Alnylam Announces Publication of ILLUMINATE-A Phase 3 Study Results for Lumasiran in The New England Journal of Medicine

March 31, 2021

- ILLUMINATE-A Phase 3 Study Evaluated the Efficacy and Safety of Lumasiran in Adult and Pediatric Patients with Primary Hyperoxaluria Type 1 (PH1) -

- Lumasiran Demonstrated a Clinically Significant Reduction in Urinary Oxalate, a Primary Determinant of Progression to Renal Failure in PH1, Compared to Placebo -

- Manuscript Marks the Tenth Publication of Clinical Trial Results for Alnylam Programs in The New England Journal of Medicine, Highlighting the Impact of RNAi Therapeutics as a New Class of Medicines -

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 31, 2021-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that pivotal trial results from the ILLUMINATE-A Phase 3 study of lumasiran, an RNAi therapeutic targeting *hydroxyacid oxidase 1 (HAO1)* – the gene encoding glycolate oxidase (GO) – for the treatment of primary hyperoxaluria type 1 (PH1), were published online in The *New England Journal of Medicine* (*NEJM*). In November 2020, OXLUMO™ (lumasiran) was approved by the U.S. Food and Drug Administration for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients, and received marketing authorization from the European Commission for the treatment of PH1 in all age groups. OXLUMO is the first-ever treatment approved for PH1 and the first RNAi therapeutic evaluated in both children and adults. The full manuscript titled “Phase 3 Trial of Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1,” will appear in the April 1, 2021 issue of *NEJM*.

The data reported in the ILLUMINATE-A Phase 3 study publication demonstrated that RNAi-mediated targeting of liver GO by lumasiran led to substantial and sustained reductions in urinary oxalate—the toxic metabolite responsible for the debilitating and life-threatening clinical manifestations of PH1. Relative to placebo, treatment with lumasiran resulted in a clinically significant (53.5 percent) reduction in 24-hour urinary oxalate excretion from baseline to month 6 – the primary endpoint of the study.

Improvements were also observed in a number of secondary endpoints, including the proportion of patients achieving normal[a] or near-normal[b] levels of urinary oxalate, with 84 percent of lumasiran-treated patients meeting this endpoint compared with no patients (0 percent) on placebo. Patients treated with lumasiran also experienced favorable effects on exploratory endpoints related to nephrocalcinosis and the rate of renal stone events[c] compared with placebo.

Lumasiran administration was associated with an encouraging safety and tolerability profile, with no serious or severe adverse events (AEs). The most common AEs that occurred more frequently with lumasiran than placebo were injection site reactions (38 versus 0 percent). All injection site reactions were mild and transient and did not result in discontinuation of treatment.

“PH1 often presents in early life, with kidney stones, nephrocalcinosis, renal failure and, in advanced stages, systemic spread of oxalate throughout the body with life-threatening consequences. Oxalate drives disease manifestations and progression, and is the toxic mediator of end-organ damage in PH1,” said Prof. Yaacov Frishberg, M.D., Head of Division of Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel, and lead co-author on the manuscript. “We believe the publication of the ILLUMINATE-A Phase 3 study results in the NEJM is a testament to lumasiran as an oxalate-lowering therapy which is expected to confer significant clinical benefit to children and adults living with this disease.”

“Publication of the ILLUMINATE-A results in NEJM is an exciting achievement, highlighting the tremendous unmet need for novel therapies for this devastating disease and the role lumasiran is playing to fill this need. We are thrilled by the fact that this is now the tenth publication in NEJM on results from clinical studies of Alnylam’s RNAi therapeutics, a noteworthy milestone underscoring the impact of RNAi on clinical research and the practice of medicine,” said Pritesh J. Gandhi, PharmD., Vice President and General Manager, Lumasiran Program at Alnylam. “We look forward to reporting and publishing additional data from the ILLUMINATE program including in patients under the age of six and those with impaired kidney function later this year.”

A total of 38[d] of 39 patients completed the ILLUMINATE-A 6-month primary analysis period and all eligible patients transitioned to the study extension period. Results from the 12-Month extension period were presented at the American Society of Nephrology (ASN) virtual congress in October 2020 and demonstrated sustained efficacy with no safety findings leading to discontinuation in the study.

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 ILLUMINATE-A Phase 3 Study

ILLUMINATE-A (NCT03681184) is a six-month randomized, double-blind, placebo-controlled, global, multicenter Phase 3 study (with a 54-month extension period) to evaluate the efficacy and safety of lumasiran in 39 patients, age six and older, with a documented diagnosis of PH1. Patients were randomized 2:1 to receive three monthly doses of lumasiran or placebo followed by quarterly doses at 3 mg/kg. The primary endpoint was the percent change in 24-hour urinary oxalate excretion from baseline to the average of months 3 to 6 in the patients treated with lumasiran as compared to placebo. Treatment arms were stratified at randomization based upon mean 24-hour urinary oxalate during screening (≤1.7 or >1.7 mmol/24hr /1.73m^2). Key secondary and exploratory endpoints were designed to evaluate additional measures of urinary oxalate, plasma oxalate, estimated glomerular filtration rate (eGFR), nephrocalcinosis, renal stone events, safety and tolerability.

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), OXLUMO™ (lumasiran), and Leqvio® (inclisiran) being developed and commercialized by Alnylam's partner Novartis. Alnylam has a deep pipeline of investigational medicines, including six 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 and engage with us on Twitter at @Alnylam, on LinkedIn, or on Instagram.

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, the role of OXLUMO as an oxalate-lowering therapy which is expected to confer significant clinical benefit to children and adults living with PH1 and its ability to meet an unmet need for novel therapies for the treatment of PH1, and Alnylam's ability to achieve 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; 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; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, 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 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, Regeneron and Vir; 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 Annual Report on Form 10-K 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.

Footnotes:

[a] 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); [b] near-normal is defined as urinary oxalate levels at or below 1.5 x ULN (≤ 0.771 mmol/24 hr/1.73 m^2); [c]a renal stone event was defined as an event which includes at least one of the following: visit to healthcare provider because of a renal stone, medication for renal colic, stone passage, macroscopic hematuria due to a renal stone; [d]one patient discontinued study drug after receiving a single dose and withdrew from the study after Month 3. Parent/guardian stopped participation due to patient's inability to comply with protocol-specific testing.

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