Alnylam Pharmaceuticals Inc "RNAi Roundtable" Webcast Series: Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type I

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PRESENTATION

Joshua Brodsky, Alnylam Pharmaceuticals, Inc. - Director of IR & Corporate Communications

Good afternoon, everyone. Thank you for joining us today for this RNAi roundtable, where we'll be discussing lumasiran in development for the treatment of primary hyperoxaluria Type 1. I'm Josh Brodsky, Director of Investor Relations and Corporate Communications at Alnylam.

With me today are Pritesh Gandhi, Vice President and General Manager of the lumasiran program; Tracy McGregor, Senior Director of Clinical Research; and Dr. Michael Somers, Associate Chief of the division of Nephrology at Boston Children's Hospital and Harvard Medical School.

Before I hand it over to Pritesh, let me start with a few brief comments. Today's RNAi roundtable is the third in a series of roundtable webinars that we're hosting this summer and early fall to review progress across our various programs.

Today's event is expected to run approximately 75 minutes. Pritesh will moderate a Q&A session at the conclusion of the presentations. And if you'd like to submit a question, you can do so at any time during the event, by typing your question in the ask a question field. Finally, as a reminder, we will be making forward-looking statements during this webinar, and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And now with that, I will turn it over to Pritesh. Pritesh, go ahead.

Pritesh J. Gandhi, Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs & GM of the Lumasiran Program

Thanks, Josh, and thank you all for joining the call. I hope you are all continuing to stay safe and healthy. Next slide, please.

I will start with a brief background on Alnylam and our pipeline and then hand it off to Dr. Somers, who will provide a disease overview on primary hyperoxaluria type 1 or PH1. As many of you know, Alnylam is the leading RNAi therapeutics company, committed to advancing a whole new class of medicines for a wide range of human diseases. Based on a Nobel prize winning technology, we can, in essence, silence any gene in the human genome. With this elegant mechanism, we can significantly reduce disease-causing proteins or toxic metabolites that contribute to the clinical manifestations of various conditions. At Alnylam, we have been successfully harnessing the R&I pathway to build an organic product engine for sustainable innovation and bringing medicines to patients with high unmet medical need, around the globe.

Next slide, please. Let us now turn to Alnylam's commercial products and late-stage development programs. Our pipeline is focused on 4 strategic therapeutic areas or stars. These include genetic medicines, cardiometabolic diseases, infectious diseases and CNS or ocular diseases. Presently, we have 2 commercially available products. ONPATTRO for hereditary ATTR amyloidosis with polyneuropathy, and GIVLAARI for acute hepatic porphyrias. The pivotal clinical trial with lumasiran ILLUMINATE-A represented the sixth positive Phase III study for an investigational RNAi therapeutics across our clinical pipeline. This includes patisiran, givosiran, inclisiran and now lumasiran. We truly believe this underscores the transformational potential of this modality as a whole new class of medicines. Over the recent few years, positive Phase III results across our various investigational agents in our pipeline has demonstrated the high probability of clinical success we have achieved. And it also reflects the power of a reproducible and modular platform.

Next slide, please. In the interest of time, I will just briefly touch on our early-stage clinical pipeline. We have 6 programs in Phase I or Phase II development. Overall, we expect our organic product engine to continue to deliver sustainable innovation with 2 to 4 INDs per year.

Next slide, please. The focus of today's RNAi roundtable is lumasiran. As you know, we have now completed our lumasiran regulatory filings with both the FDA and the EMA. The FDA granted priority review status for lumasiran with a PDUFA action date of December 3, 2020. With regard to our MAA filing with the EMA, our application has been validated, and lumasiran has received an accelerated assessment designation. Assuming favorable reviews from the regulatory bodies, this positions us to potentially bring lumasiran to the U.S. market by the end of 2020 and to the EU market shortly thereafter, for patients with PH1.

