Alnylam Announces U.S. Food and Drug Administration (FDA) Approval of OXLUMO™ (lumasiran), the First and Only Treatment Approved for Primary Hyperoxaluria Type 1 to Lower Urinary Oxalate Levels in Pediatric and Adult Patients

Nov 24,2020

– First RNAi Therapeutic Approved in U.S. for Use in Both Children and Adults, and Third RNAi Medicine to Receive FDA Approval in Less than Three Years –

– Approval Based on Results from Both ILLUMINATE-A and ILLUMINATE-B Phase 3 Studies, Demonstrating Clinically Significant Reductions in Urinary Oxalate and Encouraging Safety and Tolerability Across a Broad Spectrum of Patient Ages –

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

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 24, 2020-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today that the U.S. Food and Drug Administration (FDA) approved OXLUMO™ (lumasiran) injection for subcutaneous use, the first-ever therapy available for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. PH1 is an ultra-rare genetic disease characterized by oxalate overproduction. The excess production of oxalate results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones, nephrocalcinosis, progression to kidney failure, and systemic organ dysfunction. In ILLUMINATE-A – the largest controlled Phase 3 study ever conducted in PH1 – OXLUMO was shown to significantly reduce levels of urinary oxalate relative to placebo, with the majority of patients achieving normal[1] or near-normal[2] levels. OXLUMO demonstrated an encouraging safety and tolerability profile, with injection site reactions (ISRs) as the most common drug-related adverse reaction. In the ILLUMINATE-B pediatric Phase 3 study, the safety and efficacy of OXLUMO were demonstrated in patients under the age of six, and results showed reduction of urinary oxalate and an overall safety and tolerability profile consistent with that demonstrated in ILLUMINATE-A.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20201124005407/en/

OXLUMO™ (lumasiran) packaging and product vial (Photo: Business Wire)

"The approval of OXLUMO is a further testament to the impact RNAi therapeutics can have in transforming the treatment of severe, life-threatening diseases like PH1. Results from the ILLUMINATE-A and ILLUMINATE-B studies demonstrate that OXLUMO addresses the underlying pathophysiology of PH1 in adults, children and infants, and we believe this newly approved medicine has the potential to change the course of this progressive disease," said Akshay Vaishnaw, M.D., Ph.D., President of R&D at Alnylam. "OXLUMO marks our third FDA approval in less than three years, positioning us to meet or exceed our *Alnylam 2020* strategy and goals, and further highlighting the productivity of our RNAi platform and the speed at which we can bring innovative medicines to patients. For patients and families impacted by PH1, this is an historic moment, as OXLUMO represents the first, targeted therapeutic option available to them. We are grateful to all the investigators, staff and patients who participated in the ILLUMINATE clinical studies, and to their families, caregivers and patient advocates. This moment is what we all had hoped for."

The FDA approval of OXLUMO was primarily based on positive results from the randomized, double-blind, placebo-controlled ILLUMINATE-A Phase 3 study, with results presented in June 2020 at the 57th European Renal Association – European Dialysis and Transplant Association Virtual Congress. The FDA also took into consideration positive interim results from the single-arm, open-label ILLUMINATE-B Phase 3 pediatric study. Primary analysis results from the ILLUMINATE-B study were presented in October 2020 at the virtual American Society of Nephrology Annual Congress.

In ILLUMINATE-A, the efficacy and safety of OXLUMO were evaluated in 39 patients ages six and older with relatively preserved renal function (estimated glomerular filtration rate [eGFR] at or above 30 mL/min/1.73m^2) and a documented diagnosis of PH1. The study, conducted in eight countries around the world, is the largest interventional study conducted specifically in PH1. Patients were randomized 2:1 to receive three monthly doses of OXLUMO or placebo at 3 mg/kg followed by a quarterly dosing regimen. The study showed that OXLUMO met its primary endpoint, percent change in 24-hour urinary oxalate (corrected for body surface area and averaged from months three to six). Specifically, treatment with OXLUMO resulted in a 65 percent mean reduction in urinary oxalate relative to baseline versus 12 percent reduction reported in response to placebo, resulting in a mean treatment difference of 53 percent relative to placebo ($p=1.7x10^{-14}$). In addition, OXLUMO achieved statistically significant results for all six tested secondary endpoints, including the proportion of patients achieving urinary oxalate levels at or below upper limit of normal[1] (13/25 patients or 52 percent; p=0.001) and at or below 1.5x upper limit of normal[2] (21/25 patients or 84 percent; $p=8.3 \times 10^{-7}$), compared with none (0/13) of the patients receiving placebo. During the primary analysis period, OXLUMO demonstrated an encouraging safety and tolerability profile, with no serious or severe adverse events. The most common adverse reaction was ISRs (reported in at least 20 percent of patients); ISRs occurred at various time points during the study period and included erythema, pain, pruritus, and swelling. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment.

