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Regeneron and Alnylam Report Promising Data from Ongoing Phase 1 Study of ALN-HSD in NASH Patients and Healthy Volunteers

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Target knockdown and safety results support continued clinical development

Regeneron and Alnylam intend to initiate a Phase 2 study in late 2022

Detailed results to be presented at an upcoming medical congress

TARRYTOWN, N.Y and CAMBRIDGE, Mass., Sept. 15, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals (Nasdaq: **REGN**) and Alnylam Pharmaceuticals, Inc. (Nasdaq: **ALNY**) announced today preliminary Phase 1 data supporting the clinical advancement of ALN-HSD, an investigational RNAi therapeutic targeting *HSD17B13* in development for the treatment of nonalcoholic steatohepatitis (NASH).

After single-dose evaluation in healthy adult volunteers (Part A), multiple doses of ALN-HSD are being studied in adult patients with NASH (Part B). Patients in the first two Part B cohorts (200 and 400 mg quarterly) have completed at least 6 months on the study; remaining cohorts are exploring a lower dose or a later biopsy time point. In the first two Part B cohorts, ALN-HSD was associated with robust target knockdown and numerically lower liver enzymes and biopsy-derived nonalcoholic fatty liver disease (NAFLD) Activity Score (NAS)* over six months in patients receiving ALN-HSD (N=20) relative to placebo (N=4). The study was not powered to achieve statistical significance on these endpoints, and the primary outcome measure is frequency of adverse events. ALN-HSD has exhibited an encouraging safety and tolerability profile to date; the most common treatment-emergent adverse event in healthy subjects treated with ALN-HSD (N=44) was injection site reaction in five patients; all injection site reactions were mild in severity. No treatment-related serious adverse events have been reported in either healthy volunteers or patients with NASH to date. Based on these results, the companies plan to initiate a Phase 2 study in adult patients with NASH in late 2022.

"We are excited to share these initial results, indicating what we believe to be a favorable profile for ALN-HSD and supporting continued clinical development of this investigational medicine, particularly given the significant prevalence and unmet need in NASH – a progressive liver disease and a leading cause of liver transplant," said Kevin Sloan, Ph.D., Vice President, Development Programs and Program Leader for the ALN-HSD program at Alnylam. "Our RNAi platform is ideally suited for this genetic target. We look forward to reporting detailed results from this study at an upcoming medical congress and to share details of the Phase 2 study design in partnership with our colleagues at Regeneron."

"The Regeneron and Alnylam collaboration continues to produce compelling clinical and pre-clinical stage therapeutic candidates targeting notoriously hard-to-treat diseases such as NASH and Alzheimer's," said Aris Baras, M.D., Senior Vice President and Head of the Regeneron Genetics Center. "By building on each company's deep expertise in human genetics as well as drug technology and development capabilities, we are progressing ALN-HSD to Phase 2 assessment and are rapidly moving *PNPLA3*- and *CIDEB*-targeting therapeutics towards first-in-human studies, resulting in an exciting portfolio of potential future genetic medicines for NASH."

* The NAFLD Activity Score (NAS) is a widely accepted scoring system developed by the NASH Clinical Research Network for use in clinical trials. The score is based on histological assessment of liver biopsies and is comprised of a sum of steatosis, ballooning, and lobular inflammation component scores.

About the Phase 1 Study Design
The Phase 1 trial is a randomized, double-blind, placebo-controlled, multi-center, single-ascending dose (SAD) and multiple-dose (MD) study designed to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of ALN-HSD in healthy adult subjects and adult patients with NASH. The primary endpoint of the study is the frequency of adverse events. The study was conducted in two parts. Part A enrolled 58 healthy adult subjects randomized 3:1 to receive a single ascending dose of 25, 100, 200, 400, or 800 mg of ALN-HSD or placebo; Part A of the study is complete. Part B enrolled 45 patients with NASH randomized 4:1 to receive two doses of 25, 200, or 400 mg of ALN-HSD or placebo, quarterly. Patients in the first two cohorts (200 and 400 mg) have completed at least 6 months on the study; remaining cohorts are exploring a lower dose or a later biopsy time point. Secondary and exploratory endpoints of the study include the characterization of plasma and urine PK of ALN-HSD and the evaluation of the drug PD effect.

