Alnylam Announces U.S. Food and Drug Administration (FDA) Acceptance of Supplemental New Drug Application for ONPATTRO® (patisiran) for the Treatment of the Cardiomyopathy of ATTR Amyloidosis

Feb 21, 2023

– PDUFA Date Set for October 8, 2023 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 21, 2023-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=53334096&newsitemid=20230221005335&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=ab89ebf6375400561d25aa77b05df082)(Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that the U.S. Food and Drug Administration (FDA) has accepted for filing the Company's supplemental New Drug Application (sNDA) for patisiran, an investigational RNAi therapeutic in development for the treatment of the cardiomyopathy of transthyretin-mediated (ATTR) amyloidosis. The FDA has set an action date of October 8, 2023 under the Prescription Drug User Fee Act (PDUFA). In their file acceptance letter, the FDA stated that they have not identified any review issues. The Agency also noted that they are planning to hold an advisory committee meeting to discuss the application. Patisiran is the established name for ONPATTRO®, which is currently approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary ATTR amyloidosis in adults.

"ATTR amyloidosis with cardiomyopathy is an increasingly recognized cause of heart failure for which there are limited treatment options. The FDA's acceptance of our sNDA for patisiran is a positive step forward as we work to bring patients with ATTR amyloidosis with cardiomyopathy a new treatment option that addresses the underlying cause of disease and has the potential to meaningfully improve functional capacity and quality of life," said Rena N. Denoncourt, Vice President, TTR Franchise Lead. "The acceptance also marks another important milestone as we continue to build an industry-leading franchise for the treatment of ATTR amyloidosis."

The application to the FDA was based on positive results from APOLLO-B, a randomized, double-blind, placebo-controlled, multicenter, global Phase 3 study that demonstrated favorable effects of patisiran on both functional capacity and quality of life in patients with ATTR amyloidosis with cardiomyopathy relative to placebo at 12 months. The majority of adverse events were mild or moderate in severity, and the overall safety profile in APOLLO-B was consistent with prior clinical trials and post-marketing experience with ONPATTRO. The 12-month results from the study were presented (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.alnylam.com%2Fpress-release%3Fid%3D26936&esheet=53334096&newsitemid=20230221005335&lan=en-US&anchor=presented&index=2&md5=9da4fa4689ea9e0e65cd4e121ec05be9) at the 18th International Symposium on Amyloidosis (ISA) on September 8, 2022 and at the Heart Failure Society of America's Annual Scientific Meeting on September 30, 2022.

ONPATTRO Indication and Important Safety Information

Indication

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Important Safety Information

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

For additional information about ONPATTRO, please see the full U.S. Prescribing Information (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2Fsites%2Fdefault%2Ffiles%2Fpdfs%2FONPATTRO-Prescribing-Information.pdf&esheet=53334096&newsitemid=20230221005335&lan=en-US&anchor=Prescribing+Information&index=3&md5=20a8e8fc7f8a5d1276bbeefa7d0194ca).

About ONPATTRO® (patisiran)

ONPATTRO (patisiran) is an RNAi therapeutic that is approved in the United States and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults. ONPATTRO is also approved in the European Union, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy, and in Japan for the treatment of hATTR amyloidosis with polyneuropathy. ONPATTRO is an intravenously administered RNAi therapeutic targeting transthyretin (TTR). It is designed to target and silence TTR messenger RNA, thereby reducing the production of TTR protein before it is made. Reducing the pathogenic protein leads to a reduction in amyloid deposits in tissues.

About ATTR Amyloidosis

Transthyretin-mediated (ATTR) amyloidosis is a rare, rapidly progressive, debilitating disease caused by misfolded transthyretin (TTR) proteins which accumulate as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal (GI) tract. There are two different types of ATTR amyloidosis – Hereditary ATTR (hATTR) amyloidosis, caused by a TTR gene variant, and Wild-type ATTR (wtATTR) amyloidosis, which occurs without a TTR gene variant. hATTR amyloidosis affects approximately 50,000 people worldwide, while wtATTR amyloidosis is estimated to impact 200,000 – 300,000 people worldwide.

About LNP Technology

Alnylam has licenses to Arbutus Biopharma LNP intellectual property for use in RNAi therapeutic products using LNP technology.

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 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), 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?

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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 P^{5}x25*" 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; 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 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 uses of previously approved RNAi therapeutics in development and is not intended to convey conclusions about efficacy or safety as to those investigational therapeutics or uses. Patisiran has not been approved by any regulatory agency for the treatment of ATTR amyloidosis with cardiomyopathy. No conclusions can or should be drawn regarding its safety or effectiveness in treating cardiomyopathy in this population. There is no guarantee that any investigational therapeutics or expanded uses of commercial products will successfully complete clinical development or gain health authority approval.

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