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Alnylam Pharmaceuticals and The Medicines Company Announce Publication of Phase 1 Clinical Data with Inclisiran (ALN- PCSsc) in the New England Journal of Medicine

Interim Results from ORION-1 Phase 2 Study of Inclisiran to be Presented in Late-Breaking Clinical Trial Session at the American Heart Association Scientific Sessions on November 15, 2016

CAMBRIDGE, Mass. & PARSIPANY, N.J.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, and The Medicines Company (Nasdaq:MDCO), a leading biopharmaceutical development and cardiovascular product company, today announced that results from the Phase 1 study of inclisiran (in-CLEE-si-ran), the recommended International Nonproprietary Name (INN) for ALN-PCSsc, were published in *The New England Journal of Medicine* (NEJM). Inclisiran is an investigational RNAi therapeutic targeting PCSK9 - a genetically validated protein regulator of LDL receptor metabolism - being developed for the treatment of hypercholesterolemia. The paper can be found online here.

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Results from the study showed doses ≥300 mg (single or multiple doses) significantly reduced PCSK9 and LDL cholesterol for at least 6 months. Moreover, inclisiran was found to be generally well tolerated.

"The published findings from our Phase 1 trial with inclisiran add to the clinical evidence supporting PCSK9 as a therapeutic target for significantly lowering LDL cholesterol, as well as the ability of RNAi therapeutic candidates to inhibit synthesis of liver-derived target proteins in a potent and durable manner," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D and Chief Medical Officer of Alnylam. "We believe that inclisiran represents an innovative and differentiated approach for the treatment of hypercholesterolemia."

Inclisiran is currently being studied in the ORION-1 Phase 2 study by The Medicines Company. With more than 500 patients enrolled, ORION-1 is the largest study of a GalNAc-siRNA conjugate to date. The Medicines Company recently announced positive top-line results from the day 90 interim analysis of the Phase 2 study demonstrating significant and durable LDL-C reduction that validates the potential for a triannual or biannual dosing regimen. Top-line results also showed that inclisiran was generally well tolerated, with no evidence of drug-related elevations of liver enzymes, neuropathy adverse events, or changes in renal function. The Medicines Company plans to present complete interim results from the ongoing study in a Late-Breaking Clinical Trial Session at the American Heart Association (AHA) Scientific Sessions on November 15, 2016.

"We look forward to presenting the interim results of the ORION-1 Phase 2 data at AHA this week including Day 90 follow-up results for all 501 patients and a preliminary analysis of Day 180 follow-up for up to 200 patients," said David Kallend, MBBS, Vice President and Global Medical Director at The Medicines Company. "Based on the strong results from the Phase 1 study, we hope to further elucidate the hypothesis of triannual or biannual dosing of inclisiran with the ORION-1 results."

The NEJM publication highlights key results from the Phase 1 clinical trial of inclisiran, including safety and pharmacodynamic measures (PCSK9, LDL cholesterol, exploratory lipid parameters).

In the single-ascending-dose (SAD) phase, pharmacodynamic measures showed:

- Doses ≥300 mg reduced PCSK9 at day 84 (up to a least-squares mean (LSM) reduction of 74.5%);
- Doses ≥100 mg reduced LDL cholesterol at day 84 (up to a LSM reduction of 50.6%);
- Reductions in PCSK9 and LDL cholesterol were maintained at day 180 with little variation over the 6-month period for doses ≥300 mg.

In the multiple-dose (MD) phase, pharmacodynamic measures showed:

- Reduced PCSK9 (up to a LSM reduction of 83.8%) and LDL cholesterol (up to a LSM reduction of 59.7%) at day 84;
- Levels of PCSK9 and LDL cholesterol remained reduced in all the inclisiran cohorts at day 196.

Safety and side effect profile evaluations showed:

- Inclisiran was generally well tolerated following single and multiple subcutaneous dose administration;
- No serious adverse events (SAEs) or discontinuations due to AEs were reported;
- All observed adverse events (AEs) were mild or moderate in severity;
- There was one Grade 3 GGT elevation considered related to statin therapy.

The lead development responsibility for inclisiran transitioned from Alnylam to The Medicines Company in August 2015. The two companies are now working to advance inclisiran in the ORION development program, a comprehensive global clinical development plan designed to support regulatory approval and market access worldwide.

About the Inclisiran Phase 1 Study

The Phase 1 trial of inclisiran was conducted in the U.K. as a randomized, single-blind, placebo-controlled, single ascending- and multi-dose, subcutaneous dose-escalation study. The study enrolled 69 volunteer subjects with elevated baseline LDL-C (≥ 100 mg/dL), with subjects randomized 3:1, drug: placebo. The study was performed in two phases: a single ascending dose (SAD) phase and a multiple dose (MD) phase. The MD phase also included subjects both on and off stable doses of statin co-medication. The primary objective of the Phase 1 study was to evaluate the safety, side effect profile, and pharmacodynamics effects of inclisiran.

About Hypercholesterolemia

Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of coronary artery disease, the leading cause of death in the U.S. Some forms of hypercholesterolemia can be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation) and medicines such as statins. However, a large proportion of patients with hypercholesterolemia are not achieving adequate LDL-C levels with currently available therapies such as statins, including genetic familial hypercholesterolemia (FH) patients, acute coronary syndrome patients, high-risk patient populations (e.g., patients with coronary artery disease, diabetes, symptomatic carotid artery disease, etc.) and other patients that are statin intolerant. Severe forms of hypercholesterolemia are estimated to affect more than 500,000 patients worldwide, and as a result, there is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies.

About GalNAc Conjugates and Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugates

GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology enables subcutaneous dosing with increased potency and durability, and a wide therapeutic index. This ESC-GalNAc-conjugate delivery platform is being employed in nearly all of Alnylam's pipeline programs, including inclisiran and several other programs in clinical development.

About RNAi

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of 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, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines. Alnylam's pipeline of investigational RNAi therapeutics is focused in 3 Strategic Therapeutic Areas (STArs): Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and

Hepatic Infectious Disease, with a pipeline of RNAi therapeutics that address the major global health challenges of hepatic infectious diseases. In early 2015, Alnylam launched its "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, Alnylam expects to achieve a company profile with 3 marketed products, 10 RNAi therapeutic clinical programs - including 4 in late stages of development - across its 3 STArs. The company's demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Ionis, Novartis, Roche, Takeda, Merck, Monsanto, The Medicines Company, and Sanofi Genzyme. In addition, Alnylam holds an equity position in Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 200 peer-reviewed papers, including many in the world's top scientific journals such as *Nature, Nature Medicine, Nature Biotechnology, Cell, New England Journal of Medicine,* and *The Lancet*. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information about Alnylam's pipeline of investigational RNAi therapeutics, please visit www.alnylam.com.

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, including the potential dosing regimen, the timing of clinical studies and the presentation of clinical data, its expectations regarding its STAr pipeline growth strategy, and 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 our 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.

The scientific information discussed in this news release relating to inclisiran is preliminary and investigative. Inclisiran has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this therapeutic.

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 three critical therapeutic areas: serious infectious disease care, cardiovascular care and surgery and perioperative care. The Company is headquartered in Parsippany, New Jersey, with global innovation centers in California and Switzerland.

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 whether clinical trials for inclisiran, will advance in the clinical process 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 the Company will make regulatory submissions for inclisiran on a timely basis, or at all; whether

its 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 October 27, 2016, which are incorporated herein by reference. The Company specifically disclaims any obligation to update these forward-looking statements.

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