Regeneron and Alnylam Report Positive Interim Phase 1 Clinical Data on ALN-APP, an Investigational RNAi Therapeutic for Alzheimer's Disease and Cerebral Amyloid Angiopathy

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- Single Doses of ALN-APP Demonstrated Dose-Dependent, Rapid and Sustained Reduction of sAPPα and sAPPβ in Cerebrospinal Fluid, with Up to 90% at Highest Dose to Date -

- Encouraging Clinical Safety and Tolerability Profile Observed with Single Dosing to Date -

- Results Provide First Demonstration of Gene Silencing by RNAi Therapeutics in the Human Brain Using Alnylam's Proprietary C16 Platform -

TARRYTOWN, N.Y. and CAMBRIDGE, Mass., April 26, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) and Alnylam Pharmaceuticals, Inc. (Nasdaq: **ALNY**) announced today positive interim results from the ongoing single ascending dose part of the Phase 1 study of ALN-APP, an investigational RNAi therapeutic targeting amyloid precursor protein (APP) in development for the treatment of Alzheimer's disease and cerebral amyloid angiopathy (CAA).

Twenty patients have been enrolled in three single-dose cohorts in Part A of the ongoing Phase 1 study in patients with early-onset Alzheimer's disease. In this study to date, single doses of ALN-APP, which are administered by intrathecal injection, have been well tolerated. All adverse events were mild or moderate in severity, with available cerebrospinal fluid data for white blood cells and protein appearing similar to placebo. Early data for neurofilament light chain from a subset of cohorts (2 of 3 studied) looked comparable to placebo. Patients treated with ALN-APP experienced dose-dependent, rapid and sustained reduction in cerebrospinal fluid of both soluble APPα (sAPPα) and APPβ (sAPPβ), biomarkers of target engagement, with maximum reduction of 84% and 90%, respectively. Median decreases of both biomarkers of greater than 70% was sustained for at least three months at the highest dose tested. Detailed interim results from this study are planned to be reported at an upcoming scientific conference.

"ALN-APP, via its upstream targeting mechanism, has the potential to address the underlying cause of two devastating CNS diseases, Alzheimer's disease and CAA, which affect many millions of people and their families around the world. Thus, we are excited by these interim clinical data for ALN-APP, which demonstrate rapid, substantial and sustained target protein reduction and encouraging safety and tolerability to date," said Pushkal Garg, M.D., Chief Medical Officer of Alnylam. "We look forward to continuing to advance ALN-APP through the Phase 1 study, which will inform our future development plans in both Alzheimer's disease and CAA."

These early results establish the first human translation of Alnylam's proprietary C16-siRNA conjugate platform for central nervous system (CNS) delivery and are the first clinical demonstration of gene silencing in the human brain using an RNAi therapeutic.

"Establishing human proof of concept with ALN-APP is a major step in our efforts to expand our organic product engine to extrahepatic tissues like the CNS, a critical goal in our P^5x25 strategy," said Yvonne Greenstreet, MBChB, Chief Executive Officer of Alnylam. "This further reinforces our belief that RNAi therapeutics have the potential to become a new class of medicines for silencing genes implicated in causing CNS diseases. Given these encouraging interim data, we are accelerating our efforts with Regeneron to bring forward additional genetically validated development candidates for other neurologic diseases, many of which have few or no therapeutic options for patients."

"When we entered into this collaboration, the idea that you could profoundly silence disease-causing genes in the brain was simply a bold dream. The current data suggest that this dream is closer to becoming a reality, offering hope for the many patients suffering from incurable neurological diseases," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "This approach to preventing production of amyloid precursor protein (APP) – as opposed to trying to clear amyloid plaques after they have already formed – provides a new way to potentially combat the scourge of Alzheimer's disease, which has devastated so many families and proven historically difficult to treat."

Further exploration of single-doses of ALN-APP is ongoing in Part A of the Phase 1 study (Canada, Netherlands, United Kingdom and United States) to evaluate longer term safety and duration of action and to identify the multi-dose regimen for Part B. Part B will include patients from Part A, and has received regulatory approval to proceed in Canada where the majority of the Part A clinical trial patients have been enrolled. Additional preclinical data, as well as the emerging clinical data announced today, will be shared with the FDA, which has placed a partial clinical hold on Part B in the U.S. due to findings observed in prior non-clinical chronic toxicology studies.

In addition to ALN-APP, Regeneron and Alnylam have named ten targets in the CNS as part of their exclusive collaboration established in 2019 to discover RNAi therapeutics for eye and CNS diseases.

About the Phase 1 Study of ALN-APP
The Phase 1 study is a multi-center, randomized, double-blind, placebo-controlled trial designed to evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamic effects of ALN-APP in patients with early-onset Alzheimer's disease (EOAD). The study is being conducted in two parts: single ascending dose phase and multiple dose phase in patients with EOAD. The planned enrollment for this study is up to 60 patients.

