Alnylam Reports Positive Topline Results from APOLLO-B Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy

Aug 03, 2022

– Patisiran Met the Primary Endpoint with a Statistically Significant Improvement in 6-Minute Walk Test Compared to Placebo at 12 Months –

– Patisiran Also Met the First Secondary Endpoint with a Statistically Significant Improvement in Quality of Life, as Measured by the Kansas City Cardiomyopathy Questionnaire, Compared to Placebo at 12 Months –

– Patisiran Demonstrated Encouraging Safety and Tolerability Profile in Patients with ATTR Amyloidosis with Cardiomyopathy –

– Company Plans to File a Supplemental New Drug Application in U.S. in Late 2022 –

– Full Data Will Be Presented at the 18th International Symposium on Amyloidosis –

– Alnylam to Host Conference Call Today at 8:00 am ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 3, 2022-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=65b7fd906d15b70baf323ab6fb86f4af)(Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that the APOLLO-B Phase 3 study of patisiran, an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy, met the primary endpoint of change from baseline in the 6-Minute Walk Test (6-MWT) at 12 months compared to placebo (p-value 0.0162). The study also met the first secondary endpoint of change from baseline in quality of life compared to placebo, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (p-value 0.0397).

The study also included additional secondary composite outcome endpoints to be tested in a hierarchical manner. A non-significant result (p-value 0.0574) was found on the secondary composite endpoint of all-cause mortality, frequency of cardiovascular events, and change from baseline in 6-MWT over 12 months compared to placebo. As a result, formal statistical testing was not performed on the final two composite endpoints, which were not powered for statistical significance given the short duration of the study — all-cause mortality and frequency of all-cause hospitalizations and urgent heart failure visits in patients not on tafamidis at baseline (nominal p-value 0.9888), and in the overall population (nominal p-value 0.5609). Patisiran also demonstrated an encouraging safety and tolerability profile, with deaths numerically favoring the patisiran arm.

“We are thrilled that APOLLO-B successfully met all its major objectives, which we believe for the first time validates the hypothesis that TTR silencing by an RNAi therapeutic can be an effective approach for treating the cardiomyopathy of ATTR amyloidosis,” said Pushkal Garg, M.D., Chief Medical Officer of Alnylam. “ATTR amyloidosis with cardiomyopathy is an increasingly recognized cause of heart failure, affecting greater than 250,000 patients around the world. These patients have limited treatment options, and disease progression is common. As such, we are encouraged to see the potential of patisiran to improve the functional capacity and quality of life of patients living with this fatal, multi-system disease. I want to thank all the patients, caregivers, investigators, and study staff who have and continue to participate in

APOLLO-B. We look forward to sharing full results at an upcoming conference in September, and based on these positive results, we plan to submit a supplemental NDA for patisiran with the U.S. Food and Drug Administration in late 2022."

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 double-blind treatment period. After 12 months, all patients will receive patisiran in an open-label extension period.

The primary endpoint of APOLLO-B is the change from baseline in the 6-MWT at 12 months compared to placebo. The secondary endpoints evaluate the efficacy of patisiran vs. placebo over 12 months in a hierarchical manner with the following measures:

- Health-related quality of life with the KCCQ change from baseline at 12 months;
- Composite of all-cause mortality, frequency of cardiovascular (CV) events (CV hospitalizations and urgent heart failure (HF) visits) and change from baseline in 6-MWT;
- Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; and
- Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in the overall study population.

Exploratory endpoints included cardiac biomarkers and various imaging tools to further characterize the potential burden of cardiac involvement in these patients.

The overall safety profile of patisiran during the 12-month double-blind period was encouraging.

- 5 patients (2.8 percent) on patisiran and 8 patients (4.5 percent) on placebo died. Furthermore, the number of deaths in the all-cause mortality efficacy analysis was 4 (2.2 percent) in the patisiran arm and 10 (5.6 percent) in the placebo arm, determined in accordance with the pre-defined statistical analysis plan, which excluded death due to COVID-19, and treated cardiac transplant as a death event consistent with other studies in the field.
- The patisiran and placebo arms had similar frequencies of adverse events (AEs) (91.2 percent and 94.4 percent, respectively) and serious adverse events (SAEs) (33.7 percent and 35.4 percent, respectively). AEs reported in greater than or equal to 5 percent of patisiran patients and seen at least 3 percent more frequently with patisiran compared with placebo were infusion-related reactions (12.2 percent vs. 9 percent, respectively), arthralgia (7.7 percent vs. 4.5 percent, respectively), and muscle spasms (6.6 percent vs. 2.2 percent, respectively). No SAEs occurred at least 2 percent more frequently in patisiran versus placebo treated patients.