In ILLUMINATE-B, a study in PH1 patients under the age of six with relatively preserved renal function (eGFR above 45 mL/min/1.73m^2), OXLUMO was evaluated in 18 patients during the primary analysis, including infants as young as three months old. It was administered according to a weight-based dosing regimen across three body weight categories (less than 10 kg; 10 to less than 20 kg, and 20 kg or higher). In the primary analysis, OXLUMO demonstrated a 72 percent mean reduction in spot urinary oxalate:creatinine ratio from baseline to month six (averaged from months three to six) – the primary endpoint of the study. The reduction of oxalate was consistent across all three body weight categories. In addition, OXLUMO demonstrated positive results across secondary endpoints, including additional measures of oxalate. There were no serious or severe adverse events related to study drug, and the overall safety and tolerability profile of OXLUMO was consistent with that observed in the

ILLUMINATE-A pivotal study.

“PH1 patients experience progressive and often inevitable decline in kidney function. As the disease advances, so does the risk of end-stage kidney disease and systemic spread of oxalate beyond the kidneys endangering other organs, including the eyes, bones, skin and heart. This condition, systemic oxalosis, leads to multi-organ dysfunction and death. The age of onset, rate of disease progression, and associated clinical manifestations can vary significantly from patient to patient, even among members of the same family, making PH1 a particularly challenging condition to diagnose and treat. Until today, there had been no approved nonsurgical treatment options available that curb oxalate overproduction in patients with PH1, with liver transplantation being the only preemptive treatment approach to address the underlying metabolic defect in these patients,” said Jeffrey M. Saland, M.D., Professor and Chief, Pediatric Nephrology and Hypertension, Jack and Lucy Clark Department of Pediatrics, Mount Sinai Kravis Children’s Hospital, New York City and Investigator on the ILLUMINATE-A trial. “The consistent efficacy and safety profile of OXLUMO demonstrated in the ILLUMINATE-A and -B trials both in adults and children from as young as a few months old, combined with an infrequent dosing regimen that leads to rapid and sustained reduction of oxalate production, make OXLUMO an attractive therapeutic option to reduce the oxalate burden responsible for the severe clinical manifestations that individuals suffer due to PH1.”

“Many people impacted by PH1 face persistent anxiety related to the unpredictable nature of their condition, in terms of the uncertainty of how quickly their disease may progress, and the prospect of needing intensive dialysis and a kidney/liver transplant that threaten their physical, emotional and financial health,” said Kim Hollander, Executive Director of the Oxalosis and Hyperoxaluria Foundation. “The FDA approval of OXLUMO represents a new path forward for many, providing an effective treatment option and a sense of hope.”

“PH1 has had a profound impact on my son’s life from a physical, emotional and social standpoint. As a young boy, it has been draining for him to be constantly in pain, live through countless kidney stones – experiencing them on a regular basis – have limited control of his body, miss out on school and not be able to participate in sports,” said Amy Bowders, the mother and caregiver of a 12-year old boy diagnosed with PH1. “With the approval of OXLUMO, we are truly hopeful and optimistic about the future for patients affected by PH1.”

OXLUMO 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.

OXLUMO was reviewed by the FDA under Priority Review and had previously been granted Breakthrough Therapy, Orphan Drug, and Rare Pediatric Disease Designations. With the approval of OXLUMO, the FDA has granted Alnylam a pediatric rare disease priority review voucher that entitles the Company to designate a single new drug application to qualify for a priority review in the future. On November 19, the European Commission granted marketing authorization for OXLUMO for the treatment of PH1 in all age groups, following a positive opinion from the Committee for Medicinal Products for Human Use (CHMP). Lumasiran was previously granted Priority Medicines (PRIME) Designation by the European Medicines Agency (EMA) as well as Orphan Designation in the European Union. Lumasiran was also granted an Accelerated Assessment by the EMA, which is awarded to medicines deemed to be of major public health interest and therapeutic innovation and is designed to bring new treatments to patients more quickly.

The safety and efficacy of OXLUMO are also being evaluated in the ongoing ILLUMINATE-C Phase 3 clinical trial in patients of all ages with advanced PH1, including patients on dialysis. Together, the ILLUMINATE studies comprise a comprehensive clinical development program intended to demonstrate the safety and efficacy of OXLUMO across the full spectrum of patients diagnosed with PH1.

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

Conference Call Information:

Alnylam management will discuss the FDA approval via conference call today, November 24, 2020 at 8:00 a.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 11:00 a.m. 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.

Footnotes:

[1]Normal is defined as urinary oxalate levels at or below the upper limit of normal (ULN; ≤ 0.514 mmol/24 hr/1.73 m^2). [2]Near-normal is defined as urinary oxalate levels at or below 1.5 x ULN (≤ 0.771 mmol/24 hr/1.73 m^2)

IMPORTANT SAFETY INFORMATION

Adverse Reactions
The most common adverse reaction that occurred in patients treated with OXLUMO was injection site reaction (38%). Symptoms included erythema, pain, pruritus, and swelling.