Next slide. Before handing it over to Dr. Somers, I'll provide an overview of PH1. PH1 is an autosomal recessive disease that is characterized by hepatic overproduction of oxalate. Under normal physiological conditions, AGT or alanine-glyoxylate aminotransferase converts glyoxylate to glycine. In patients with PH1, there is a defect or deficiency in AGT, resulting in an overproduction of hepatic oxalate. Oxalate combines with calcium to form calcium oxalate crystals that initially deposit and accumulate in kidneys, resulting in recurrent stones, which can be excruciatingly painful and can also result in nephrocalcinosis and progressive renal insufficiency. In patients on an end-stage renal disease, oxalate will deposit in extra renal tissues, resulting in systemic oxalosis, causing cardiomyopathy, vision loss and pathological factors. Presently, there are no approved therapies for patients with PH1.

With that background, I will now turn it over to Dr. Somers to provide a disease overview of PH1. First, as an introduction, Dr. Somers received his medical education at the University of Vermont College of Medicine. He completed his residency in pediatrics at the Mayo Clinic, and a fellowship in pediatric nephrology at Boston Children's Hospital. Presently, he's associate chief and (inaudible) Chair in pediatric nephrology in the division of nephrology at Boston Children's Hospital, where he's also the Medical Director of the renal dialysis unit. Dr. Somers is an associate professor of Pediatrics at Harvard Medical School and currently serves as the President of the American Society of Pediatric Nephrology. Dr. Somers?

Michael Somers,

Thank you, Pritesh. It's my pleasure to give an overview of primary hyperoxaluria and oxalosis.

Next slide, please. I'm going to share with you some cases, 3 cases of patients that I actually was involved with their care. Case one is a 2-month old girl, who developed several days of spinning up and some diarrhea and was brought to pediatrician for what was thought to be mild dehydration, she was found, however, to have significant kidney failure with the serum creatinine, the measure of kidney function some 50x normal. And she was started on peritoneal dialysis, the form of dialysis usually done for small babies. Her initial diagnostic evaluation was negative other than having some bright kidneys on ultrasound, which is a nonspecific finding.

About a year later, her ultrasound was repeated and showed calcified kidneys, and she was referred to us in Boston for more specific evaluation, where we were able to make a diagnosis of PH1 by genetic analysis, shifted her dialysis therapy to hemodialysis and intensified it to almost daily hemodialysis and then got her ready for a successful kidney liver transplant at 20 months of age.

Next slide. Case 2 is a teenage boy who had a several year history of some abdominal discomfort and back pain that was chalked up to constipation and muscle pulls. He came in after several days of increasingly severe flying pain and was found to have kidney stones in both kidneys as well as calcification in the kidney tissue and decreased kidney function. We suspected a diagnosis of PH1. We did urine studies that pointed in that direction. This was in the days before genetic study could be done, and he had a confirmatory liver biopsy. Over the next dozen years, he required more than 20 urologic procedures or admissions for kidney stones, leading to increasing problems with his kidney function. By age 25, he was on 6 times a week hemodialysis. And a year later, he underwent a successful liver kidney transplant.

Next slide. In my third case is a young adult. She was in graduate school. Since her time in college, she's been plagued by recurring episodes of kidney stone, had seen several urologists who've taken out many kidney stones and done their composition analysis and told her they were made of calcium and oxalate and told her to drink more. When she came to us, we suspected PH1, confirmed that by genetic testing. We found she had a type of PH that's amenable to therapy with a vitamin, Vitamin B6, pyridoxine. We put her on this vitamin and she no longer had kidney stones. She had already had significant kidney injury, and her kidney function has slowly been declining, and she's now started an evaluation for a kidney transplant.

Next slide. So there are some common gains in all these clinical cases. First, you can see the disease spectrum is broad, different age groups with both acute and indolent presentations. The diagnosis was often delayed with clinical clues that we either ignored or underappreciated. Sometimes, this was related to decreased clinical resources and actually finding the clinician knowledgeable about PH1. And lastly, the treatment options were ineffective. There were ongoing medical complications and an exorable decline in kidney function.

Next slide. As you've already heard, the initial problems with PH1 and any form of hyperoxaluria lies with the liver, an inborn error and hepatic metabolism that results in enhanced oxalate production. PH1 accounts for 80% of cases of

hyperoxaluria. And with PH1, large oxalate burdens get generated throughout life.

