NEWS RELEASE

Alnylam Presents Positive Results from the KARDIA-2 Phase 2 Study of Zilebesiran Added to Standard of Care Antihypertensives in Patients with Inadequately Controlled Hypertension

4/7/2024

– Study Met Primary Endpoint Demonstrating Clinically Significant Additive Reductions in Ambulatory Systolic Blood Pressure of Up to 12.1 mmHg Across Three Independent Study Cohorts at Month 3 –

– A Single Dose of Zilebesiran Resulted in Clinically Significant Additive Reductions in Office Systolic Blood Pressure at Month 3 and in Time-Adjusted Office Systolic Blood Pressure at Month 6 Across Three Independent Study Cohorts –

– Zilebesiran Demonstrated an Encouraging Safety and Tolerability Profile When Added to Standard of Care Antihypertensives –

– Alnylam to Host Webcast Investor Event Today at 7:00 p.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- **Alnylam Pharmaceuticals, Inc.** (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced positive results from the KARDIA-2 Phase 2 study evaluating the efficacy and safety of a single subcutaneous dose of zilebesiran when added to one of three standard of care antihypertensives including a thiazide-like diuretic (indapamide), calcium channel blocker (amlodipine) or angiotensin receptor blocker (olmesartan). Zilebesiran is an investigational RNAi therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension with the potential for biannual

dosing. The results were presented today as a late-breaking clinical trial at the 2024 American College of Cardiology (ACC) Annual Scientific Session. The Company previously **announced** positive topline results from the KARDIA-2 study in March 2024.

The KARDIA-2 study achieved its primary endpoint demonstrating clinically and statistically significant additive, placebo-adjusted reductions of up to 12.1 mmHg in 24-hour mean systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring (ABPM) when zilebesiran was added to a thiazide-like diuretic, calcium channel blocker or angiotensin receptor blocker, measured independently at Month 3. The study achieved the key secondary endpoint evaluated at Month 3, demonstrating clinically significant additive reductions in office SBP across all three independent cohorts. At Month 6, zilebesiran demonstrated clinically significant and sustained placebo-adjusted, time-adjusted reductions in office SBP when added to indapamide, amlodipine and olmesartan, despite the addition of rescue antihypertensives at Month 3. In addition, zilebesiran resulted in clinically significant placebo-adjusted, time-adjusted reductions in 24-hour mean SBP, assessed by ABPM, when added to indapamide and amlodipine, sustained to Month 6. A non-statistically significant result was observed when zilebesiran was added to the maximum dose of olmesartan when evaluated by time-adjusted change from baseline in 24-hour mean SBP, assessed by ABPM at Month 6.

“Although many effective oral treatments are available, a large proportion of patients with hypertension are not managed to guideline-recommended targets. Inconsistent adherence to complex, daily, oral medication regimens as well as therapeutic inertia on the part of clinicians may be important contributors to this treatment gap,” said Akshay Desai, M.D., Director of the Cardiomyopathy and Heart Failure Program, Brigham and Women’s Hospital. “Even in those who are treated, residual blood pressure variability may ultimately enhance risk for cardiovascular events. Zilebesiran may help to address many of these limitations of current treatment options. Although further evidence is needed to ensure long term efficacy and safety in a broader population, these data are encouraging and the potential to reduce blood pressure consistently with two injections a year might be transformative for clinical practice.”

KARDIA-2 Study Results

The KARDIA-2 study results are as follows:

Key Endpoint	Indapamide (2.5 mg)	Amlodipine (5 mg)	Olmesartan (40 mg)
Primary Endpoint:			
Change from Baseline to Month 3 in 24-Hour Mean SBP, Assessed by ABPM	- 12.1 mmHg (p<0.001)	- 9.7 mmHg (p<0.001)	- 4.0 mmHg (p=0.036)
Key Secondary Endpoints:			
Change from Baseline to Month 3 in	- 18.5 mmHg (p<0.001)	- 10.2 mmHg (p<0.001)	- 7.0 mmHg (p<0.001)

Office SBP			
Time Adjusted Change from Baseline Through Month 6 in 24-Hour Mean SBP, Assessed by ABPM	- 11.0 mmHg (p<0.001)	- 7.9 mmHg (p<0.001)	- 1.6 mmHg (p=0.26)
Time Adjusted Change from Baseline Through Month 6 in Office SBP	- 13.6 mmHg (p<0.001)	- 8.6 mmHg (p<0.001)	- 4.6 mmHg (p<0.001)

The final key secondary endpoint evaluated the proportion of patients with 24-hour mean SBP assessed by ABPM <130 mmHg and/or reduction ≥20 mmHg without rescue antihypertensive medication at Month 6. As outlined in the study protocol, after three months of treatment, all patients were permitted to receive rescue antihypertensives as needed based on rescue response criteria. Across all cohorts, a higher percentage of placebo-treated patients required treatment with rescue antihypertensives compared to zilebesiran-treated patients. Additionally, the odds of meeting the SBP response criteria were significantly higher with zilebesiran in the indapamide and amlodipine cohorts, compared to placebo.

