



## Alnylam Initiates KARDIA-2 Phase 2 Study of Investigational Zilebesiran (ALN-AGT) in Patients with Inadequately Controlled Hypertension

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– KARDIA-2 will Evaluate Efficacy and Safety of Zilebesiran when Used in Combination with Conventional Antihypertensive Medications –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 8, 2021-- [Alnylam Pharmaceuticals, Inc.](#) (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced initiation of KARDIA-2, a global Phase 2 study to evaluate the efficacy and safety of zilebesiran (formerly known as ALN-AGT), an investigational subcutaneous RNAi therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension. KARDIA-2 will evaluate the efficacy and safety of zilebesiran administered biannually as a concomitant therapy in patients whose blood pressure is not adequately controlled by standard of care antihypertensive medications.

The primary endpoint of KARDIA-2 is the change from baseline in 24-hour mean systolic blood pressure (SBP) after three months of treatment, as measured by ambulatory blood pressure monitoring (ABPM). Additional endpoints will include change from baseline in blood pressure at six months and time-averaged reduction of blood pressure as a measure of tonic control. Safety will be assessed throughout the study. KARDIA-2 has been activated at clinical sites in the U.S. and will be conducted at approximately 80 clinical study centers worldwide.

"Hypertension remains one of the top preventable causes of death around the world. Despite the availability of efficacious interventions, most patients on antihypertensive medications fail to achieve guideline-recommended goals for blood pressure control, increasing their risk for cardiovascular events, primarily stroke and heart attack. A lack of patient adherence to therapy with daily oral medications contributes to the challenges of achieving tonic blood pressure control," said Weinong Guo, M.D., Ph.D., Senior Vice President of Clinical Development at Alnylam. "With the global prevalence of hypertension expected to increase by up to 20 percent by 2025, the initiation of KARDIA-2 represents Alnylam's commitment to advance zilebesiran as an innovative potential treatment with an infrequent dosing regimen that could one day help address this global public health crisis."

KARDIA-2 is the second Phase 2 study evaluating zilebesiran in hypertension, with KARDIA-1, [announced earlier this year](#), assessing zilebesiran as monotherapy across different doses administered quarterly and biannually. These Phase 2 studies are based on encouraging Phase 1 data, including [results presented earlier this year](#) at the 2021 Joint Meeting of the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH). Additional clinical results from the Phase 1 study of zilebesiran will be presented at the American Heart Association (AHA) Scientific Sessions 2021, being held November 13-15, 2021.

### About KARDIA-2 Phase 2 Study

The KARDIA-2 Phase 2 trial is a randomized, double-blind (DB), placebo-controlled study to evaluate the efficacy and safety of zilebesiran used as a concomitant therapy in adults with hypertension despite treatment with standard of care antihypertensive medications. This global, multicenter trial will enroll approximately 800 adults with hypertension. Patients who meet all inclusion/exclusion criteria during a screening period will be randomized to receive open-label therapy with olmesartan, amlodipine or indapamide as their protocol-specified background antihypertensive medication during a run-in period of at least four weeks. Following the run-in period, eligible patients will be randomized 1:1 to receive 600 mg zilebesiran or placebo concomitantly with their protocol-specified background antihypertensive medication during a 6-month DB period. After three months, additional conventional oral antihypertensives may be added to the protocol-specified background antihypertensive medication for elevated blood pressure. Once the DB period has concluded, protocol-specified background antihypertensive medications will be discontinued, and patients may be eligible to participate in a separate zilebesiran open-label extension study.

The study's primary efficacy endpoint is the change from baseline in 24-hour mean systolic blood pressure (SBP), as measured by ambulatory blood pressure monitoring (ABPM), after three months of treatment. Additional endpoints include the change in 24-hour mean SBP after six months of treatment assessed by ABPM, change in office SBP at months three and six, and change in 24-hour mean diastolic blood pressure (DBP) measured by ABPM — as well as office DBP — at months three and six. Safety will be assessed throughout the study. For more information on KARDIA-2 (NCT05103332), please visit [clinicaltrials.gov](#), email [clinicaltrials@alnylam.com](mailto:clinicaltrials@alnylam.com) or call 877-256-9526 in North America and +31 20 369 7861 in Europe.

