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Alnylam Presents Results from Natural History Study of Patients with Familial Amyloidotic Cardiomyopathy (FAC) and Presents Complete Results from Phase 2 Clinical Trial for Revusiran, an Investigational RNAi Therapeutic for the Treatment of FAC

Natural History Study Results Describe an Average Decline of Approximately 140 Meters in 6-Minute Walk Distance (6-MWD) over 18 Months, Further Validating Co-Primary Endpoint in ENDEAVOUR Phase 3 Study of Revusiran in FAC

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), a leading RNAi therapeutics company, announced today results from a retrospective natural history study evaluating disease progression in transthyretin (TTR)-mediated amyloidosis (ATTR amyloidosis) patients with familial amyloidotic cardiomyopathy (FAC). Amongst other findings, study results showed a mean decline of 140 meters in 6-minute walk distance (6-MWD) over an 18-month period in FAC patients with mild-to-moderate heart failure. These natural history findings support the company's co-primary endpoint for its Phase 3 ENDEAVOUR clinical study with revusiran. In addition, Alnylam announced today that it presented complete results from its Phase 2 clinical trial with revusiran in a poster at the American College of Cardiology (ACC) Annual Scientific Session being held March 14 - 16 in San Diego. Consistent with preliminary results presented last year, revusiran achieved an up to 98.2% knockdown of serum TTR - the disease-causing protein - and was found to be generally well tolerated in the Phase 2 trial in FAC patients. Alnylam is developing revusiran (ALN-TTRsc), an investigational RNAi therapeutic targeting TTR, for the treatment of FAC.

"With our recently initiated ENDEAVOUR Phase 3 study, we are committed to the advancement of revusiran as a potential disease-modifying therapy for ATTR amyloidosis patients with cardiomyopathy. As presented at ACC today, these Phase 2 study results provide further evidence that revusiran is generally well tolerated in TTR cardiac amyloidosis patients with significant disease burden. Moreover, we continue to be impressed with the level of TTR knockdown achieved with revusiran of up to 98.2%," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President, R&D, and Chief Medical Officer of Alnylam. "In addition, we have now reported our FAC natural history study results. Specifically, this retrospective analysis evaluated disease progression in FAC patients and demonstrated a clear and robust decline in 6-minute walk distance over an 18-month period. These findings give us confidence that our ENDEAVOUR Phase 3 trial of revusiran in FAC patients is appropriately designed to show the potential impact of TTR lowering on functional decline. In addition, these data provide important context for our ongoing Phase 2 open-label extension study of revusiran in TTR cardiac amyloidosis, where we plan on reporting data at least once per year beginning in late 2015."

ATTR amyloidosis is an inherited, progressively debilitating, and often fatal disease caused by mutations in the TTR gene. These mutations cause misfolding of the TTR protein and the formation of amyloid fibrils that deposit in tissues. One of the clinical manifestations of ATTR amyloidosis is FAC, in which TTR amyloid deposition in the heart leads to cardiac wall thickening and heart failure. FAC is fatal within 2.5 to 5 years of diagnosis and treatment is currently limited to supportive care. Senile systemic amyloidosis (SSA) is a non-hereditary form of TTR cardiac amyloidosis caused by idiopathic deposition of wild-type TTR; its prevalence is generally unknown, but is associated with advanced age.

"TTR cardiac amyloidosis represents a significant unmet medical need for the growing population of older adults with this condition, for which there is no approved therapy. TTR cardiac amyloidosis is known to be associated with a high rate of mortality and hospitalization, in addition to a progressive decline in function. Our natural history study results confirm the significant disease burden in patients with FAC, with a median survival of under three years after presentation to the centers, and a steep rate of functional decline as measured by 6-MWD," said Mathew S. Maurer, M.D., Arnold and Arlene Goldstein Professor of Cardiology, Columbia University. "I look forward to continuing to work with Alnylam as they advance revusiran in clinical development, including in the ongoing Phase 3 ENDEAVOUR study. Indeed, we are hopeful that an RNAi therapeutic that stops production of the disease-causing protein has the potential to halt progression in patients with FAC and provide an important treatment option for management of this disease."