Next slide, please. The kidney gets involved because with this large oxalate burden, your body eliminates oxalate through the kidneys. Unfortunately, when the burden becomes too high, the oxalate can deposit in the kidneys itself causing nephrocalcinosis or the oxalate can combine with calcium in the urine to cause kidney stones. Ongoing oxalated-mediated injury to the kidney eventually leads to progressive loss of kidney function, due both to the injury from the kidney stones and the deposition of oxalate in the kidney tissue as well as the inflammation that the deposition causes.

Next slide. I want to spend a few moments talking about the kidney and how the kidney responds to injury because I think that this is quite important to understand the ramifications of PH1 therapy and novel PH1 therapies. The kidney is composed of building blocks called nephrons. Each nephron has the glomeruli that filters the blood and a tubule that fine tunes this filtrate. Normally, upwards of 1 million nephrons are formed in each kidney prior to birth. About 4 weeks before most of us are born, our kidney stops developing nephrons and we never make nephrons again in our lives. We make so many nephrons because there's an underlying inherent tendency towards obsolescence of these nephrons. As we all go through life, we lose nephron. An adequate kidney function depends on there being enough functioning nephrons for our entire lifespan.

Next slide. So renal reserve is a concept that relates back to how many functioning nephrons we have. You'll have stable kidney function, if your renal reserve is in balance with the functional demands your body is making on your kidneys.

Next slide. Loss of renal reserve, for instance, by some injury or ongoing entry that's accelerating the normal loss of kidney filter units over time, means that long-term functional capacity can be compromised. And as a result, you have decline in renal function. In the medical world, we often term kidney function GFR, standing for glomerular filtration rate, how well are kidneys filtering impurities? You'll go from a stage of good GFR to a stage of bad GFR.

Next slide, please. This is a standing electron micrograph of the glomerulus. As a nephrologist, I always like to show people how neat the kidney is. But you can see the glomerulus is made of the tight bundle of the capillary. If you do a cross section, you can appreciate the little ports that allows filtration to occur across the glomerulus.

Next slide. This is a stain of a biopsy of a kidney, much as I would look at with the pathologist after I biopsy the kidney. And I share it with you so you can again see the glomerulus in the middle. And around it, you can see the tubular elements, and you can see how well positioned and intricate the histology is.

Next slide. In the setting of oxalate deposition, you can see how this normal histology is markedly petered. The oxalate crystals cuts issues with both the glomeruli and also with the tubules and you can see the background kidney tissue, there are lots of little blue purple specs. This is inflammatory cells and scarring that's occurred as a result of this oxalate deposition.

Next slide. The consequence of oxalate injury or the consequence of any injury to the kidney that causes there to be loss of filtering units is what is termed hyperfiltration. In other words, you injure filtering units, the ones that are left that can work, step up to the plate and work harder, by working harder, they accelerate their normal tendency towards obsolescence, and they wear out quicker. This whole sort of process will lead to a state of chronic kidney disease.

Next slide. In chronic kidney disease, there's some underlying functional impairment of the kidney so that your GFR, again, think of that as your percent kidney function, can decline over time. We have stages of GFR from relatively good GFR in chronic kidney disease of more than 90% to a GFR of less than 15%, where you've reached a point in chronic kidney disease, where medically, it's hard to treat your chronic kidney disease with just medications and you need some form of renal replacement therapy with dialysis or a kidney transplant. We term that end-stage kidney disease.

Next slide. It's important to understand that interventions to prevent disease progression need to happen early in the course of chronic kidney disease. Remember, there's this inexorable progression of chronic kidney disease as more and more filtering units are lost. And so with lower kidney function, this needs to be kept in mind especially in terms of new therapies and expectations for cures.

Next slide. Going back to PH1, in the setting of kidneys that are being damaged by ongoing oxalate deposition, the ability for the kidney to eliminate oxalate from the body declined. And as a result, oxalate starts getting deposited outside of the kidney, notably in the bone, the eyes, the heart and the skin. And this state of systemic oxalate deposition, that we call oxalosis, leads to even more profound and adverse health consequences.

Next slide. You've heard some basic demographics about PH1. It's autosomal recessive inheritance means that it tends to be seen somewhat higher in geographically isolated populations or in populations where the increase consanguinity. In an era of specific population genetics, there is interesting data. For instance, from the National Heart, Lung and Blood Institute, Exome Sequencing Project, the estimates that -- the proportion of Americans affected

with PH1 is probably not the low-low level that we've always saw, but the prevalence is probably some 5x more common. This again underscores potentially some problem we have with diagnosing this condition.

