The Medicines Company and Alnylam Pharmaceuticals Announce Initiation of Phase III Clinical Trials of Inclisiran

November 6, 2017

– Patient dosing commenced –

– Comprehensive Phase III clinical program to assess LDL-C lowering and safety in a wide range of patients –

– Efficient, focused and rapid program designed to support US and EU regulatory filings –

PARSIPPANY, N.J. & CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 6, 2017-- The Medicines Company (NASDAQ: MDCO) and Alnylam Pharmaceuticals, Inc. (NASDAQ: ALNY) today announced the initiation of the Phase III clinical program for inclisiran, with the commencement of patient dosing on November 1, 2017 in the ORION-11 trial, a Phase III study of inclisiran versus placebo in patients with atherosclerotic cardiovascular disease (ASCVD), or ASCVD-risk equivalents (*e.g.*, type 2 diabetes and familial hypercholesterolemia), and elevated LDL-cholesterol (LDL-C) despite maximum tolerated doses of LDL-C lowering therapies.

The ORION-11 trial is a double-blind study in which 1,500 eligible patients will be randomized 1:1 to receive either inclisiran or placebo. The primary objective of the study is to evaluate the effect of inclisiran treatment on percent change in LDL-C levels from baseline at Day-510 and time-adjusted percent change in LDL-C levels from baseline between Day-90 and Day-540.

Building on the highly-successful ORION-1 Phase II trial, which defined the optimal dosing of inclisiran for the Phase III clinical program, in ORION-11, the starting dose of inclisiran is 300 mg given subcutaneously on Day-1 and Day-90, followed by maintenance doses of 300 mg of inclisiran given subcutaneously on Day-270 and Day-450. The treatment and observation duration of ORION-11 is 18 months. Approximately 100 clinical sites in seven European countries and South Africa are participating in the study, which is being performed in partnership with Pharmaceutical Product Development, LLC (PPD), a leading global contract research organization.

Principal Investigator for ORION-11, Professor Kausik Ray, Professor of Public Health, Imperial College London, United Kingdom, and Honorary Consultant Cardiologist, Imperial College NHS Trust, said, “We are very excited to have commenced the inclisiran Phase III clinical program with the ORION-11 trial. The ease of dosing – small volume, subcutaneous injections twice a year, most likely given by healthcare professionals – promises to improve patient adherence to lipid therapy, which has been a significant problem with all other approaches. Data from the ORION-1 Phase II trial gives us considerable confidence in inclisiran’s potential effectiveness, dosage regimen and safety profile, underscoring the remarkable potential for inclisiran to become a best-in-class therapeutic for millions of patients.”

The ORION-11 trial is one of four Phase III pivotal trials for inclisiran, which also include the ORION-10 trial in approximately 1,500 ASCVD patients treated in North America; the ORION-9 trial in approximately 400 patients with heterozygous familial hypercholesterolemia (FH) treated in North America, Europe, Israel and South Africa; and the ORION-5 trial in approximately 60 patients with homozygous FH treated in Europe, the Middle East and North America. The Company continues to expect that all of these trials will commence before the end of 2017 and, subject to the progress and results of the Phase III clinical program for inclisiran, that data from the four trials that comprise the program will support the submission of a New Drug Application (NDA) in the United States and a Marketing Authorization Application (MAA) in the European Union at or around the end of 2019.

David Kallend, MBBS, Senior Vice President and Global Medical Director of The Medicines Company, stated, “We expect a rolling start for all four pivotal trials, and we believe the entire LDL-C lowering program will be completed in the second half of 2019 in anticipation of regulatory submissions in United States and the European Union. The trials cover the entire spectrum of today’s subjects who need LDL-C lowering beyond established treatments for atherosclerotic cardiovascular disease, including secondary prevention for those with prior heart attacks, strokes and peripheral artery disease, and primary prevention for those with familial hypercholesterolemia or other risk factors, such as type 2 diabetes and 20% or greater risk of a major cardiovascular event.”

Kevin Fitzgerald, Ph.D., Senior Vice President of Research at Alnylam, said, “We are delighted by the progress that investigators and our partner, The Medicines Company, have made with inclisiran, and we look forward to watching its progress in this comprehensive Phase III program in thousands of patients. In addition, these studies will provide substantial safety data that we expect will support the overall safety profile of our RNAi therapeutics platform.”

Anshul Thakral, Senior Vice President and Global Head of Biotech at PPD, said, “We are pleased to partner with The Medicines Company to conduct the ORION Phase III trials using our innovative approach to chronic disease studies, which includes a closed-loop site network and patient enrollment solution. We believe that these trials can rapidly accumulate pivotal data to support NDA and MAA submissions for inclisiran and we’re excited to contribute to the development of this potentially important new therapy.”