### About Zilebesiran

Formerly known as ALN-AGT, zilebesiran (pronounced "zile-BEE-siran") is an investigational, subcutaneously administered RNAi therapeutic targeting angiotensinogen (AGT) in development for the treatment of hypertension in high unmet need populations. AGT is the most upstream precursor in the Renin-Angiotensin-Aldosterone System (RAAS), a cascade which has a demonstrated role in blood pressure regulation and its inhibition has well-established antihypertensive effects. Zilebesiran inhibits the synthesis of AGT in the liver, potentially leading to durable reductions in AGT protein and ultimately, in the vasoconstrictor angiotensin (Ang) II. Zilebesiran 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 zilebesiran have not been established or evaluated by the FDA, EMA or any other health authority.

### About Hypertension

Hypertension is a complex multifactorial disease clinically defined by most major guidelines as a systolic blood pressure (SBP) of above 140 mm Hg and/or a diastolic blood pressure (DBP) greater than 90 mm Hg, though AHA/ACC guidelines have a lower threshold of a SBP above 130 mm Hg and/or a DBP greater than 80 mm Hg. More than one billion people worldwide live with hypertension.<sup>i</sup> In the U.S. alone, approximately 47 percent of adults live with hypertension, with more than half of patients on medication remaining above the blood pressure target level. Despite the availability of antihypertensive medications, there remains a significant unmet medical need, especially given the poor rates of adherence to existing daily oral medications and daily peak and trough effects, resulting in inconsistent blood pressure control and an increased risk for stroke, heart attack and premature death.<sup>ii</sup> In particular, there are a number of high unmet need settings where novel approaches to hypertension warrant additional development focus, including patients with poor medication adherence, difficult-to-treat and resistant hypertension, and in patients with high

cardiovascular risk.

### **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) is leading 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 genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS)/ocular diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust RNAi therapeutics platform. Alnylam’s commercial RNAi therapeutic products are ONPATTRO<sup>®</sup> (patisiran), GIVLAARI<sup>®</sup> (givosiran), and OXLUMO<sup>®</sup> (lumasiran), as well as Leqvio<sup>®</sup> (inclisiran), which is 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 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](http://www.alnylam.com) and engage with us on Twitter at [@Alnylam](https://twitter.com/Alnylam), on [LinkedIn](https://www.linkedin.com/company/alnylam), or on [Instagram](https://www.instagram.com/alnylam).

### **Alnylam Forward Looking Statements**

Various statements in this release concerning Alnylam’s expectations, plans, aspirations, and goals, including those related to encouraging results from the Phase 1 study of zilebesiran (formerly known as ALN-AGT), the design and conduct of the KARDIA-2 and KARDIA-1 Phase 2 studies of zilebesiran and the planned initiation of the study in the U.S. and worldwide, Alnylam’s commitment to advancing zilebesiran as a potential treatment to help address the worldwide burden of uncontrolled hypertension, the potential that inhibiting the synthesis of AGT in the liver leads to durable reductions in AGT protein and ultimately, in the vasoconstrictor angiotensin (Ang) II, Alnylam’s aspiration to become a leading biotech company, and the planned achievement of its “Alnylam P5x25” 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 planned leadership transition at year end 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 vutrisiran; 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, including vutrisiran, 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 (and potentially vutrisiran, if approved) 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, 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 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.

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

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<sup>i</sup> Hypertension. World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/hypertension>. Published September 2019. Accessed November 2021.

<sup>ii</sup> Carey, R. M., Muntner, P., Bosworth, H. B., & Whelton, P. K. (2018). Prevention and Control of Hypertension: JACC Health Promotion Series. Journal of the American College of Cardiology, 72(11), 1278–1293. <https://doi.org/10.1016/j.jacc.2018.07.008>

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