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Novartis announces NEJM publication of three pivotal trials showing durable and potent efficacy of inclisiran, an investigational first-in-class siRNA cholesterol-lowering therapy

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- *Inclisiran, an investigational medicine, showed durable and potent reduction of low-density lipoprotein cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalents and heterozygous familial hypercholesterolemia (HeFH)*[1,2]
- *Inclisiran reduced LDL-C at 17 months by 52% in patients with ASCVD (ORION-10), 50% for ASCVD and ASCVD risk equivalents (ORION-11) and by 50% in HeFH patients (ORION-9); all of whom had elevated LDL-C levels despite maximally tolerated lipid-lowering therapy*[1,2]
- *Inclisiran's novel siRNA mechanism of action could potentially enable a unique twice-yearly subcutaneous dosing regimen administered by a healthcare provider*
- *Inclisiran is currently under review by the U.S. Food and Drug Administration and European Medicines Agency for use in adults with ASCVD or HeFH who have elevated LDL-C while being on a maximum tolerated dose of a lipid-lowering therapy*

East Hanover, N.J., March 18, 2020 — Novartis announced today the publication of three pivotal Phase III clinical trials for inclisiran, a potential first-in-class small interfering RNA (siRNA) investigational agent for hyperlipidemia in adults. The findings were published in two online articles ahead of print in *The New England Journal of Medicine*. The primary endpoints were achieved in all three trials. Namely, percentage change in LDL-C from baseline to 17 months and time-adjusted percentage change in LDL-C from baseline from 3 through 18 months. This demonstrates that after two starter doses, twice-yearly subcutaneous dosing with inclisiran resulted in durable and potent LDL-C reductions versus placebo. Inclisiran was well-tolerated with a safety profile similar to placebo[1, 2].

Hyperlipidemia refers to the high level of lipids (fats, cholesterol, triglycerides), such as LDL-C, found in the blood that are either acquired or a result of genetic disorders[3]. The length of time a person has elevated LDL-C levels is understood to be causal to ASCVD which can lead to a cardiovascular event such as a heart attack or stroke[4,5]. LDL-C is the most readily modifiable risk factor for ASCVD[6-11]. People who are on lipid-lowering therapies often do not reach optimal LDL-C levels, leaving them at increased risk for significant morbidity and mortality associated with this condition[12,13]. Approximately 40 million patients in the US have been diagnosed with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (FH) and are at risk of a cardiovascular event[14].

ORION 10 and 11

One article reported the results from the ORION-10 and -11 studies, which evaluated the use of inclisiran in addition to maximally tolerated lipid-lowering therapies in patients with ASCVD (ORION-10) or ASCVD and ASCVD risk equivalents (ORION-11) through 18 months.

In ORION-10 and -11, at 17 months inclisiran resulted in placebo-adjusted LDL-C reduction of 52% and 50% respectively and time-adjusted reduction from 3 through 18 months of 54% and 49% respectively[1].

Treatment-emergent adverse events were generally similar between the inclisiran and placebo groups.

“Inclisiran and its twice-yearly dosing schedule in three large trials consistently delivered potent and sustained cholesterol-lowering and was generally well tolerated,” said Kausik Ray, M.D., ORION-11 principal investigator, Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Deputy Director of Imperial Clinical Trials Unit, Imperial College, London. “These data provide support for this groundbreaking approach to reducing LDL-C in patients who are not achieving LDL-C treatment goals with the current standard of care.”

“Elevated LDL-C is an important modifiable risk factor for cardiovascular events for millions of people, particularly those with ASCVD,” said ORION-10 principal investigator R. Scott Wright, M.D., Professor of Medicine, Consultant in Cardiology, Mayo Clinic in Rochester, Minnesota. “The data from ORION-10 shows that inclisiran results in significant and sustained reductions in LDL-C over a six-month period with a safety profile similar to placebo.”

ORION 9

A separate article on ORION-9 highlighted results of treatment with inclisiran in HeFH, a rare hereditary disease that causes high levels of LDL-C and leads to early onset of ASCVD. In this study, inclisiran reduced LDL-C by 50%* at 17 months with a time-adjusted reduction of 45% from 3 through 18 months, compared to placebo. There was a robust reduction of LDL-C with all FH genotypes[2].

Treatment-emergent adverse events were similar between inclisiran and placebo[2].

“Familial hypercholesterolemia remains a difficult condition to treat but the potential addition of inclisiran gives hope to many FH patients to help meet and maintain guideline-recommended LDL-C levels with two injections of inclisiran per year,” said Frederick Raal, M.D., University of the Witwatersrand, Department of Medicine, University of the Witwatersrand Kallend, South Africa.

In all three Phase III trials, patients received inclisiran or placebo in addition to maximally tolerated lipid-lowering therapy. The twice-yearly dosing regimen, which followed two starter doses, was administered subcutaneously by a healthcare provider.

“These results show that inclisiran has the potential to substantially reduce LDL cholesterol in people who cannot get to goal on statin therapy alone,” said David Platt, M.D., Vice President, Clinical Development and Medical Affairs, Cardiovascular, Renal & Metabolism Medical Unit, Novartis U.S. “ASCVD presents a continual challenge to healthcare practitioners and patients due to the difficulty of lowering and maintaining cholesterol levels over time. We are meeting those challenges by developing first-in-class medicines like inclisiran, which offers a re-imagined dosing schedule that works with a patient’s routine follow-up visits by offering twice-yearly dosing by their healthcare provider.”

Inclisiran is currently under review by the U.S. Food and Drug Administration and European Medicines Agency for use in adults with ASCVD or HeFH who have elevated LDL-C while being on a maximum tolerated dose of a lipid-lowering therapy. If approved, inclisiran will be the first and only cholesterol-lowering treatment in the siRNA class.

**Observed percentage, analysis for imputed values of missing numbers also performed.*

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 in 482 patients with clinical or genetic evidence of heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-C, despite maximum tolerated dose of statin, with or without other lipid-modifying therapy, and who required additional LDL-C reduction[2]. Inclisiran was administered in two starter doses and then every 6 months thereafter.

ORION-10 was a pivotal Phase 3, 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 ASCVD and elevated LDL-C, despite maximum tolerated dose of LDL-C-lowering therapies (e.g., a statin or ezetimibe). The study was conducted at 145 sites in the United States[1].

ORION-11 was a pivotal Phase 3, 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 maximum tolerated dose of statin therapy (with or without ezetimibe)[6]. The international study was conducted at 70 sites in seven countries[1].

About inclisiran

Inclisiran, an investigational cholesterol-lowering therapy, was added to the pipeline from the Novartis acquisition of The Medicines Company. Inclisiran will potentially be the first and only LDL-C lowering siRNA medicine. It is intended to be administered by a healthcare professional with 2 starter doses 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 with GalNAc allowing for targeted uptake by hepatocytes. In hepatocytes, inclisiran silences PCSK9 expression, increasing 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. A cardiovascular outcomes study, ORION-4, is ongoing.

In the Phase III studies, 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, dypspnea, 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[1,2].

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.

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

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