Alnylam Presents Positive Results from the KARDIA-1 Phase 2 Dose-Ranging Study of Zilebesiran, an Investigational RNAi Therapeutic in Development for the Treatment of Hypertension in Patients at High Cardiovascular Risk

Nov 11, 2023

– Zilebesiran Met Primary Endpoint Demonstrating Up to 16.7 mmHg Placebo-Adjusted Reduction of 24-Hour Mean Systolic Blood Pressure at Three Months of Treatment –

– Study Met Key Secondary Endpoints Showing Consistent and Sustained Reductions of Systolic Blood Pressure and Durable Tonic Blood Pressure Control Through Month 6 –

– Data Support Quarterly or Biannual Dosing –

– Zilebesiran Demonstrated an Encouraging Safety and Tolerability Profile in Adult Patients with Mild-to-Moderate Hypertension –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 11, 2023-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=02e6a9390c5b398a17279a212042555a) (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced positive results (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcapella.alnylam.com%2F2023%2F11%2F11%2Fzilebe-aha-2023&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=positive+results&index=2&md5=f68829575e85ec938439d0fb45b2e174) from the KARDIA-1 Phase 2 study of zilebesiran, an investigational RNAi therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of patients with hypertension and high cardiovascular risk. The study results were presented during the American Heart Association (AHA) Scientific Sessions being held in Philadelphia, Pennsylvania from November 11-13, 2023. The Company previously announced (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.alnylam.com%2Fpress-release%3Fid%3D27706&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=announced&index=3&md5=433f0c711d0bb8dd4f092be770d5c0ca) positive topline results from the KARDIA-1 study in September 2023.

The KARDIA-1 study achieved its primary endpoint, with single doses of zilebesiran demonstrating clinically significant reductions in 24-hour mean systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring (ABPM) at Month 3 across all doses, with the 150 mg, 300 mg, and 600 mg doses achieving placebo-adjusted reductions of 14.1 mmHg, 16.7 mmHg, and 15.7 mmHg, respectively (all p-values less than 0.0001). The study also met key secondary endpoints across all doses, including demonstration of durable efficacy out to 6 months. At the 150 mg Q6M, 300 mg Q6M, 300 mg Q3M, and 600 mg Q6M doses, zilebesiran showed placebo-adjusted reductions in 24-hour mean SBP measured by ABPM of 11.1 mmHg, 14.5 mmHg, 14.1 mmHg, and 14.2 mmHg, respectively, at Month 6 (all p-values less than 0.0001). Zilebesiran demonstrated an encouraging safety and tolerability profile that the Company believes supports continued development.

"These KARDIA-1 results are impressive, showing that in a diverse group of patients with mild-to-moderate hypertension, zilebesiran can safely achieve clinically significant reductions in systolic blood pressure and tonic blood pressure control administered subcutaneously with either quarterly or bi-annual dosing," said Professor George L. Bakris, M.D., Board-Certified Hypertension Specialist and Director of the American Heart Association Comprehensive Hypertension Center, University of Chicago Medicine. "I continue to be encouraged and optimistic that zilebesiran has the potential to become not only a novel treatment for hypertension but also a transformative therapy to lower cardiovascular and renal risk in patients with hypertension, an area where new and innovative therapies are desperately needed."

KARDIA-1 Study Results

The KARDIA-1 Phase 2 study is a randomized, double-blind, placebo-controlled, multi-center global dose-ranging study designed to evaluate the efficacy and safety of subcutaneously administered zilebesiran as monotherapy in adults with mild-to-moderate hypertension.

The study enrolled 394 adults representing a diverse patient population, of which more than 40% were female and nearly 25% were Black, with untreated hypertension or who were on stable therapy with one or more anti-hypertensive medications. Any patients taking prior antihypertensive medications completed at least a two- to four-week wash-out before randomization. Patients were randomized to one of five treatment arms: 150 mg zilebesiran once every six months (Q6M); 300 mg zilebesiran Q6M; 300 mg zilebesiran once every three months (Q3M); 600 mg zilebesiran Q6M; or placebo.

The primary endpoint was the change from baseline in 24-hour mean SBP at Month 3, assessed by ABPM. Key secondary endpoints in this study include additional measures of blood pressure reduction at Month 3 and Month 6, and the proportion of patients achieving treatment response criteria at Month 6, defined as 24-hour mean ambulatory SBP <130 mmHg and/or reduction ≥20 mmHg without additional antihypertensive medications.

At six months, the study met its primary endpoint and all key secondary endpoints. The placebo-adjusted study results presented today are as follows:

Key Endpoints	**150 mg Q6M**	**300 mg Q6M**	**300 mg Q3M**	**600 mg Q6M**
Primary Endpoint				
Change from Baseline to Month 3 in 24-Hour Mean Ambulatory SBP	-14.1 mmHg (p less than 0.0001)	-16.7 mmHg (p less than 0.0001) *		-15.7 mmHg (p less than 0.0001)
Key Secondary Endpoints				

Change from Baseline to Month 6 in 24-Hour Mean Ambulatory SBP	-11.1 mmHg (p less than 0.0001)	-14.5 mmHg (p less than 0.0001)	-14.1 mmHg (p less than 0.0001)	-14.2 mmHg (p less than 0.0001)
Change from Baseline to Month 3 in Office SBP	-9.6 mmHg (p less than 0.0001)	-12.0 mmHg (p less than 0.0001) *		-9.1 mmHg (p less than 0.0001)
Change from Baseline to Month 6 in Office SBP	-7.5 mmHg (p=0.0025)	-10.5 mmHg (p less than 0.0001)	-12.1 mmHg (p less than 0.0001)	-10.2 mmHg (p less than 0.0001)

* 300 mg Q6M and Q3M groups were pooled for Month 3 endpoints

  - The final key secondary endpoint evaluating the proportion of patients achieving treatment response criteria at Month 6 was also met, with the odds of meeting response criteria being significantly higher across all zilebesiran regimens compared to placebo (p less than 0.001).

