Alnylam Announces Approval of GIVLAARI™ (givosiran) by the U.S. Food and Drug Administration (FDA)

November 20, 2019

− GIVLAARI Approved for the Treatment of Adults with Acute Hepatic Porphyria (AHP) Based on ENVISION Phase 3 Study Results Showing Significant Reduction in the Rate of Porphyria Attacks in Patients with AHP –

− FDA Approval Received in Less Than Four Months after New Drug Application (NDA) Filing Acceptance –

− GIVLAARI Becomes Second RNAi Therapeutic from Alnylam Approved by FDA in Last 16 Months and First-Ever Approval for a GalNAc-Conjugate RNA Therapeutic, a Landmark in Advancement of Precision Genetic Medicines –

− Alnylam to Host Conference Call Today at 2:15 p.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 20, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the U.S. Food and Drug Administration (FDA) approved GIVLAARI ™(givosiran) injection for subcutaneous use for the treatment of adults with acute hepatic porphyria (AHP). AHP is a family of ultra-rare, genetic diseases characterized by debilitating, potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life. Long-term complications of AHP can include chronic neuropathic pain, hypertension, chronic kidney disease and liver disease. GIVLAARI was shown to significantly reduce the rate of porphyria attacks that required hospitalizations, urgent healthcare visits or IV hemin administration at home.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20191120005849/en/

GIVLAARI™ (givosiran) packaging and product vial (Photo: Business Wire)

"We believe the approval of GIVLAARI represents a landmark event for the advancement of precision genetic medicines, providing new hope for patients and their caregivers living with the debilitating manifestations of AHP and unpredictable nature of AHP attacks, as well as for the doctors who diagnose and treat these patients. We are grateful to the investigators, patients and families who have helped make this new treatment option a reality for the AHP community. We also commend the FDA for recognizing the immense medical need and granting this approval so quickly," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. "GIVLAARI now becomes our second RNAi therapeutic to be approved in the last 16 months, and the world's first-ever GalNAc-conjugate RNA therapeutic to be approved, representing a watershed moment for a technology uniquely pioneered by Alnylam scientists. We believe today's news reinforces the promise and potential of RNAi therapeutics as a whole new class of medicines and brings us one important step closer to fulfilling our *Alnylam 2020* goals of building a multi-product, global commercial company with a deep clinical pipeline to drive growth and an organic product engine to fuel sustainable innovation."

The FDA approval of GIVLAARI was received in less than four months after acceptance of the NDA, and was based on positive results from the ENVISION Phase 3 study, a randomized, double-blind, placebo-controlled, multinational study of 94 patients with AHP, at 36 study sites in 18 countries – the largest ever interventional study conducted in AHP. In ENVISION, AHP patients on GIVLAARI experienced 70% (95% CI: 60%, 80%) fewer porphyria attacks compared to placebo. GIVLAARI also resulted in a similar reduction in intravenous hemin use, as well as reductions in urinary aminolevulinic acid (ALA), and urinary porphobilinogen (PBG).

In the pivotal ENVISION study, the most common adverse reactions (reported in at least 20% of patients) with GIVLAARI were nausea (27%) and injection site reactions (25%). Other adverse reactions seen in patients treated with GIVLAARI (occurring over 5% more frequently than placebo) include rash, serum creatinine increase, transaminase elevations and fatigue. As previously reported, one patient in the GIVLAARI clinical development program experienced an anaphylactic reaction which resolved with medical management.

"Adults with AHP now have a new treatment option that has demonstrated the ability to reduce the frequency of porphyria attacks by specifically addressing factors associated with attacks and other disease manifestations of AHP," said Manisha Balwani[i], M.D., M.S, Associate Professor of the Department of Genetics and Genomic Sciences and Department of Medicine at the Icahn School of Medicine at Mount Sinai and principal investigator of the ENVISION study. "With the approval of GIVLAARI, and based on the efficacy data from the ENVISION study, I hope to see my patients and those across the country be able to live more normal lives with fewer porphyria attacks."