About ORION-11

ORION-11 is a Phase III, placebo-controlled, double-blind, randomized study in 1,500 patients with ASCVD (coronary heart disease, cerebrovascular disease and peripheral arterial disease), or ASCVD-risk equivalents (*e.g.*, type 2 diabetes, FH and 20% or greater risk of a cardiovascular event as assessed by Framingham risk score or equivalent), and elevated LDL-C despite maximum tolerated doses of LDL-C lowering therapies, designed to evaluate the efficacy, safety, and tolerability of subcutaneous inclisiran injection(s).

Patients may be included if they are ?18 years of age with serum LDL-C ?1.8 mmol/L (?70 mg/dL) for ASCVD patients or ?2.6 mmol/L (?100 mg/dL) for ASCVD-risk equivalent patients, and fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.

Patients on statins should be receiving a maximally-tolerated dose, which means the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Patients not receiving statins must have documented evidence of intolerance to all doses of at least two different statins. Lipid-lowering therapies (such as a statin and/or ezetimibe) should be stable for ?30 days before screening with no planned medication or dose change during study participation. Patients on monoclonal antibodies directed towards PCSK9 within 90 days of screening are excluded. Other exclusion criteria comprise standard clauses commonly used in pivotal licensing trials for lipid-lowering therapies.

Lipids and lipoproteins will be measured at various visits, including LDL-C, total cholesterol, triglycerides, HDL-cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol and apolipoprotein, as well as PCSK9 and high-sensitivity C-reactive protein.

Safety assessments, including adverse events, serious adverse events, electrocardiograms, concomitant medications and safety laboratory parameters, will also be collected during the study. An independent Data Monitoring Committee will review safety data on a regular basis.

About inclisiran

Inclisiran (formerly known as PCSK9si or ALN-PCSsc) is an investigational GalNAc-conjugated RNAi therapeutic targeting PCSK9 – a genetically-validated protein regulator of LDL receptor metabolism – being developed for the treatment of hypercholesterolemia. In contrast to anti-PCSK9 monoclonal antibodies that bind to PCSK9 in blood, inclisiran is a first-in-class investigational medicine that acts by turning off PCSK9 synthesis in the liver.

The Medicines Company and Alnylam Pharmaceuticals, Inc. are collaborating in the advancement of inclisiran pursuant to the terms of their 2013 agreement. Under the terms of that agreement, Alnylam completed certain pre-clinical studies and the Phase I clinical study, with The Medicines Company leading and funding the development of inclisiran from Phase II forward, as well as potential commercialization.

About ASCVD and risk equivalent disease

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually. Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated LDL-C is a major risk factor for the development of CVD and has recently been described as causative. Lowering LDL-C has been shown to reduce the risk of cardiovascular death or heart attack, and within the range of effects achieved so far, the clinical risk reduction is linearly-proportional to absolute LDL-C reduction.

Approximately 100 million people worldwide are treated with lipid lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death, nonfatal myocardial infarction (MI) and nonfatal stroke or associated events. However, residual risk for cardiovascular events remains and statins are associated with well-known limitations. First, not all subjects reach LDL-C levels associated with optimal protection against clinical events. Second, not all subjects tolerate statins or are able to take statins at sufficiently-intensive doses. Third, observational studies have demonstrated that >50% of patients do not adhere to statin therapy for more than six months.

There is an unmet need for additional treatment options beyond currently-available treatments for lowering of the LDL-C level to reduce cardiovascular risk.

Despite statins alone or in combination with other lipid lowering medications, current therapies for the management of elevated LDL-C remain insufficient in some subjects. This is particularly true in patients with pre-existing CHD and/or diabetes or a history of FH, who are at the highest risk and require the most intensive management.

About PCSK9 and PCSK9 inhibition

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in controlling the levels of low-density lipoprotein receptors (LDLR) on the surface of hepatocytes. PCSK9 is expressed and secreted into the bloodstream predominantly by the liver, binds LDLR both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, thereby increasing the circulating LDL-C levels. Loss of function mutations in PCSK9 have been found to lead to increased LDLR in the liver, reduced serum LDL-C, and a lower risk for CHD, with no apparent negative health consequences.