Next slide. What do PH1 patients look like, while the majority of them will present early on with life in life with kidney stones or with calcium deposition in the kidney, about 2/3 to 3/4 of these individuals.

Next slide. This is data from a group of patients with PH1 in Europe to underscore that's showing that the vast majority of patients either presented with stones with a nephrocalcinosis or calcium deposits in their kidney in red or with both stones and nephrocalcinosis in green.

So what do PH -- next slide, please. What do PH patients look like? So we've just mentioned how they often present early in life, often after nephrocalcinosis or nephrolithiasis. But what's also significant is the onset of symptoms and the time to diagnosis usually varies. In other words, there's often a lag or a delay to diagnosis and the consequence of this time often leads to end-stage kidney disease. And in some cohorts, 40% or more patients have end-stage kidney disease by the time a diagnosis is made. Again, underscoring why it's so important to try to be more timely in making a diagnosis.

Next slide. This is data from a European registry of individuals with PH1. Again, it shows, as we've talked about, that most patients are diagnosed early in life. But in this cohort, 70% of them had more than a year of symptoms before diagnosis. And as you can see, about 1/4 of them were diagnosed more than 20 years of age.

Next slide. The ramifications of being diagnosed later on in life is that you're more -- much more likely to be diagnosed in the setting of end-stage kidney disease. Again, from that European registry, individuals diagnosed at less than 18 years of age, only 1/3 of them were already in end-stage kidney disease, whereas 75% of those diagnosed after 18 years of age had end-stage kidney disease.

Next slide. Understanding genetics has also shed some light on understanding the progression to end-stage kidney disease, depending on the underlying genetic mutation you may have. Nearly 200 mutations in the AGXT gene have been described. And these mutations can be classified as either null, meaning you're making none at AGT [sign] or missense, meaning the AGT that's produced, it cannot be used. It's been shown that a specific mutation called G170R, and in this diagram, these are the patients with the yellow, the purple and the red lines to the right, that fair mutations slowed down the progression to end-stage kidney disease.

And what underlies this is the fact that this mutation -- next slide, please, is sensitive to pyridoxine. You'll remember the third case I shared with you that young woman had one of these genetic mutations that was pyridoxine-sensitive. In some cohorts, up to 30% of patients will have this sort of mutations. With this mutations, providing pyridoxine helps to stabilize the enzyme that can be produced, increases its strength, improves its delivery to the right compartment in the liver and could substantially blunt ongoing oxalate production. It will not, however, change the damage that has already happened to the kidney or potentially the path that the kidney has already started to go down, leading to kidney failure.

Next slide. So who should we consider for a diagnosis PH in the medical world, we should consider any child who have kidney stones or nephrocalcinosis, since these are relatively rare happenings for a child. We should consider an adult with recurring stones or with calcium deposition in the kidney. Certainly, anyone with a family history of hyperoxaluria. Someone who presents would decrease kidney function and a history of stones. Or people who present with end-stage kidney disease without a clear etiology.

Next slide. How do we go about diagnosing PH1? It's not as complex as many people think. We can do urinary oxalate studies that will let us know whether there's an increased burden of oxalate being produced and excreted through the kidneys. We can check plasma oxalate levels. And now in the era of genetic testing, we can do AGXT Gene Analysis and look for specific mutations in this gene. It's very rare that we have to progress to liver biopsy in the current era.

Next slide. What do we do once we've made a diagnosis of PH1? Well, a lot of supportive management in those patients who may be amenable to pyridoxine therapy, giving them pyridoxine. Otherwise, we give medicines like citrate or phosphate or magnesium that helps to increase the solubility of oxalate in urine, although oxalate will still precipitate out year-end. We do lots and lots of hydration, having people drink litres and litres of fluid a day to try to decrease the risk of the oxalate coming out of solution in their urine.

Next slide. Sometimes we put in NG tubes or G tubes so we can deliver these huge amounts of fluid. We're vigilant about diet and making sure there's not excess oxalate being provided in diet. We make sure that the urinary tract is being managed by a competent urologist to decrease the renal injury that may ensue from episodes of nephrolithiasis. And lastly, we hope that patients go to a center with expertise in PH1 so that we can blunt their progression through end-stage kidney disease.