Pregnancy and Lactation
No data are available on the use of OXLUMO in pregnant women. No data are available on the presence of OXLUMO in human milk or its effects on breastfed infants or milk production. Consider the developmental and health benefits of breastfeeding along with the mother’s clinical need for OXLUMO and any potential adverse effects on the breastfed child from OXLUMO or the underlying maternal condition.

For additional information about OXLUMO, please see the full Prescribing Information.

About OXLUMO™ (lumasiran)
OXLUMO is an RNAi therapeutic targeting hydroxyacid oxidase 1 (HAO1) for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. HAO1 encodes glycolate oxidase (GO), an enzyme upstream of the disease-causing defect in PH1. OXLUMO works by degrading HAO1 messenger RNA and reducing the synthesis of GO, which inhibits hepatic production of oxalate – the toxic metabolite responsible for the clinical manifestations of PH1. In the pivotal ILLUMINATE-A study, OXLUMO was shown to significantly reduce levels of urinary oxalate relative to placebo, with the majority of patients reaching normal or near-normal levels. Injection site reactions (ISRs) were the most common drug-related adverse reaction. In the ILLUMINATE-B pediatric Phase 3 study, OXLUMO demonstrated an efficacy and safety profile consistent to that observed in ILLUMINATE-A. OXLUMO utilizes Alnylam’s Enhanced Stabilization Chemistry (ESC)-GalNAc conjugate technology

designed to increase potency and durability. OXLUMO is administered via subcutaneous injection once monthly for three months, then once quarterly thereafter at a dose based on actual body weight. For patients who weigh less than 10 kg, ongoing dosing remains monthly. OXLUMO should be administered by a healthcare professional. For more information about OXLUMO, visit OXLUMO.com.

About Primary Hyperoxaluria Type 1 (PH1)
PH1 is an ultra-rare genetic disease that affects an estimated one to three individuals per million in the United States and Europe. PH1 is characterized by oxalate overproduction in the liver. The excess oxalate results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones and nephrocalcinosis. Renal damage is caused by a combination of tubular toxicity from oxalate, calcium oxalate deposition in the kidneys, and urinary obstruction by calcium oxalate stones. PH1 is associated with a progressive decline in kidney function, which exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and deposition of oxalate in bones, eyes, skin, and heart, leading to severe illness and death. Management options to date were limited to hyperhydration, crystallization inhibitors and, in a minority of patients with a specific genotype, pyridoxine (vitamin B6). These measures do not adequately address oxalate overproduction but instead help to delay inevitable progression to kidney failure and the need for intensive dialysis as a bridge to a dual or sequential liver/kidney transplant. Liver transplantation is the only intervention that addresses the underlying metabolic defect, but is associated with high morbidity and mortality, and life-long immunosuppression. Until today, there were no approved pharmaceutical therapies for PH1.

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 (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), GIVLAARI® (givosiran), and OXLUMO™ (lumasiran). Alnylam has a deep pipeline of investigational medicines, including six 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 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 safety and efficacy of OXLUMO as demonstrated in the ILLUMINATE-A and ILLUMINATE-B Phase 3 studies and the potential for OXLUMO to address the underlying pathophysiology of PH1 in adults, children and, infants and change the course of this progressive disease, the potential for OXLUMO to be an attractive therapeutic option that can reduce the oxalate burden responsible for the severe clinical manifestations associated with PH1, Alnylam's expectation regarding the timing for commercial availability of OXLUMO in the U.S. and Alnylam's plans, assuming additional regulatory approvals, to bring lumasiran to patients with PH1 around the world, and expectations regarding the potential for Alnylam to meet or exceed 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by Alnylam products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to Alnylam's business, the effectiveness or timeliness of steps taken by Alnylam to mitigate the impact of the pandemic, and Alnylam's ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; 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, 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 or its other marketed products, including OXLUMO; obtaining, maintaining and protecting intellectual property; intellectual property matters including potential patent litigation relating to its platform, products or product candidates; obtaining regulatory approval for its product candidates, and maintaining regulatory approval and obtaining pricing and reimbursement for its products, including ONPATTRO, GIVLAARI, and OXLUMO; progress in continuing to establish an ex-United States infrastructure; successfully launching, marketing and selling its approved products globally, including ONPATTRO, GIVLAARI, and OXLUMO, and achieving net product revenues for ONPATTRO within its revised expected range during 2020; 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 within the ranges of guidance provided by Alnylam through the implementation of further discipline in operations to moderate spend and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to establish and maintain strategic business alliances and new business initiatives; Alnylam's dependence on third parties, including Regeneron, for development, manufacture and distribution of certain products, including eye and CNS products, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20201124005407/en/

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom
(Investors and Media)
+1-617-682-4340

Josh Brodsky
(Investors)
+1-617-551-8276

Source: Alnylam Pharmaceuticals, Inc.