"The FDA approval of GIVLAARI is an important milestone for our community, as we now have a new treatment option for adults living with acute hepatic porphyria," said Kristen Wheeden, Executive Director, American Porphyria Foundation. "AHP can have a profound impact on the lives of patients and their families. Porphyria attacks are associated with severe, incapacitating pain, often requiring hospitalization for management. In addition, many patients struggle on a daily basis with chronic symptoms related to their disease. The approval of GIVLAARI is exciting for our community."

Alnylam is committed to helping people access the medicines they are prescribed and will be offering comprehensive support services for people prescribed GIVLAARI through Alnylam Assist®. Visit AlnylamAssist.com for more information or call 1-833-256-2748.

GIVLAARI is expected to be available for shipment to healthcare providers in the U.S. by year-end. HCPs can initiate the process now by visiting www.AlnylamAssist.com and completing and submitting a Start Form.

In August, Alnylam announced a U.S. gastrointestinal (GI) disease education and promotional agreement for GIVLAARI with Ironwood Pharmaceuticals, Inc., a GI healthcare company. Under the agreement, Alnylam will leverage Ironwood's leading capabilities in GI to help raise awareness of AHP among gastroenterologists and other healthcare practitioners in the U.S. Ironwood will also participate in GIVLAARI promotional efforts, augmenting Alnylam's broader commercialization activities.

GIVLAARI was reviewed by the FDA under Priority Review and had previously been granted Breakthrough Therapy and Orphan Drug Designations in the U.S. GIVLAARI is currently being reviewed under accelerated assessment by the European Medicines Agency (EMA) for the treatment of patients with AHP, after receiving Priority Medicines (PRIME) Designation and Orphan Drug Designation from the EMA.

Visit GIVLAARI.com for more information, including full Prescribing Information.

Conference Call Information
Alnylam management will discuss the FDA approval via conference call today, November 20, 2019 at 2:15 p.m. ET. A webcast presentation will also be available on the Investors page of the Company's website, www.alnylam.com. To access the call, please dial 800-239-9838 (domestic) or +1-323-794-2551 (international) five minutes prior to the start time and refer to conference ID 6976021. A replay of the call will be available beginning at 5:00 pm ET on the day of the call. To access the replay, please dial 888-203-1112 (domestic) or +1-719-457-0820 (international) and refer to conference ID 6976021.

IMPORTANT SAFETY INFORMATION

Contraindications
GIVLAARI is contraindicated in patients with known severe hypersensitivity to givosiran. Reactions have included anaphylaxis.

Anaphylactic Reaction
Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering GIVLAARI. Monitor for signs and symptoms of anaphylaxis. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.

Hepatic Toxicity
Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients receiving GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment.

Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment with GIVLAARI for severe or clinically significant transaminase elevations. In patients who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. The dose may be increased to the recommended dose of 2.5 mg/kg once monthly if there is no recurrence of severe or clinically significant transaminase elevations at the 1.25 mg/kg dose.

Renal Toxicity
Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment with GIVLAARI. In the placebo-controlled study, 15% of patients receiving GIVLAARI experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment with GIVLAARI as clinically indicated.

Injection Site Reactions
Injection site reactions were reported in 25% of patients receiving GIVLAARI in the placebo-controlled trial. Symptoms included erythema, pain, pruritus, rash, discoloration, or swelling around the injection site. One (2%) patient experienced a single, transient, recall reaction of erythema at a prior injection site with a subsequent dose administration.

Drug Interactions
Concomitant use of GIVLAARI increases the concentration of CYP1A2 or CYP2D6 substrates, which may increase adverse reactions of these substrates. Avoid concomitant use of GIVLAARI with CYP1A2 or CYP2D6 substrates for which minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP1A2 or CYP2D6 substrate dosage in accordance with approved product labeling.

Adverse Reactions
The most common adverse reactions that occurred in patients receiving GIVLAARI were nausea (27%) and injection site reactions (25%).

For additional information about GIVLAARI, please see full Prescribing Information.

About GIVLAARI™ (givosiran)

GIVLAARI is an RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of adults with acute hepatic porphyria (AHP). In the pivotal study, GIVLAARI was shown to significantly reduce the rate of porphyria attacks that required hospitalizations, urgent healthcare visits or IV hemin administration at home compared to placebo. GIVLAARI is Alnylam's first commercially-available therapeutic based on its Enhanced Stabilization Chemistry ESC-GalNAc conjugate technology to increase potency and durability. GIVLAARI is administered via subcutaneous injection once monthly at a dose based on actual body weight and should be administered by a healthcare professional. GIVLAARI works by specifically reducing elevated levels of aminolevulinic acid synthase 1 (ALAS1) messenger RNA (mRNA), leading to reduction of toxins associated with attacks and other disease manifestations of AHP. For more information about GIVLAARI, visit GIVLAARI.com.