Next slide. Why do we want to do this? Because end-stage kidney disease markedly reduces the lifespan of the patient with PH1. This diagram shows in red patients with PH1 who don't have end-stage kidney disease, seen that

their survival is nearly 100% as they go through their first 60 years of life versus those with end-stage renal disease, whose loss of life become quite significant by middle age.

Next slide. When a patient with PH1 goes on to dialysis, their course on dialysis is also more complex. In the dotted line on top are patients without PH1 on dialysis. The bottom line are patients with PH1, and you can see survival on dialysis with PH1 as a primary diagnosis is significantly lower than survival with other causes of end-stage kidney disease.

Next slide. This mortality in PH1 patients can be due to dialysis complications but can be due to a lot of other complications.

Next slide, many of them related to systemic oxalosis or the tendency for oxalate to deposit in various organs of your body as your kidney function declines.

Next slide. The systemic finance with PH1 can be quite daunting. Kidneys that are just filled with kidney stones on the left-hand portion of this slide, phones that are markedly abnormal in composition and in structure in the middle of the slide. And on the right side, that's vessel walls with huge oxalate deposits in them, leading to increased blood vessel injury.

Next slide. Frighteningly, large numbers of patients with PH1 can suffer visual impairment from oxalate deposition in their retina. This shows a retina of the patient with PH1 over time, and you can see there's increasing oxalate deposition.

Next slide. This deposition doesn't go away. The top panels, they're the left eye, the bottom panels are the right eye of a patient who had a successful kidney-liver transplant, no longer is producing high amounts of oxalate. However, their oxalate crystals in their retina stays stable at 5, 7 and 9 years after transplant.

Next slide. All of this burden leads to decreased survival in PH1 patients. And as you can see from the chart on the left and on the right as well, that survival by age is markedly decreased over a normal population.

Next slide. Part of this has to do with the fact that our therapies are not very effective. Dialysis in PH1 patients actually isn't efficient enough to decrease the oxalate that they're producing by the time they reach end-stage kidney disease even though we intensify their dialysis.

Next slide. Transplantation is an option in those patients with pyridoxine sensitive mutations. They may be able to get just an isolated kidney transplant if they're lucky enough that the pyridoxine blunts their oxalate production to negligible amounts. Other patients need to get a combined liver-kidney transplant so that their liver that is otherwise normal but has the inborn error of metabolism is removed and a new liver that can handle oxalate is placed with a new kidney.

Next slide. Kidney-liver transplants in patients with PH1 can either be sequential or combined, meaning the liver first or the liver or kidney together.

Next slide. There are potential benefits or risk to either of these maneuvers, but it doesn't seem to make a difference in terms of survival for patients. Senior survival data between a combined liver kidney transplant sequential liver kidney transplant is pretty much similar with about 70% long-term patient survival. So again, the kidney liver transplant cures the oxalosis, but you still have large disease, burden over time with lots of patients life over time because of their post-transplant course.

Next slide. This shows sequential liver-kidney versus combined liver-kidney outcomes for both how long the liver transplant lap and for how long the kidney transplant laps on the right. And no difference between those different maneuvers, whether you do it sequentially or combined.

Next slide. What I want to stress though is that the kidney that you're given as a kidney transplant is not a cure. Largely because the chronic immunologic injury, all renal allografts lose function over time. Unlike the liver that can regenerate after injury, renal allografts can't heel as they're injured post-transplant. And so although dialysis can serve as a bridge to re-transplantation, morbidity and mortality on dialysis is sequentially higher than with the renal allograft. And although we try to transplant our patients, we know that inevitably, they're going to need to be transplanted again.

Next slide. So in summary, PH1 is an inherited disorder of oxalate overproduction, leads to kidney failure and systemic oxalosis with fatal consequences. It presents early in life but there's often a significant lag between presentation and diagnosis. Clinician ignorance of PH1 complicates its diagnosis and its management. And end-stage kidney disease accelerates its morbidity and mortality. Currently, liver-kidney transplants the best therapy for PH1 patients with ESKD or systemic oxalosis. But we need better therapies and a successful therapy came at preventing abnormal oxalate synthesis and reducing abnormal oxalate accumulation.