	Background Medication					
	Indapamide (2.5 mg)		Amlodipine (5 mg)		Olmesartan (40 mg)	
	Placebo (N=57)	Zilebesiran (N=53)	Placebo (N=102)	Zilebesiran (N=103)	Placebo (N=134)	Zilebesiran (N=117)
Response Criteria Met	14.0%	64.2%	13.7%	39.8%	17.2%	26.5%
Odds Ratio 95% CI	12.4 (p<0.001)		5.1 (p<0.001)		1.8 (p=0.077)	

Zilebesiran demonstrated an encouraging safety and tolerability profile when added to standard of care antihypertensives.

Safety Event	Indapamide (2.5 mg)		Amlodipine (5 mg)		Olmesartan (40 mg)	
	Placebo (N=64)	Zilebesiran (N=63)	Placebo (N=121)	Zilebesiran (N=118)	Placebo (N=152)	Zilebesiran (N=149)
At Least 1 Adverse Event (AE), %	39.1	49.2	47.1	54.2	48.0	58.4
At Least 1 Serious AE (SAE), %	3.1	0	0.8	2.5	2.6	2.7
AEs of Clinical Interest						
Hypotension/Orthostatic Hypotension, %	0	0	3.3	5.9	2.0	4.7
Laboratory Values						
Hyperkalemia (potassium >5.5nmol/L), %	0	3.2	0.8	6.8	2.0	6.7
Confirmed by Repeat Measure, %	0	1.6	0	1.7	0	1.3
Kidney Function Impact (≥30% decrease from baseline in eGFR (mL/min/1.73m2), %	1.6	12.7	4.1	8.5	2.6	6.7
Confirmed by Repeat Measure, %	0	4.8	1.7	0.8	0.7	2.7
Kidney Function Impact (>2x increase from baseline in creatinine), %	0	0	0	0	0	2.0
Confirmed by Repeat Measure, %	0	0	0	0	0	0.7

Most laboratory abnormalities of interest were mild, occurred in the first three months of treatment and resolved upon repeat measure within one to two weeks without intervention. There were no deaths reported, and no AEs

led to study discontinuation during the six-month double-blind period.

“The KARDIA program has built a robust body of evidence, with more than six hundred patients having received zilebesiran in Phase 2 trials, demonstrating clinically significant blood pressure reductions with encouraging safety as both a monotherapy and as an add-on therapy, with the potential for both quarterly and biannual dosing,” said Simon Fox, Ph.D., Vice President, Zilebesiran Program Lead at Alnylam. “At Alnylam, we are aiming to disrupt cardiovascular disease, and in collaboration with our partner Roche, we are committed to moving zilebesiran forward in the hope of changing the hypertension treatment paradigm for patients. We are taking that next step with our recently initiated third Phase 2 study, KARDIA-3, designed to evaluate zilebesiran as an add-on therapy in high cardiovascular risk patients with uncontrolled hypertension despite receiving two or more antihypertensives.”

The KARDIA-2 Phase 2 study is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of zilebesiran, when added to standard of care antihypertensive medications, in adults with mild-to-moderate hypertension. This global, multicenter study enrolled 672 adults with hypertension. Patients who met all inclusion criteria and none of the exclusion criteria during a screening period were first randomized into three different cohorts to receive open-label therapy with indapamide, amlodipine or olmesartan as their protocol-specified background antihypertensive medication during a run-in period of at least four weeks. Following the run-in period, eligible patients with elevated SBP were randomized 1:1 to receive a single dose of 600 mg zilebesiran or placebo in addition to their protocol-specified background antihypertensive medication for six months.

To review the KARDIA-2 study results and the KARDIA-1 subgroup results presented at ACC, please visit **Capella**.

Investor Webcast Information

Alnylam management and Akshay Desai, M.D., Director of the Cardiomyopathy and Heart Failure Program, Brigham and Women’s Hospital, will discuss the KARDIA-2 results via webcast on April 7, 2024, at 7:00 p.m. ET. The webcast will be available on the Investors section of the Company’s website at **www.alnylam.com/events** . An archived webcast will be available on the Company’s website approximately two hours after the event.

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 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 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 X (formerly Twitter) at **@Alnylam** , or on **LinkedIn** , **Facebook** , or **Instagram** .

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-2 Phase 2 study of zilebesiran or the enrollment or conduct of the KARDIA-3 Phase 2 study, 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 P5x25" 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, risks and uncertainties relating to: Alnylam's ability 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; the pre-clinical and clinical results for Alnylam's product candidates, including zilebesiran; actions or advice of regulatory agencies and Alnylam's ability to obtain regulatory approval for its product candidates, including zilebesiran, 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; obtaining, maintaining and protecting intellectual property; 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; 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 maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Roche; the outcome of litigation; 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 2023 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.

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i Hypertension. World Health Organization. **https://www.who.int/news-room/fact-sheets/detail/hypertension**. 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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