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Alnylam Presents Updated Results from Phase 1/2 Study of ALN-CC5 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Results Provide Continued Evidence Supporting Potential for ALN-CC5 to Reduce Dose and Frequency of Eculizumab in Patients with PNH -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, today presented new results from Part C of its Phase 1/2 clinical trial with ALN-CC5, a subcutaneously administered investigational RNAi therapeutic targeting complement component 5 (C5) for the treatment of complement-mediated diseases, in a poster presentation at the 58th Annual Meeting of the American Society of Hematology (ASH), held December 3 - 6, 2016 in San Diego, California.

Part C evaluated the tolerability and clinical activity of ALN-CC5 in patients (N=6) with paroxysmal nocturnal hemoglobinuria (PNH), a rare hematologic disease where acquired mutations in the PIG-A gene lead to complement-mediated destruction of red blood cells (RBC). In an exploratory analysis, ALN-CC5 was evaluated in combination with eculizumab, an approved anti-C5 monoclonal antibody used for treatment of PNH. New results show that ALN-CC5-mediated knockdown of serum C5 has the potential to enable effective sparing of eculizumab in patients with PNH. These data further support development of ALN-CC5 to potentially reduce the dose level and frequency of eculizumab in patients with PNH, and to improve disease control in patients with an inadequate response to eculizumab.

The Company also announced today that Sanofi Genzyme has decided not to exercise its opt-in right for the development of ALN-CC5 in territories outside of the United States, Canada and Western Europe, providing Alnylam with full global control of the program for further development and potential commercialization.

"There remains significant unmet medical need for novel medicines to treat complement-mediated diseases, including PNH. We believe ALN-CC5, both as monotherapy and in combination with anti-C5 monoclonal antibodies, represents an opportunity to change disease management by achieving clamped inhibition of hepatic C5 synthesis," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D and Chief Medical Officer of Alnylam. "In our Phase 1/2 study in PNH, we previously generated evidence that ALN-CC5 may enable a reduced dose and frequency of anti-C5 monoclonal antibody therapy and may improve disease control in patients with an inadequate response to therapy. We're pleased to now extend these findings showing initial evidence for effective control of hemolysis in patients with PNH with a once-monthly reduced dose eculizumab regimen during six months of ongoing ALN-CC5 pharmacology. We look forward to further exploring the therapeutic potential of ALN-CC5 through future studies in PNH and other complement-mediated diseases."

Clinical Activity Results

In the Phase 1/2 study, a total of 6 patients with PNH were enrolled in Part C of the trial, including patients who were eculizumab naive (N=3) and patients who were receiving background eculizumab therapy (N=3). ALN-CC5 was administered at weekly doses of 200 or 400 mg for 2 to 16 weeks and achieved C5 knockdown of up to 98 percent and residual serum C5 levels less than 1 microgram per milliliter (mcg/mL). Upon completion of ALN-CC5 dosing and in the setting of ongoing ALN-CC5 pharmacology, investigators elected to treat patients with 600 mg or 900 mg of eculizumab every 4 weeks, enabling an exploratory analysis of the potential of ALN-CC5 to reduce the dose and frequency of eculizumab. As of the data transfer date of October 13, 2016, results showed that PNH patients who had previously been naive to eculizumab (N=3) achieved sustained control of disease hemolysis with normalization of lactate dehydrogenase (LDH) to less than or at approximately 1.5 times upper limit of normal (ULN) for up to 6 months while on a spared eculizumab regimen of 600 mg every 4 weeks. For patients who entered the study on background eculizumab (N=3), effective disease control with normalization of LDH to less than or at approximately 1.5 times ULN was achieved for up to 5 months while on a spared once-monthly regimen of 900 mg eculizumab. Using an assay for eculizumab plasma levels, both sparing regimens achieved stable eculizumab trough levels greater than 100 mcg/mL during the 5 to 6 month period. In aggregate, these results support the potential to achieve effective management of hemolysis in PNH during ALN-CC5 pharmacology with a spared eculizumab dosing regimen representing a 50 to 67 percent reduction in dose and a 2-fold extension of dose interval relative to the labeled eculizumab maintenance dose and regimen.

Safety Results

As previously reported, ALN-CC5 was generally well tolerated in patients with PNH after multiple doses for up to 16 weeks of

dosing. During the course of spared eculizumab dosing, as of the data transfer date of October 13, 2016, there were no serious adverse events (SAEs) or discontinuations due to adverse events (AEs) in the study, and the majority of reported AEs were mild or moderate in severity. One patient developed an episode of breakthrough hemolysis in the setting of an upper respiratory tract infection; this AE was moderate in severity and was considered unrelated to study drug by the investigator.

To view the ALN-CC5 clinical results described in this press release, please visit www.alnylam.com/capella.

About the ALN-CC5 Phase 1/2 Study Design

The Phase 1/2 trial of ALN-CC5 was conducted in three parts. Parts A and B were randomized (3:1, drug:placebo), double-blind, placebo-controlled, SAD and MAD studies, respectively, which enrolled 56 healthy adult volunteers. These parts of the study were designed to evaluate safety and tolerability of single and multiple subcutaneous doses of ALN-CC5. Additional objectives included clinical activity as measured by knockdown of serum C5 and levels of residual C5, and by effects on inhibition of serum complement activity, including measurements of CAP and CCP activity, as well as serum sheep red blood cell hemolytic activity. A total of 5 SAD cohorts were enrolled in the study, with fixed doses ranging from 50 to 900 mg. A total of 6 MAD cohorts were enrolled in the study with fixed doses of 100, 200, 400, or 600 mg, where healthy adult volunteers received subcutaneous doses of ALN-CC5 or placebo for up to 14 weeks. Part C is an open-label, multi-dose study that enrolled 6 patients with PNH, to assess safety, tolerability, and clinical activity of ALN-CC5, administered for up to 16 weeks. This part of the study included an exploratory evaluation of ALN-CC5 effects on levels of LDH, a measure of endogenous red blood cell hemolysis.

About ALN-CC5

ALN-CC5 is an investigational RNAi therapeutic targeting component 5 of the complement pathway (C5), currently in early stage clinical development for the treatment of complement-mediated diseases. The safety and efficacy of ALN-CC5 have not been evaluated by the U.S. Food and Drug Administration or any other health authority. The complement system plays a central role in immunity as a protective mechanism for host defense, but its dysregulation results in life-threatening complications in a broad range of human diseases including paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic-uremic syndrome (aHUS), myasthenia gravis, neuromyelitis optica, and membranous nephropathy, amongst others. C5, which is predominantly expressed in liver cells, is a genetically and clinically validated target; loss of function human mutations are associated with an attenuated immune response against certain infections and intravenous anti-C5 monoclonal antibody (mAb) therapy has demonstrated clinical activity and tolerability in a number of complement-mediated diseases. A subcutaneously administered RNAi therapeutic that silences C5 represents a novel approach to the treatment of complement-mediated diseases. ALN-CC5 utilizes Alnylam's ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index.

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 delivery platform is being employed in nearly all of Alnylam's pipeline programs, including 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 RNAi therapeutics, including ALN-CC5 to be used either as a monotherapy or and in combination with anti-C5 monoclonal antibodies for the treatment of complement-mediated diseases, 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 referenced in this news release relating to ALN-CC5 is preliminary and investigative. ALN-CC5 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 its safety or effectiveness.

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