Alnylam Announces Receipt of Complete Response Letter from U.S. FDA for Supplemental New Drug Application for Patisiran for the Treatment of the Cardiomyopathy of ATTR Amyloidosis

Oct 09, 2023

– FDA Cites Insufficient Evidence of Clinical Meaningfulness –

– No Clinical Safety, Study Conduct, Drug Quality or Manufacturing Issues Identified –

– CRL Does Not Pertain to, nor Impact Commercial Availability of, ONPATTRO® (patisiran) for Existing Indication for the Treatment of the Polyneuropathy of Hereditary ATTR Amyloidosis in Adults –

– Alnylam to Host Investor Conference Call Today, Monday, October 9, 2023 at 8:30 a.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 9, 2023-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=7a11176544764e2e2d3d8f0a57eb4142)(Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) in response to the Company's supplemental New Drug Application (sNDA) for patisiran for the treatment of the cardiomyopathy of transthyretin-mediated (ATTR) amyloidosis.

Patisiran is the established name for ONPATTRO®, which is approved by the FDA for the treatment of the polyneuropathy of hereditary ATTR amyloidosis in adults. The CRL does not pertain to, nor does it impact commercial availability of, ONPATTRO for this existing indication.

The CRL indicated that the clinical meaningfulness of patisiran's treatment effects for the cardiomyopathy of ATTR amyloidosis had not been established, and therefore, the sNDA for patisiran could not be approved in its present form. The CRL did not identify any issues with respect to clinical safety, study conduct, drug quality or manufacturing.

As a result of the CRL, the Company will no longer pursue an expanded indication for patisiran in the U.S. The Company remains dedicated to the ATTR amyloidosis community and will continue to focus on the HELIOS-B Phase 3 study of vutrisiran, an investigational RNAi therapeutic subcutaneously administered once every three months in development for the treatment of the cardiomyopathy of ATTR amyloidosis, and ALN-TTRsc04, which utilizes the Company's IKARIA technology, with the potential for greater than 90% TTR knockdown with once annual dosing.

"First and foremost, our hearts go out to patients with the cardiomyopathy of ATTR amyloidosis who are living with a rapidly progressive, debilitating and fatal disease and face significant unmet need. While we are disappointed by this decision, we are committed to supporting them and are well positioned to address their needs with continued innovation that can potentially help improve their outcomes and treatment experience," said Yvonne Greenstreet, MBChB, Chief Executive Officer of Alnylam Pharmaceuticals. "We remain confident in the HELIOS-B Phase 3 study of vutrisiran and look forward to sharing topline results in early 2024. If successful, we believe vutrisiran will offer convenient, quarterly subcutaneous dosing with a therapeutic profile that may potentially include cardiovascular outcome benefits. Beyond vutrisiran, we are excited about the potential for ALN-TTRsc04, which may allow for greater TTR knockdown and less frequent dosing, providing patients with ATTR amyloidosis an optimized treatment regimen."

The sNDA for patisiran was supported by positive results from the APOLLO-B Phase 3 study. In APOLLO-B, patisiran met the primary endpoint as well as the first secondary endpoint at Month 12, demonstrating a significant difference compared to placebo in functional capacity, as measured by the 6-Minute Walk Test (6-MWT), and health status and quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, respectively.

New results (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcapella.alnylam.com%2F2023%2F10%2F08%2Fpati-hfsa-2023&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=New+results&index=2&md5=ef9d759f3f029528cfa4e92a5d247200) from an interim analysis of the ongoing open-label extension (OLE) period of the APOLLO-B Phase 3 study were presented at the Heart Failure Society of America (HFSA) Annual Scientific Meeting (ASM) 2023, which demonstrate the sustained treatment effect of patisiran on functional status, health status and quality of life and cardiac biomarkers over 24 months. These findings reinforce the long-term treatment effect of TTR silencing by an RNAi therapeutic in patients with ATTR amyloidosis and provide strong support for the Company's continued evaluation of vutrisiran and ALN-TTRsc04.

