

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 atherosclerotic cardiovascular disease (ASCVD), a deadly form of cardiovascular disease[5,6,14]. 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[14]. 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[5,6].

Administered in-office as a subcutaneous injection, inclisiran integrates seamlessly into a patient's healthcare routine[5,6].

No significant safety or tolerability concerns have been identified with the long-term administration of inclisiran. In the Phase III trials, inclisiran was well-tolerated with a safety profile shown to be comparable to placebo[5,6]. The most common adverse reactions reported (≥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. Adverse events at the injection site were generally mild and none were severe or persistent[5,6].

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.

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

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