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

Sep 08, 2022

– Study Results Validate the Hypothesis That TTR Silencing by an RNAi Therapeutic has the Potential to be an Effective Approach for Treating Cardiomyopathy of ATTR Amyloidosis –

– Patisiran met Primary Endpoint, Demonstrating Significant Clinical Benefit on Functional Capacity (6-MWT) Compared to Placebo at Month 12 –

– Patisiran Also met the First Secondary Endpoint, Demonstrating Significant Clinical Benefit on Health Status and Quality of Life, as Measured by the Kansas City Cardiomyopathy Questionnaire, Compared to Placebo at Month 12 –

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

– Alnylam to Host Conference Call Today at 8:00 a.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 8, 2022-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=b30ce497a7de492eeda58bc103ce827e)(Nasdaq: ALNY), the leading RNAi therapeutics company, today announced positive results from the APOLLO-B Phase 3 study of patisiran, an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy. The results were presented today in a late-breaker session at the 18th International Symposium on Amyloidosis (ISA). The Company previously announced (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.alnylam.com%2Fpress-release%3Fid%3D26851&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=announced&index=2&md5=20125e9b66db381e4ff3c1c951c59752) positive topline results from the APOLLO-B study in August 2022.

The 12-month study achieved its primary endpoint, with patisiran demonstrating a statistically significant and clinically meaningful benefit on functional capacity, as measured by the 6-Minute Walk Test (6-MWT), compared to placebo, with a median difference of 14.7 meters (p-value 0.0162) favoring patisiran. The study also met its first secondary endpoint, demonstrating a statistically significant and clinically meaningful benefit on health status and quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, compared to placebo with least squares (LS) mean difference of 3.7 points (p-value 0.0397) favoring patisiran. The study also included additional secondary composite outcomes endpoints. A non-significant result (p-value 0.0574) was found on the 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. Patisiran also demonstrated an encouraging safety and tolerability profile in patients with ATTR amyloidosis with cardiomyopathy.

“The results of the APOLLO-B Phase 3 study are impressive, as I believe they underscore the potential for patisiran to provide a benefit on functional capacity and quality of life in patients living with ATTR amyloidosis with cardiomyopathy. Furthermore, these results were seen after

only 12 months of treatment," said Mathew Maurer, M.D., Arnold and Arlene Goldstein Professor of Cardiology at Columbia University Irving Medical Center. "The cardiac manifestations associated with ATTR amyloidosis can have a devastating impact on patients' lives and current treatment options are limited. With the rapidly progressive nature of the disease, there is a significant need for treatments like patisiran, which has the potential to be a new option for patients and physicians to treat the cardiomyopathy of ATTR amyloidosis."

APOLLO-B Study Results

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 will receive patisiran in an open-label extension.

At 12 months, the study results presented today are as follows:

- For 6-MWT, the median change from baseline to Month 12 was -8.15 meters for the patisiran group and -21.345 meters for the placebo group; the Hodges-Lehmann estimate of the median difference was 14.7 meters (p-value 0.0162) favoring patisiran.
- For KCCQ-OS, the LS mean change from baseline to Month 12 was +0.300 for the patisiran group and -3.408 for the placebo group, with an LS mean difference of 3.7 points (p-value 0.0397) favoring patisiran.
- Secondary composite outcome endpoints were tested in a hierarchical manner; however, the secondary composite outcomes endpoints did not achieve statistical significance.
    - A non-significant result (win ratio 1.27, 95% CI: 0.99, 1.61; 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.
    - The final two composite endpoints were not powered for statistical significance given the sample size and 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 (Hazard Ratio (HR) 0.997, 95% CI: 0.620, 1.602; nominal p-value 0.9888), and in the overall study population (HR 0.883, 95% CI: 0.582, 1.341; nominal p-value 0.5609).
    - Efficacy analysis of all-cause mortality excluded deaths due to COVID-19 (1 patisiran patient) and treated heart transplants in the same manner as deaths (2 placebo patients), as pre-specified in the statistical analysis plan. Per this definition, there were 4 deaths (2.2%) observed in patisiran-treated patients and 10 deaths (5.6%) observed in the placebo group.
- Patisiran achieved a rapid and sustained reduction in serum TTR levels, with a mean percent reduction from baseline in serum TTR reduction of 87% at Month 12

- A beneficial effect on the exploratory endpoint, NT-proBNP, a measure of cardiac stress, was observed in the patisiran arm compared to placebo.
  - The adjusted geometric mean fold change from baseline at Month 12 in NT-proBNP was 1.11 for the patisiran group and 1.38 for the placebo group, indicating a 20% reduction in the patisiran arm compared to placebo (nominal p-value 1.825×10^{-5}).

Patisiran also demonstrated an encouraging safety and tolerability profile, including no cardiac safety concerns relative to placebo, during the 12-month treatment period. The majority of adverse events (AEs) were mild or moderate in severity. Treatment emergent AEs occurring in 5% or more patients in the patisiran group and observed at least 3% more commonly than in the placebo group included infusion-related reactions (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%). In the safety analysis there were 5 deaths (2.8%) observed in patisiran-treated patients and 8 deaths (4.5%) observed in the placebo group.