Recently-developed and approved PCSK9-blocking monoclonal antibodies reduce circulating PCSK9 levels and lower LDL-C levels. Preliminary reports indicate that treatment with such antibodies can lead to the reduction of cardiovascular events compared with placebo. Results from the first completed large cardiovascular outcomes trial (FOURIER) were reported in March 2017. Repatha® (evolocumab) significantly reduced the risk of cardiovascular events. The study in approximately 27,000 subjects with clinically evident ASCVD met its primary composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, nonfatal MI or nonfatal stroke).

About RNAi

RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine. By harnessing the natural biological process of RNAi occurring in our cells, a major new class of medicines, known as RNAi therapeutics, is on the horizon. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, and which yielded inclisiran (licensed to The Medicines Company), function upstream of today’s medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing proteins, thus preventing them from being made. This is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases.

About The Medicines Company

The Medicines Company is a biopharmaceutical company driven by an overriding purpose – to save lives, alleviate suffering and contribute to the economics of healthcare. The Company’s mission is to create transformational solutions to address the most pressing healthcare needs facing patients, physicians and providers in serious infectious disease care and cardiovascular care. The Company is headquartered in Parsippany, New Jersey, with a global innovation center in California.

About Alnylam Pharmaceuticals

Alnylam (NASDAQ: ALNY) is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, and hepatic infectious diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust discovery platform and deep pipeline of investigational medicines, including four product candidates that are in late-stage development. Looking forward, Alnylam will continue to execute on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Alnylam employs over 600 people in the U.S. and Europe and is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam or on LinkedIn.

The Medicines Company Forward Looking Statements

Statements contained in this press release that are not purely historical may be deemed to be forward-looking statements for purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Without limiting the foregoing, the words "believes," "anticipates," "expects," “potential,” and similar expressions are intended to identify forward-looking statements. These forward-looking statements involve known and unknown risks and uncertainties that may cause the Company's actual results, levels of activity, performance or achievements to be materially different from those expressed or implied by these forward-looking statements. Important factors that may cause or contribute to such differences include the timing and success of a commercial launch of inclisiran

in the United States; the Company’s broader commercial strategy for and competition for inclisiran; whether clinical trials for inclisiran will advance on a timely basis, or at all, or succeed in achieving their specified endpoints; whether physicians, patients and other key decision makers will accept clinical trial results; whether physicians will prescribe and patients will use inclisiran, if it becomes available; whether the Company will make additional regulatory submissions for inclisiran on a timely basis, or at all; whether the Company’s regulatory submissions will receive approvals from regulatory agencies on a timely basis, or at all; and such other factors as are set forth in the risk factors detailed from time to time in the Company's periodic reports and registration statements filed with the Securities and Exchange Commission, including, without limitation, the risk factors detailed in the Company's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 9, 2017, which are incorporated herein by reference. The Company specifically disclaims any obligation to update these forward-looking statements.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, Alnylam's views with respect to the potential for inclisiran to be a safe and effective treatment for hypercholesterolemia, the timing of clinical studies and potential regulatory filings for approval of inclisiran and the expected safety database to be generated through the Phase III studies of inclisiran, its expectations regarding the development and potential commercialization of inclisiran by its partner The Medicines Company, and expectations regarding its "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, Alnylam's ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its product candidates, the pre-clinical and clinical results for its product candidates, which may not be replicated or continue to occur in other subjects or in additional studies or otherwise support further development of product candidates for a specified indication or at all, actions or advice of regulatory agencies, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing, delays, interruptions or failures in the manufacture and supply of its product candidates, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its intellectual property rights against third parties and defend its patent portfolio against challenges from third parties, obtaining and maintaining regulatory approval, pricing and reimbursement for products, progress in establishing a commercial and ex-United States infrastructure, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage its growth and operating expenses, obtain additional funding to support its business activities, and establish and maintain strategic business alliances and new business initiatives, Alnylam's dependence on third parties for development, manufacture and distribution of products, the outcome of litigation, the risk of government investigations, and unexpected expenditures, as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings that Alnylam makes with the SEC. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Inclisiran has not been approved by the U.S. Food and Drug Administration, the European Medicines Agency or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

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Source: The Medicines Company

The Medicines Company
Media
Meg Langan, 973-290-6319
Vice President
margaret.langan@themedco.com
or
Investors
Krishna Gorti, M.D., 973-290-6122
Vice President, Investor Relations
krishna.gorti@themedco.com
or
Alnylam Pharmaceuticals
Investors and Media
Christine Regan Lindenboom, 617-682-4340
Vice President
clindenboom@alnylam.com
or
Investors
Josh Brodsky, 617-551-8276
Associate Director
jbrodsky@alnylam.com