Alnylam Uncovers Genetic Mutations in INHBE That Protect Against Abdominal Obesity

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- Publication in Nature Communications Reports that People with Loss of Function Mutations in the INHBE Gene Have Reduced Abdominal Fat, a Favorable Metabolic Profile, and are at Lower Risk of Cardiovascular Disease and Type 2 Diabetes -

- Alnylam to Pursue INHBE as a Therapeutic Target for Cardiometabolic Disease -

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 27, 2022-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company and collaborators have identified mutations in the *INHBE* gene associated with protection against abdominal obesity and metabolic syndrome – a condition impacting more than 20 percent of adults worldwide. The discovery leveraged sequencing data from more than 360,000 individuals in UK Biobank, and was published in the 13th issue of *Nature Communications*. The published data show that rare mutations in the liver-expressed *INHBE* gene are associated with lower waist-to-hip ratio adjusted for body mass index (WHRadjBMI), a surrogate for abdominal fat that is causally linked to type 2 diabetes and coronary heart disease. Findings support the potential of *INHBE* to be evaluated as a novel therapeutic target for the treatment of cardiometabolic disease. The Company plans to pursue a development candidate for *INHBE* and its gene product, Activin E, leveraging its liver IKARIA™ platform.

"We are thrilled that our investment in genetic databases like UK Biobank is proving to be fruitful in identifying novel targets in highly prevalent diseases with continued unmet need," said Paul Nioi, Ph.D., Vice President, Discovery and Translational Research, and the Leader of Alnylam's Human Genetics Group. "There is a well-established causal link between increased waist-to-hip ratio and a person's risk of cardiometabolic conditions. By exploring the genetic determinants of waist-to-hip ratio in this study, important insights into the mechanisms that contribute to body fat distribution were uncovered helping identify potential therapeutic targets for abdominal obesity, like *INHBE*. The results of this exome-wide analysis suggest that targeting *INHBE* is predicted to have broad beneficial effects on all facets of metabolic syndrome with potential reductions in the risk of type 2 diabetes and coronary heart disease. We are currently testing this hypothesis, with the goal of pursuing a development candidate targeting *INHBE* in the near future."

"We are delighted to see that the uniquely detailed data within UK Biobank - generously donated by our half a million participants - is accelerating research into important health conditions. Thanks to the collaboration with leading life sciences companies in the UK Biobank Exome Sequencing Consortium, the UK Biobank resource is helping to rapidly identify new therapeutic targets for abdominal obesity," said Professor Naomi Allen, UK Biobank Chief Scientist.

Using whole exome-sequencing data from UK Biobank, Alnylam and collaborators mined for gene variants associated with lower WHRadjBMI in more than 360,000 individuals of European ancestry, revealing "loss of function" in *INHBE* as a novel genetic factor contributing to a healthier fat distribution. Rare predicted loss of function (pLOF) variants in *INHBE*, were carried by one in 587 individuals and were associated with lower abdominal fat. *In vitro* characterization of the most common *INHBE* pLOF variant in the study, indicated an approximately 90% reduction in secreted activin E levels. Further analysis of *INHBE* pLOF carriers revealed a favorable metabolic profile, including decreased triglycerides, increased high-density lipoprotein cholesterol, and decreased fasting glucose. There were no associations suggesting adverse effects of *INHBE* pLOF, and carriers of these variants did not show evidence of excess mortality. The study also detected associations with lower WHRadjBMI for variants in *ACVR1C*, encoding an activin receptor, further highlighting the involvement of activins in regulating fat distribution.

About UK Biobank

UK Biobank is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants. The database, which is regularly augmented with additional data, is globally accessible to approved researchers and scientists undertaking vital research into the most common and life-threatening diseases. UK Biobank's research resource is a major contributor to the advancement of modern medicine and treatment and has enabled several scientific discoveries that improve human health.

The UK Biobank Exome Sequencing Consortium (UKB-ESC)

In 2018, Alnylam and partners Regeneron, AbbVie, AstraZeneca, Biogen, and Pfizer announced an agreement with UK Biobank to form the UK Biobank Exome Sequencing Consortium (UKB-ESC), a pre-competitive consortium that aims to sequence the whole exomes of 500,000 volunteer participants in the biomedical resource. The goal of the consortium, which represents the largest ever effort to use genome sequencing to map the DNA of a group of people, is to uncover insights that allow researchers to pinpoint new drug targets at the core of human disease in order to develop effective treatments for patients. To date, the UKB-ESC has made whole-exome sequencing data from 450,000 participants available to the global health community for research purposes and will continue to make all sequenced data available at no cost under the terms of the UKB-ESC charter and the founding principles of UK Biobank.

About Cardiometabolic Disease

Cardiometabolic diseases are the number one cause of death in the world; these include but are not limited to cardiovascular disease, obesity, diabetes mellitus, and non-alcoholic fatty liver disease. An estimated 47 million people in the U.S. alone are living with some form of cardiometabolic disease. Despite the availability of many well-established treatments for cardiometabolic diseases, the substantial mortality associated with this group of diseases underscores the high unmet medical need for new therapeutic options, including those directed to novel disease-modifying targets, and with potential to address poor medication adherence.

About IKARIA™ Platform

Alnylam's IKARIA platform takes advantage of more than two decades of experience in developing RNAi therapeutics. IKARIA enables an extended

duration of activity in preclinical studies, with potential for annual dosing in humans, and has design features which provide exquisite specificity, further widening the potential therapeutic index, with enhanced target reduction levels.

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), AMVUTTRA™ (vutrisiran), and Leqvio® (inclisiran) being developed and commercialized by Alnylam's partner, Novartis. Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam is executing on its "*Alnylam P^{5}x25*" 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.

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 pursuing *INHBE* as a therapeutic target for cardiometabolic disease and its goal to identify a development candidate targeting *INHBE* in the near future, Alnylam's aspiration to become a leading biotech company, and the planned achievement of its *"Alnylam P^{5}x25"* 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 P^{5}x25"* strategy; Alnylam's ability to discover and develop novel drug candidates, including a development candidate targeting *INHBE*, and delivery approaches, and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for its product candidates; 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 OXLUMO, ONPATTRO and 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 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.

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