Thank you so much.

Pritesh J. Gandhi, Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs & GM of the Lumasiran Program

Thank you, Dr. Somers, for that comprehensive disease overview that was truly instructive, we will have Dr. Summer as part of our Q&A session. Tracy will now describe our clinical development program and detailed efficacy and safety data from our clinical trials. By way of introduction, Tracy McGregor is Senior Director of Clinical Research at Alnylam. She was a contributing author of one of the recently published kidney health initiative manuscript that discussed endpoints for clinical trials in primary hyperoxaluria.

Tracy?

Tracy McGregor,

Thanks, Pritesh. And thanks, again, Dr. Somers, for that wonderful overview. Next slide, please.

The Lumasiran Clinical Development Program started with a Phase I/II dose range finding study that studied healthy adults and PH1 patients with an extension study for the PH1 patients. We then have 3 Phase III studies in PH1 patients to cover the full age and disease spectrum. Today, I'll present data on the 20 patients (inaudible) dosed with lumasiran, who are now in the open-label extension study and from the ILLUMINATE-A study of patients with an eGFR of at least 30 mls per minute and who are 6 years or older. ILLUMINATE-B is a single arm, open-label trial of patients with a similar disease status, but who are younger than 6 years of age. And finally, ILLUMINATE-C is an open-label trial in patients with advanced PH1, including those who may be on hemodialysis, and this study is open to all ages.

Next slide. As Dr. Somers presented, the long-term sequela is primary hyperoxaluria includes renal insufficiency, renal failure and systemic oxalosis. Because this is a rare disease with variable progression, the use of surrogate endpoints for clinical trials would allow for more efficient approval of newly emerging treatment. The kidney health initiative, a joint effort of the American Society of Nephrology and the U.S. Food and Drug Administration accepted a project proposal from the Oxalosis and Hyperoxaluria Foundation to evaluate such endpoints in primary hyperoxaluria. The working group included clinicians, scientists, pharmaceutical companies and representatives from the FDA. We evaluated a number of candidate markers for primary hyperoxaluria and concluded that urinary oxalate is reasonably likely to predict clinical benefit due to its causal role in stone formation and kidney damage in CKD stages 1 through 3a, and plasma oxalate is likely associated with the risk of systemic oxalosis in CKD Stages IIIb through Stage V.

Next slide. In our Phase I/II study as well as in our Phase III trials, we assess urinary oxalate to measure the efficacy of lumasiran. In our early Phase I/II study, we used an enzymatic assay, which is available at multiple clinical laboratories. As urinary oxalate is our primary endpoint in our Phase III studies, we developed a validated liquid chromatography, tandem mass spectrometry assay that meets FDA and EMA regulatory requirement. The 2 methods are highly correlated, as shown in the figure to the right. This plot shows oxalate results from both assays measured in samples taken from the same collection. It can be appreciated that the LC tandem mass spec assay has a slightly higher value than the enzymatic assay, but the percent reduction from baseline was similar with both methods.

Next slide. 20 patients with PH1 enrolled in Part b of the Phase I/II dose range finding study. Eligibility for these patients included ages 6 to 64 years, estimated glomerular filtration rate of at least 45 ml per minute, and urinary oxalate excretion of at least 0.7 millimoles per day when corrected for BSA. All 20 patients completed the study and elected to enroll in the Phase II open-label extension study. All of the patients receiving 1 milligram per kilogram monthly transitioned to 3 milligrams per kilogram quarterly early on in the study. And as of last September, patients been on study for a median of 10.4 months with a range of 7 to 17 months.

Next slide. At enrollment in the extension study, most patients were pediatric with an average age of 16 years, more than half were female, and the mean weight was 50 kilograms. Prior to their first dose of lumasiran in the parent study, patients had an average eGFR of 77.3. Their mean 24-hour urinary oxalate excretion was 1.69 millimoles per day, when corrected for BSA, which is about 4x the upper limit of normal. And their mean 24-hour urinary oxalate to creatinine ratio was 0.17 milligrams to milligram, which is also about 4x the upper limit of normal. Almost all patients had a history of renal stones, with 6 of the 20 patients reporting a renal stone in the 1-year prior to enrolling in the Phase I/II study.