About AHP

Acute hepatic porphyria (AHP) refers to a family of ultra-rare, genetic diseases characterized by potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life. AHP is comprised of four types: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and ALA dehydratase-deficiency porphyria (ADP). Each type of AHP results from a genetic defect leading to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver. AHP disproportionately impacts women of working and childbearing age, and symptoms of the disease vary widely. Severe, unexplained abdominal pain is the most common symptom, which can be accompanied by limb, back, or chest pain, nausea, vomiting, confusion, anxiety, seizures, weak limbs, constipation, diarrhea, or dark or reddish urine. The nonspecific nature of AHP signs and symptoms can often lead to misdiagnoses of other more common conditions such as viral gastroenteritis, irritable bowel syndrome (IBS), addiction withdrawal and appendicitis. Consequently, patients with AHP can wait up to 15 years for a confirmed diagnosis. In addition, long-term complications and comorbidities of AHP can include hypertension, chronic kidney disease or liver disease including hepatocellular carcinoma.

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 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

Alnylam (Nasdaq: ALNY) is leading 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 genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS)/ocular diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust RNAi therapeutics platform. Alnylam’s commercial RNAi therapeutic products are ONPATTRO® (patisiran), approved in the U.S., EU, Canada, Japan, and Switzerland, and GIVLAARI™ (givosiran), approved in the U.S. Alnylam has a deep pipeline of investigational medicines, including five product candidates that are in late-stage development. Alnylam is executing on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Alnylam employs over 1,200 people worldwide and is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam or on LinkedIn.

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 approval of GIVLAARI™ (givosiran) injection for subcutaneous use, and the implications of such approval for patients and their caregivers, the results of the ENVISION Phase 3 clinical trial for givosiran, expectations concerning when GIVLAARI will be available for shipment to healthcare providers in the U.S., its plan to offer comprehensive support services for people prescribed GIVLAARI through Alnylam Assist®, its plans to leverage Ironwood’s capabilities in GI to help raise awareness of AHP among U.S. healthcare practitioners and assist in GIVLAARI promotional efforts, expectations regarding the review of GIVLAARI’s MAA under accelerated assessment by the EMA for the treatment of patients with AHP, and expectations regarding its “Alnylam 2020” guidance for the advancement and commercialization of RNAi therapeutics, 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, Alnylam's ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its product candidates, the pre-clinical and clinical results for its product candidates, which may not be replicated or continue to occur in other subjects or in additional studies or otherwise support further development of product candidates for a specified indication or at all, actions or advice of regulatory agencies, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing, delays, interruptions or failures in the manufacture and supply of its product candidates, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its intellectual property rights against third parties and defend its patent portfolio against challenges from third parties, obtaining and maintaining regulatory approval, pricing and reimbursement for products, including GIVLAARI, progress in establishing a commercial and ex-United States infrastructure, successfully launching, marketing and selling its approved products globally, including GIVLAARI, Alnylam’s ability to successfully expand the indication for ONPATTRO in the future, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage its growth and operating expenses and achieve a self-sustainable financial profile in the future, obtain additional funding to support its business activities, and establish and maintain strategic business alliances and new business initiatives, Alnylam's dependence on third parties, including Regeneron, for development, manufacture

and distribution of products, and Ironwood, for assistance with the education about and promotion of GIVLAARI, the outcome of litigation, the risk of 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 other filings that Alnylam makes with the SEC. 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] Dr. Manisha Balwani (the Principal Investigator in this study) receives financial compensation as a consultant for Alnylam Pharmaceuticals (the study sponsor). In addition, Mount Sinai faculty are named Co-Inventors with Alnylam on a patent related to the development of givosiran, the study drug. The Icahn School of Medicine at Mount Sinai receives payments related to this patent from Alnylam, and a portion of these payments are also distributed to faculty and other co-inventors.

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