“We believe the totality of the APOLLO-B study results provides a compelling clinical profile of patisiran for patients and families living with ATTR amyloidosis with cardiomyopathy, a fatal, multi-system disease. It was encouraging to see the impact of patisiran on functional capacity in the study, as the change from baseline in 6-MWT for patisiran-treated patients was in the range of the approximately 5 meter decline typically seen in healthy older adults over a 12-month period.[1] Furthermore, health status and quality of life in patisiran-treated patients was maintained relative to baseline, which is another important aspect of the potential benefit that patisiran treatment may provide to patients,” said Pushkal Garg, M.D., Chief Medical Officer at Alnylam. “Importantly, we believe these data validate the therapeutic hypothesis that TTR silencing by an RNAi therapeutic may be an effective approach to treating cardiomyopathy of both wild-type and hereditary ATTR amyloidosis. ATTR amyloidosis with cardiomyopathy is an increasingly recognized cause of heart failure, affecting greater than 250,000 patients around the world, and with these results, we can take another important step forward towards delivering a potential new treatment to the patients who need it, assuming favorable regulatory review.”

Alnylam plans to file a supplemental new drug application (sNDA) for patisiran as a potential treatment for ATTR amyloidosis with cardiomyopathy in the U.S. in late 2022. Additional results from the APOLLO-B study will be presented at the upcoming Heart Failure Society of America (HFSA) annual meeting being held in Washington DC, September 30 to October 3, 2022.

To view the APOLLO-B data presented at ISA, please visit, Capella (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcapella.alnylam.com%2F2022%2F09%2F08%2Fpati-isa-2022&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=Capella&index=3&md5=30d925cc967e9b9caeb9cb27d0b47753).

Other Patisiran Data: 36-Month Global Open Label Extension (OLE) and Phase 4 Observational Study Results

Alnylam also presented 36-month results from the ongoing Global OLE study of patisiran in eligible patients who completed the APOLLO Phase 3 and Phase 2 OLE studies, evaluating the effect of long-term patisiran treatment on mortality and ambulatory function.

Findings demonstrate that patients who initiated treatment with patisiran earlier in the Phase 3 APOLLO and Phase 2 OLE studies experienced greater survival as compared with the APOLLO placebo patients who initiated treatment with patisiran later during the Global OLE study. Further, those same patients who initiated patisiran earlier showed stabilized or improved ambulation versus patients in the APOLLO placebo group as assessed by polyneuropathy disability (PND) score. The long-term safety profile of patisiran was consistent with prior analyses.

These results highlight the substantial impact of earlier diagnosis and treatment with patisiran in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy.

Additional data were also presented from a Phase 4 observational study to evaluate the effectiveness of patisiran on ambulatory status in patients with hATTR amyloidosis with polyneuropathy with a V122I or T60A variant. These variants are historically associated with cardiomyopathy, thus further evidence that patients with these variants also experience polyneuropathy is emerging.

After 12 months of treatment with patisiran, 93.3% of patients (42/45) experienced stabilization or improvement in PND score from baseline. Treatment with patisiran also resulted in clinically meaningful improvements in QOL and autonomic symptoms after 12 months. Patisiran demonstrated an acceptable safety profile, consistent with existing data.

Conference Call Information

Management will discuss the APOLLO-B results via conference call on Thursday, September 8, 2022, at 8:00 a.m. ET. To access the call, please register online at https://register.vevent.com/register/BI6a961cac960e44388f73484c61dc79cf (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI6a961cac960e44388f73484c61dc79cf&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=https%3A%2F%2Fregister.vevent.com%2Fregister%2FBI6a961cac960e44388f73484c61dc79cf&index=4&md5=3ee043f0c51ceaa0e0d4de19c9fc0e01). 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=52870538&new

sitemid=20220907006229&lan=en-US&anchor=www.alnylam.com%2Fevents&index=5&md5=0c4a900fffcde40a659cc4ae7e37bdaf). 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 (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 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%2Fsites%2Fdefault%2Ffiles%2Fpdfs%2FONPATTRO-Prescribing-Information.pdf&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=Prescribing+Information&index=6&md5=020c6cb60ae9c391d410b16d22bdeb74), visit ONPATTRO.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.onpattro.com%2F&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=ONPATTRO.com&index=7&md5=9d0b588cbcaed79d45cfd6a6a7d4a076).

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%).

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^5x25" 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=52870538&newsitemid=20220907006229&lan=en-US&anchor=www.alnylam.com&index=8&md5=af5d6e3faaadb87097cb19ff3e350d72) and engage with us on Twitter at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=%40Alnylam&index=9&md5=149a04425aac0a1c7d2836eb4f83f3ae), on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=LinkedIn&index=10&md5=8129f6a829554e29a601443190f99f01), or on Instagram (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=52870538&newsitemid=20220907006229&lan=en-US&anchor=Instagram&index=11&md5=91819c5a9c6ea6056426a5e9f2150c12).

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 treatment with patisiran resulting in a statistically significant and clinically meaningful benefit on functional capacity, health status and quality of life for patients living with ATTR amyloidosis with cardiomyopathy, the potential market opportunity for patisiran if approved by regulatory authorities to treat ATTR amyloidosis with cardiomyopathy, the potential for TTR silencing by an RNAi therapeutic to be an effective approach to treating cardiomyopathy of both wild-type

and hereditary ATTR amyloidosis, the substantial impact of earlier diagnosis and treatment with patisiran in patients with hATTR amyloidosis with polyneuropathy, the planned presentation of additional data from the APOLLO-B study and the expected timing of the filing of an sNDA for patisiran in the U.S., and Alnylam's aspiration to become a leading biotech company and the planned achievement of its "Alnylam P^5x25" 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 P^5x25" 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.

[1] Enright P, Sherrill D, *Am J Prespir Crit Care Med.* 1998;158(5 Pt 1):1384-1387.

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