Next slide. The safety profile of the open-label extension study has been encouraging. All 20 patients remain on study, 1 patient-reported 2 serious adverse events associated with a car accident. The majority of adverse events were mild in severity and determined to be unrelated to lumasiran by the study investigator. The most common adverse events were injection site reactions, headache, ora fringe pain, gastroenteritis, pyrexia and vomiting. The injection site reactions, reported in 4 patients, were all mild and assessed as related to lumasiran treatment. No clinically significant laboratory changes have been observed.

Next slide. This figure shows the urinary oxalate suppression for the patients enrolled in the open-label extension study. The first point represents the baseline value prior to the first dose of lumasiran in the Phase I/II study, and all of the remaining points are from the open-label extension study. The mean maximal reduction in urinary oxalate was

76%. All patients have achieved a urinary oxalate excretion below 1.5x the upper limit of normal and 68% have had at least 1 urinary oxalate level within the normal range. The patients receiving 3 milligrams per kilogram monthly had a similar urinary oxide suppression as those receiving 1 milligram per kilogram monthly or 3 milligrams per kilogram every 3 months.

Next slide. A post-hoc analysis was conducted to evaluate the trends for renal stones over time. While renal stones are an efficacy outcome for our Phase III studies, this was not a prespecified endpoint in our early studies. Upon entry to the Phase I/II study, 6 of the 20 patients reported a total of 9 renal stone events over the prior year. During dosing in the Phase I/II study, 4 patients collectively had 7 adverse events of renal stones with a total exposure of 7.8 patient years. After enrolling in the Phase II open-label extension study, no renal stone adverse events have been reported over the 18.7 patient years of exposure.

Next slide. ILLUMINATE-A is our Phase III study of lumasiran in patients with PH1, who are at least 6 years old with the urinary oxalate excretion of at least 0.7 millimoles per day when corrected for BSA, and an estimated glomerular filtration rate of at least 30 ml per minute. Eligible patients were randomized 2:1, lumasiran or placebo. They were administered 3 milligrams per kilogram loading doses for 3 months, followed by 3 milligram per kilogram maintenance dosing every 3 months. The primary endpoint was the percent change in urinary oxalate excretion from baseline, which is the percent change from baseline to the average across months 3 through 6. Patients then continue on study in an extension phase for long-term dosing. Full results from this study were presented this past June, and I'll review them with you today. The NDA and MAA are currently under review, as Pritesh mentioned, with a PDUFA action date in December of this year.

Next slide. The baseline clinical characteristics of both arms are presented here. Overall, patients had a mean 24-hour urinary oxalate excretion of 1.82 millimoles per day corrected for BSA. The mean oxalate to creatinine ratio was also elevated at 0.218 millimoles per millimole and mean plasm oxalate of 15 micromoles per liter.

We enrolled patients with various stages of renal impairment, nearly half had mild impairment and almost 20% with various stages of moderate renal impairment. Overall, the mean eGFR was 81.6%. Just over half the patients were on pyridoxine therapy at study entry, and this treatment was continued during the placebo-controlled period. 3 quarters had baseline nephrocalcinosis by renal ultrasound. The majority had at least 1 renal stone previously and almost 40% had a renal stone in the prior year.

Next slide. Lumasiran continued to have a favorable safety profile during the double-blind period of Illuminate-A. There were no deaths, serious adverse events or severe adverse events. All adverse events, thus were mild or moderate in severity, and the most common adverse events are listed in the table on the right. These included injection site reactions, headache, rhinitis and upper respiratory infection. The injection site reactions were transient and mild in severity, none led the treatment interruption or discontinuation. There were no hepatic adverse events in either group and no clinically relevant changes in laboratory measures, vital signs or electrocardiograms related to lumasiran treatment.

Next slide. The primary endpoint in this study was the percent change in 24-hour urinary oxalate from baseline to month 6. When averaged over month 3 through 6, the lumasiran group had a decrease of 65.4%, while the placebo group had a decrease of 11.8% for a difference of 53.5%. This was highly statistically significant with a p-value of 1.7x10^-14.