About ALN-HSD
ALN-HSD is an investigational, subcutaneously administered RNAi therapeutic targeting *HSD17B13* for the treatment of NASH. It is being developed in collaboration with Regeneron following their identification of a loss-of-function variant in HSD17B13 that is associated with a reduced risk of chronic liver disease and progression from steatosis to steatohepatitis[1]. ALN-HSD utilizes Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugate technology, which enables subcutaneous dosing with increased selectivity and a wide therapeutic index. The safety and efficacy of ALN-HSD have not been evaluated by the FDA, EMA or any other health authority.

About NASH
Nonalcoholic steatohepatitis (NASH) is a highly prevalent chronic liver disease in which inflammation and liver cell injury are caused by accumulation of hepatic fat. NASH is a subset of a group of conditions called nonalcoholic fatty liver disease (NAFLD) that can lead to progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Comorbidities include obesity, metabolic syndrome, and type 2 diabetes. Approximately 16 million people in the US live with NASH, with prevalence of the disease increasing due to rising rates of obesity. NASH is projected to be the leading indication for liver transplants in developed countries within the next 10 years. There are currently no approved medical therapies for NASH.

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 new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function upstream of today's medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing or disease pathway 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 Alnylam Pharmaceuticals

Alnylam (Nasdaq: ALNY) has led 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 and prevalent diseases with unmet need. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach yielding transformative medicines. Since its founding 20 years ago, Alnylam has led the *RNAi Revolution* and continues to deliver on a bold vision to turn scientific possibility into reality. Alnylam's commercial RNAi therapeutic products are ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO® (lumasiran), and AMVUTTRA® (vutrisiran), as well as Leqvio® (inclisiran) which is being developed and commercialized by Alnylam's partner, Novartis. Alnylam has a deep pipeline of investigational medicines, including multiple product candidates that are in late-stage development. Alnylam is executing on its "Alnylam P5x25" strategy to deliver transformative medicines in both rare and common diseases benefiting patients around the world through sustainable innovation and exceptional financial performance, resulting in a leading biotech profile. Alnylam 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, on LinkedIn, or on Instagram.

About Regeneron

Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led for nearly 35 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to nine FDA-approved treatments and numerous product candidates in development, almost all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, hematologic conditions, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*®, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world.

For more information, please visit www.Regeneron.com or follow @Regeneron on Twitter.

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 initial results of the Phase 1 study of ALN-HSD in patients with NASH, the potential timing to report detailed results, Regeneron's involvement in the research, development and commercialization of ALN-HSD, Alnylam's aspiration to become a leading biotech company, and the planned achievement of its "Alnylam P^5x25" strategy, 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam's efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on Alnylam's ability to attract and retain talent and to successfully execute on its "Alnylam P5x25" strategy; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates, including ALN-HSD; the pre-clinical and clinical results for its product candidates, including ALN-HSD; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling its approved products globally; delays, interruptions or failures in the manufacture and supply of its product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication for ONPATTRO, AMVUTTRA or OXLUMO in the future; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and the risk of future 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 its other SEC filings. 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.

Regeneron Forward-Looking Statements and Use of Digital Media

This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates being developed by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, such as ALN-HSD (an investigational RNAi therapeutic targeting HSD17B13 in development for the treatment of nonalcoholic steatohepatitis (NASH)) as well as any PNPLA3- and CIDEB-targeting therapeutics for NASH referenced in this press release; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including the studies evaluating ALN-HSD discussed in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; the potential of the RNAi technology discussed in this press release for therapeutic

References

1. Abul-Husn NS., et al., 2018, *The New England Journal of Medicine*, "A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease", 378:1096-1106.

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