Findings from the natural history study were presented at a meeting with members of the Association of Black Cardiologists (ABC). This study was performed to characterize disease severity and rate of progression in a multinational population of FAC patients. Demographics and time from first visit to death were collected retrospectively on 137 FAC patients from two countries at two large amyloidosis centers: The National Amyloidosis Centre (NAC) in London (N=88); and Columbia University in New York (N=49). The majority of patients had mild-to-moderate heart failure (40% NYHA class II, 43% NYHA class III) and the V122I TTR mutation (85%), with a median age of 72 years. Serial 6-MWD data were collected retrospectively in 39 patients followed at NAC, while hospitalizations were captured in the 49 patients followed at Columbia. Median survival was 34.1 months for the pooled group of 137 patients, and median time to first cardiovascular hospitalization was 26.7 months. There was a clear decline in 6-MWD over 18 months. Specifically, at 12 and 18 months, the mean decline in 6-MWD was 106 +/- 24 meters and

140 +/- 39 meters, respectively. These results are consistent with the 91 meter and 118 meter decline compared to baseline at 12 and 18 months, respectively, observed in 10 FAC patients in the published TRACS study (Ruberg *et al., Am Heart J* 2012). There was no consistent change over time in NT-proBNP levels among 78 patients from the NAC with data available for analysis. Based on these findings, Alnylam believes that the ongoing Phase 3 ENDEAVOUR trial of revusiran in FAC patients has the potential to show an impact of TTR lowering on the co-primary endpoint of decline from baseline in 6-MWD at 18 months. In addition, Alnylam has assembled natural history data from academic collaborators on approximately 250 patients with SSA and plans to present those findings at a future meeting.

Alnylam also announced today complete results from its Phase 2 clinical trial with revusiran. The revusiran Phase 2 study was aimed at evaluating the safety, tolerability, pharmacodynamics, and preliminary clinical activity of revusiran in patients with FAC and SSA. Revusiran was found to be generally well tolerated in both FAC and SSA patients with advanced disease. The most common adverse event was a low incidence of transient mild liver function test (LFT) changes in 4 patients (15%) that, in all cases, resolved without discontinuing therapy. In 3 of the 4 patients, these elevations appeared to be clinically insignificant and were less than 1.5 times the upper limit of normal (ULN). One patient had an approximate 4-fold elevation in liver transaminases that was deemed a serious adverse event (SAE) and mild in severity; this event resolved during continued dosing. The next most common adverse event was injection site reactions (ISR) that occurred in 15% of patients. These were all mild in severity and were similar to the ISRs observed and previously reported in the revusiran Phase 1 study. There were no discontinuations and no significant changes in renal function or any other laboratory chemistry or hematologic parameters. Revusiran demonstrated clinical activity in TTR cardiac amyloidosis patients as measured by knockdown of serum TTR, the disease-causing protein. Specifically, administration of revusiran resulted in potent, rapid, and durable knockdown of serum TTR of up to 98.2%, with a mean maximum knockdown of 85.9% +/- 9.2%. After five weeks of treatment in this small study population, there were no significant changes observed in the exploratory clinical measurements performed. Alnylam has also recently initiated its Phase 2 open-label extension (OLE) study of revusiran. The study is designed to evaluate the tolerability and clinical activity of revusiran with long-term dosing for up to two years. The company expects to present results from the revusiran Phase 2 OLE study at least once annually, starting in late 2015.

Alnylam is currently enrolling subjects in its ENDEAVOUR Phase 3 trial, a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of revusiran in patients with FAC. The co-primary endpoints of the study are the change compared to baseline in 6-MWD at 18-months and the percent reduction in TTR burden between placebo- and revusiran-treated patients over 18 months. The trial is designed to enroll up to 200 FAC patients with a documented TTR mutation, including V122I or other mutations, in addition to amyloid deposits as identified by biopsy. Patients will be randomized 2:1, revusiran:placebo, with revusiran administered subcutaneously at 500 mg daily for five days then weekly for 18 months. The study was designed with 90% power to detect as little as 39% difference in the 18-month change from baseline for 6-MWD between treatment groups, with a significance level of $p < 0.05$. All patients completing the ENDEAVOUR Phase 3 study will be eligible to enroll in a Phase 3 OLE study.

In January 2014, Alnylam and Genzyme, a Sanofi company, formed an alliance to accelerate and expand the development and commercialization of RNAi therapeutics across the world. The alliance is structured as a multi-product geographic alliance in the field of rare diseases. In the case of revusiran, Alnylam and Genzyme are co-developing and co-commercializing the investigational RNAi therapeutic in North America and Western Europe, while Genzyme is developing and commercializing revusiran in the rest of world.

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 Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, Cubist, GlaxoSmithKline, Ascletis, Monsanto, The Medicines Company, and Genzyme, a Sanofi company. 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 revusiran (ALN-TTRsc) for the treatment of FAC and SSA, the design and timing of clinical studies, expectations regarding the reporting of data from clinical studies, expectations regarding its STAr pipeline growth strategy, and its plans regarding commercialization of RNAi therapeutics, including with its collaborator Genzyme, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important 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 drug 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, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its patents against infringers and defend its patent portfolio against challenges from third parties, obtaining regulatory approval for products, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage operating expenses, Alnylam's ability to 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, marketing, sales and distribution of products, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent Annual Report on Form 10-K 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 to update any forward-looking statements.

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