- Reductions in 24-hour mean blood pressure, measured by ABPM, were maintained over the full diurnal cycle, with consistently lower hourly, daytime, and nighttime blood pressure across all zilebesiran regimens compared to placebo through Month 6.

Zilebesiran demonstrated an encouraging safety profile through Month 6. Serious adverse events were reported in 6.7% of patients in the placebo group and 3.6% of patients in the zilebesiran groups. There was one death due to cardiopulmonary arrest in a zilebesiran-treated patient that was considered unrelated to study drug. Drug-related adverse events (AEs) reported in more than 5% of patients in any zilebesiran arm were injection site reaction (ISR) occurring in 6.3% of patients and hyperkalemia in 5.3% of patients. No drug-related AEs were classified as serious or severe. ISR and hyperkalemia AEs were mostly mild and transient. No hyperkalemia events were associated with acute kidney injury or led to study drug discontinuation. Four patients had drug-related AEs leading to an investigator decision to discontinue zilebesiran. These AEs included orthostatic hypotension (n=2), blood pressure elevation (n=1), and ISR (n=1). Hypotension AEs were mild or moderate, non-serious, and transient. A single event in the zilebesiran 300 mg Q3M group was treated with normal saline. Clinically relevant AEs of acute renal failure, hepatic AEs, hypotension, and hyperkalemia of any relatedness were reported in 1.3%, 3.0%, 4.3%, and 6.3% of patients receiving zilebesiran, and 0%, 1.3%, 1.3%, and 2.7% of patients receiving placebo.

“The totality of the data presented at the American Heart Association Scientific Sessions gives us confidence in zilebesiran’s potentially differentiated profile and its ability to transform the treatment landscape for patients with uncontrolled hypertension who are at high risk of future cardiovascular events,” said Simon Fox, Ph.D., Vice President, Zilebesiran Program Lead at Alnylam. “We look forward to sharing topline results from the KARDIA-2 Phase 2 study,

designed to evaluate the efficacy and safety of zilebesiran when used in combination with one other antihypertensive medication in patients with mild-to-moderate hypertension, in early 2024."

To view the KARDIA-1 Phase 2 results presented at AHA, please visit Capella (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcapella.alnylam.com%2F2023%2F11%2F11%2Fzilebe-aha-2023&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=Capella&index=4&md5=7fcfb4e649d8546b6fffb336e2f06582).

About Zilebesiran

Zilebesiran 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 (BP) regulation and its inhibition has well-established anti-hypertensive 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 infrequent subcutaneous dosing with increased selectivity and the potential to achieve tonic blood pressure control demonstrating consistent and durable blood pressure reduction throughout a 24-hour period, sustained up to six months after a single dose of zilebesiran. The safety and efficacy of zilebesiran have not been established or evaluated by the FDA, EMA or any other health authority. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche.

About Hypertension

Uncontrolled hypertension is the chronic elevation of blood pressure (BP), defined by the 2017 ACC/AHA guidelines as ≥130 mmHg systolic blood pressure (SBP) and ≥80 mmHg diastolic blood pressure (DBP). More than one billion people worldwide live with hypertension.[i] Approximately one in three adults are living with hypertension worldwide, with up to 80% of individuals remaining uncontrolled despite the availability of several classes of oral anti-hypertensive treatments. Despite the availability of anti-hypertensive medications, there remains a significant unmet medical need, especially given the poor rates of adherence to existing daily oral medications, resulting in inconsistent BP control and an increased risk for stroke, heart attack and premature death.[ii] 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 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 Pharmaceuticals (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 in 2002, 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), AMVUTTRA® (vutrisiran), GIVLAARI® (givosiran), OXLUMO® (lumasiran), 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 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 (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=www.alnylam.com&index=5&md5=53fa2e4c432723964cf39a8e077ab9c7) and engage with us on X (formerly Twitter) at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=%40Alnylam&index=6&md5=80821f1e3f64bc040e17a95e30bc95fe), or on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=LinkedIn&index=7&md5=ab9ecf41b88da95c9af5c0ea0247eca6), Facebook (https://cts.businesswire.com/ct/CT?

id=smartlink&url=https%3A%2F%2Fwww.facebook.com%2FAlnylamPharma%2F&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=Facebook&index=8&md5=acb9657149d4155dfcca64aad9ad1d4f), or Instagram (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=Instagram&index=9&md5=a1a2e7cdf0f420e5e776bae4cc5e6ffd).

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, Alnylam's views with respect to the results of the KARDIA-1 Phase 2 dose-ranging study of zilebesiran, Alnylam's views with respect to the potential role for zilebesiran as a novel, subcutaneously administered gene silencing approach to hypertension, its views that zilebesiran has the potential to be an effective and highly-differentiated treatment; its expectations regarding its aspiration to become a leading biotech company and the planned achievement of its "*Alnylam P^{5}x25*" strategy, 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; 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 vutrisiran; 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 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 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 Roche, Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the risks 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.

[i] Hypertension. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/hypertension (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.who.int%2Fnews-room%2Ffact-sheets%2Fdetail%2Fhypertension&esheet=53808166&newsitemid=20231111731245&lan=en-US&anchor=https%3A%2F%2Fwww.who.int%2Fnews-room%2Ffact-sheets%2Fdetail%2Fhypertension&index=10&md5=d159818c1118fe3f310f89122a35a509). Published September 2019. Accessed November 2021.

[ii] 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.

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