"I am delighted by the results of the APOLLO-B study, which suggest the potential for patisiran to be a treatment option for patients with ATTR amyloidosis with cardiomyopathy, assuming favorable regulatory review. In addition, the APOLLO-B data further strengthen our confidence in our Phase 3 HELIOS-B study of vutrisiran in ATTR amyloidosis with cardiomyopathy, which is expected to report out in early 2024," said Yvonne Greenstreet, MBChB, Chief Executive Officer of Alnylam. "Today's positive results advance our goal to establish an industry leading TTR franchise, which currently includes ONPATTRO® and AMVUTTRA™ for the polyneuropathy of hereditary ATTR amyloidosis. We believe these data take us one step closer to achieving our *Alnylam P5x25* vision of becoming a leading biopharma company."

Full results of the APOLLO-B study will be presented as part of a late-breaker session at the 18th International Symposium on Amyloidosis on September 8, 2022, in Heidelberg, Germany.

Patisiran is the established name for ONPATTRO, which 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.

Conference Call Information

Management will discuss the APOLLO-B topline results via conference call on Wednesday, August 3, 2022, at 8:00 am ET. To access the call, please register online at https://register.vevent.com/register/BI6ac74b5406af42c5980ba67c6f9e419d (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI6ac74b5406af42c5980ba67c6f9e419d&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI6ac74b5406af42c5980ba67c6f9e419d&index=2&md5=6adc983025851b1f64723690e2a69b2c). Participants are requested to register at a minimum 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 web page 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=52800209&newsitemid=20220803005528&lan=en-US&anchor=www.alnylam.com%2Fevents&index=3&md5=e09edf5604a64e508da33061bfd96233). An archived webcast will be available on the Company's website approximately two hours after the event.

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 amyloidosis (wtATTR), 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 ONPATTRO® (Patisiran)

ONPATTRO 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. For more information about ONPATTRO, including full Prescribing Information (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2Fwp-content%2Fuploads%2Fpdfs%2FONPATTRO-Prescribing-Information.pdf&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=Prescribing+Information&index=4&md5=d3a197bea608c6b05e70e4de63739dc5), visit ONPATTRO.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.onpattro.com%2F&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=ONPATTRO.com&index=5&md5=964e879966989a5d96e8c632dd8ab2ff).

ONPATTRO Indication and ISI

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%).

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 silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing 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) 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), GIVLAARI® (givosiran), OXLUMO® (lumasiran), AMVUTTRA™ (vutrisiran) and Leqvio® (inclisiran) 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=http%3A%2F%2Fwww.alnylam.com&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=www.alnylam.com&index=6&md5=da82bd5592166354252affd5d9d9cefd) and engage with us on Twitter at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=%40Alnylam&index=7&md5=96442b58f5db2401527eeaef4c42352c), on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=LinkedIn&index=8&md5=102ea585e3cd5e3b45cfcc4d4d08448b), or on Instagram (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=52800209&newsitemid=20220803005528&lan=en-US&anchor=Instagram&index=9&md5=5bd62b713e005ac677aace38ba43faf6).

Alnylam Forward Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, Alnylam's views with respect to the safety and efficacy of patisiran for the treatment of ATTR amyloidosis with cardiomyopathy, the potential of patisiran to improve the functional capacity and quality of life of patients living with ATTR amyloidosis with cardiomyopathy, the expected timing of the presentation of full data from the APOLLO-B study and the filing of an sNDA for patisiran in the U.S., the potential market opportunity for patisiran if approved by regulatory authorities to treat ATTR amyloidosis with cardiomyopathy, the evaluation of vutrisiran in the HELIOS-B Phase 3 study for the treatment of patients with ATTR amyloidosis with cardiomyopathy and the expected timing for data from that study, and Alnylam's aspiration to become a leading biotech company and the planned achievement of its "*Alnylam P^{5}x25*" 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 recent leadership transition 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; the pre-clinical and clinical results for its 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 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, AMVUTTRA or OXLUMO 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 current 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.

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.

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