The interim readout of the Phase 1 study of ALN-APP is focused on assessing safety, tolerability and levels of target engagement biomarkers, sAPP and sAPP.

About ALN-APP
ALN-APP is an investigational, intrathecally administered RNAi therapeutic targeting amyloid precursor protein (APP) in development for the treatment of Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). Genetic mutations that increase production of APP or alter its cleavage cause early-onset AD, early-onset CAA, or both. ALN-APP is designed to decrease APP mRNA in the central nervous system (CNS), to decrease synthesis of APP protein and all downstream intracellular and extracellular APP-derived cleavage products, including amyloid beta (Aβ). Reducing APP protein production is expected to reduce the secretion of Aβ peptides that aggregate into extracellular amyloid deposits and reduce the intraneuronal APP cleavage products that trigger the formation of neurofibrillary tangles and cause neuronal dysfunction in Alzheimer's disease. ALN-APP is the first program utilizing Alnylam's proprietary C16-siRNA conjugate technology, which enables enhanced delivery to cells in the CNS. This program is being developed in collaboration between Regeneron and Alnylam Pharmaceuticals. The safety and efficacy of ALN-APP have not been evaluated by the FDA, EMA, or any other health authority.

About Alzheimer's Disease
Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common form of dementia, affecting over 30 million people worldwide. AD is characterized by progressive memory loss and cognitive decline, with neuropathological accumulation of amyloid plaques, neurofibrillary tangles, and neuroinflammation, ultimately resulting in significant brain atrophy. Disease progression results in progressive loss of independence, increased caregiver burden, institutionalization, and premature death. Early-onset Alzheimer's disease (EOAD) refers to a subgroup of AD with symptom onset prior to the age of 65, representing approximately 4% to 6% of all AD. EOAD is the leading cause of dementia in younger individuals and is a significant cause of disability and early mortality. Available treatment options include symptomatic treatment and treatment to reduce amyloid deposits in the brain. There are currently no available treatments that have been shown to halt or reverse the progression of the disease.

About Cerebral Amyloid Angiopathy
Cerebral amyloid angiopathy (CAA) is the second most-common cause of hemorrhagic stroke. CAA is defined by progressive deposition of amyloid beta (Aβ) into the walls of small arteries, arterioles, and capillaries in the brain, causing impaired vascular reactivity, focal tissue damage, and increased risk for intracerebral hemorrhage. CAA has also been shown to be an independent contributor to cognitive impairment. There are currently no available treatment options for CAA.

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 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.

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), AMVUTTRA® (vutrisiran) and 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.

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-APP (an investigational RNAi therapeutic targeting amyloid precursor protein in development for the treatment of Alzheimer's disease and cerebral amyloid angiopathy); the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including the study evaluating ALN-APP 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 development; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the studies discussed or referenced in this press release, on any of the foregoing or any potential regulatory approval of Regeneron's Products and Regeneron's Product Candidates (such as ALN-APP); the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates (such as ALN-APP) and new indications for Regeneron's Products; the ability of Regeneron's collaborators, licensees, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron and/or its collaborators to manufacture and manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and Regeneron's Product Candidates in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates (such as ALN-APP) in clinical trials; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's Products and Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and Regeneron's Product Candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license, collaboration, or supply agreement, including Regeneron's agreements with Sanofi and Bayer (or their respective affiliated companies, as applicable), as well as Regeneron's collaboration with Alnylam Pharmaceuticals, Inc. discussed in this press release, to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection, Praluent® (alirocumab), and REGEN-COV® (casirivimab and imdevimab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2022. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update (publicly or otherwise) any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (https://newsroom.regeneron.com/) and its

Twitter feed (https://twitter.com/regeneron).

Alnylam Forward Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, expectations regarding Alnylam's aspiration to become a leading biotech company and the planned achievement of its "Alnylam P5x25" strategy, the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam's projected commercial and financial performance, should be considered forward-looking statements. 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; Alnylam's ability to successfully execute on its "Alnylam P ^{5}x25" 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; the pre-clinical and clinical results for Alnylam's product candidates, including patisiran and vutrisiran; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, including patisiran and vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; delays or interruptions in the supply of resources needed to advance Alnylam's research and development programs, including as may arise from recent disruptions in the supply of non-human primates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication for ONPATTRO or AMVUTTRA 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 a current government investigation 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 2022 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as may be updated from time to time in Alnylam's subsequent Quarterly Reports on Form 10-Q 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.

This press release discusses investigational RNAi therapeutics and is not intended to convey conclusions about efficacy or safety as to those investigational therapeutics. There is no guarantee that any investigational therapeutics will successfully complete clinical development or gain health authority approval.

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