As previously announced (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.alnylam.com%2Fpress-release%3Fid%3D27716&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=As+previously+announced&index=3&md5=8c2f85006dd53d41a3bc317ade357615), the FDA's Cardiovascular and Renal Drugs Advisory Committee met on September 13, 2023 to discuss the sNDA for patisiran and voted 9:3 that the benefits of patisiran outweigh its risks for the treatment of the cardiomyopathy of ATTR amyloidosis.

The Company intends to maintain availability of patisiran for patients with the cardiomyopathy of ATTR amyloidosis who are enrolled in the OLE period of the APOLLO-B Phase 3 study and patisiran U.S. expanded access protocol (EAP).

Conference Call Information

Alnylam management will discuss the CRL via conference call on Monday, October 9, 2023 at 8:30 a.m. ET. To access the call, please register online at https://register.vevent.com/register/BI8567d631e94e4c1eaa8da3a1ae2fcf69 (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI8567d631e94e4c1eaa8da3a1ae2fcf69&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI8567d631e94e4c1eaa8da3a1ae2fcf69&index=4&md5=c71802b12f83595728930b6394e684e9). Participants are requested to register a minimum of 15 minutes before the start of the call. A replay of the call will be available two hours after the call and archived on the same webpage for six months.

A live audio webcast of the call will be available on the Investors section of the Company's website at www.alnylam.com/events (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.alnylam.com%2Fevents&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=www.alnylam.com%2Fevents&index=5&md5=9471977b64a5a5530857ce00a75c9000). An archived webcast will be available on the Company's website approximately two hours after the event.

ONPATTRO® (patisiran) 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=53581548&newsitemid=20231009982660&lan=en-US&anchor=Prescribing+Information&index=6&md5=d4becf8ce8c2d1662bbcbfc71143a640).

About ONPATTRO® (patisiran)

ONPATTRO is an RNAi therapeutic that is approved in the United States and Canada for the treatment of the polyneuropathy of hereditary ATTR (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 an underdiagnosed, rapidly progressive, debilitating and fatal disease caused by misfolded transthyretin (TTR) proteins, which accumulate as amyloid deposits in various parts of the body, including the nerves, heart and gastrointestinal tract. Patients may present with polyneuropathy, cardiomyopathy, or both manifestations of disease. There are two different forms of ATTR amyloidosis – hereditary ATTR (hATTR) amyloidosis, which is caused by a TTR gene variant and affects approximately 50,000 people worldwide, and wild-type ATTR (wtATTR) amyloidosis, which occurs without a TTR gene variant and impacts an estimated 200,000 – 300,000 people worldwide.

About the APOLLO-B Phase 3 Study

APOLLO-B is a Phase 3, randomized, double-blind, placebo-controlled multicenter global study designed and powered to evaluate the effects of patisiran on functional capacity and quality of life in patients with ATTR amyloidosis with cardiomyopathy. The study enrolled 360 adult patients with ATTR amyloidosis (hereditary or wild-type) with cardiomyopathy at 69 sites in 21 countries. Patients were randomized 1:1 to receive 0.3 mg/kg of patisiran or placebo intravenously administered every three weeks over a 12-month treatment period. After 12 months, all patients received patisiran in a 36-month open-label extension period.

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 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 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=53581548&newsitemid=20231009982660&lan=en-US&anchor=www.alnylam.com&index=7&md5=470f196eca2d4ed1c19fe93aeb8178d9) 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=53581548&newsitemid=20231009982660&lan=en-US&anchor=%40Alnylam&index=8&md5=59fb2c260fabe335a6e4e42a5f7c8e88), or on LinkedIn (https://cts.businesswire.com/ct/CT?

id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=LinkedIn&index=9&md5=11389b5f7623debd735c736388dc863b), Facebook (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.facebook.com%2FAlnylamPharma%2F&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=Facebook&index=10&md5=2c268e3d1f43533e1b710c58f9ca4334), or Instagram (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=53581548&newsitemid=20231009982660&lan=en-US&anchor=Instagram&index=11&md5=cefe249f5ab9ebeef0dfcd1614c9f482).

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, 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; 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.

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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