In this figure, the placebo group is shown in the purple line on the top and the lumasiran group is shown as the blue line on the bottom. The rapid and sustained reduction in the lumasiran arm can be appreciated.

Next slide. This forest plot indicates the results of the subgroup analysis conducted for the primary endpoint. All of the subgroups analyzed, including demographic parameters, baseline urinary oxalate excretion, pyridoxine use and renal function, all favored lumasiran treatment over placebo.

Next slide. ILLUMINATE-A also met all of the secondary endpoints. These included additional measures of urinary oxalate as well as plasma oxalate assessments. Importantly, 84% of patients on lumasiran therapy reached a urinary oxalate level at month 6 that was below 1.5x the upper limit of normal compared to none in the placebo group. Additionally, 52% in the lumasiran group had a level that was within the normal range at this time point. Renal function was stable in both groups, but since it's a long-term clinical endpoint, it was not evaluated with formal statistics during the primary analysis period.

Next slide. Additional long-term clinical endpoints in the ILLUMINATE-A study includes renal stone event and nephrocalcinosis. For renal stone events, the number of patients who had renal stone events prior to the study and on study were similar during the first 6 months of the study as expected. Ultrasound grading of nephrocalcinosis showed that 3 patients in the lumasiran group had unilateral or bilateral improvement, while one patient in the placebo group had unilateral worsening. These are encouraging early observations, and we look forward to additional data from the extension period of this study.

Next slide. Moving on to our other Phase III trials. ILLUMINATE-B is an open-label, single-arm study in patients with PH1, who are similar in disease to the ILLUMINATE-A population but are under 6 years of age. This study also has a primary endpoint of urinary oxalate reduction after 6 months of treatment, and patients then continue into an extension period for continued dosing. Top line results from the primary analysis period are expected soon.

Next slide. ILLUMINATE-C is an open-label study to evaluate the efficacy and safety of lumasiran in patients of all ages with advanced PH1. Eligibility criteria include an elevated plasma oxalate level and an eGFR below 45. Patients are evaluated in 2 cohorts: cohort A, those not yet requiring dialysis therapy; and cohort B, are the patients already being treated with dialysis. The primary endpoint is the percent change in plasma oxalate from baseline to month 6. Again, patients will enter an extension period of the study where plasma oxalate will continue to be monitored. Additionally, features a systemic oxalosis will be assessed throughout the study. This study is actively enrolling, and the top line results are expected next year.

With that, I'd like to turn it back over to Pritesh, and thank you for the attention.

Pritesh J. Gandhi, Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs & GM of the Lumasiran Program

Thank you so much, Tracy. We really appreciate it.

Results from the ILLUMINATE-A study signals hope for patients and families who we believe may substantially benefit from lumasiran in the future, assuming regulatory approval. Let us now turn to the program opportunity and commercial preparedness.

Next slide, please. As we do in our other programs, we are now sharpening our pencils on the prevalence of patients with active and diagnosed disease where lumasiran could be a treatment option. Based on the literature, and analysis of publicly available genetic databases, the prevalence of individuals with AGXT mutations is estimated to be 4.3 per million. Approximately, 3.50 to 4 per million or an estimated 2,900 to 3,400 patients will potentially be presymptomatic or have subclinical or clinical manifestations of PH1. These include hyperoxaluria, network calcinosis, recurring stone events, renal sufficiency, systemic oxalosis or have already undergone transplantation.

As with most rare diseases, there is a delay in definitive diagnosis. And based on the literature, approximately half of the symptomatic patients are diagnosed, resulting in a diagnosed prevalence of 1.50 to 2.5 per million or approximately 1,300 to 2,100 patients. Some of the diagnosed patients have already undergone liver transplantation. Therefore, there are approximately 1.2 to 2 per million or about 1,000 to 1,700 patients that are diagnosed and need urgent medical or surgical intervention. Of course, as we bring a potentially meaningful medicine forward for patients, we continue our disease education efforts and expand our global commercial presence and infrastructure, there is an opportunity for growth to discover new patients.

Next slide, please. With regard to the market opportunity for lumasiran, as you know, PH1 is an ultra-rare disease. In clinical practice, PH1 has a low index of suspicion with many patients, we believe as many as 50%, remaining undiagnosed. Patient diagnosis can often occur later in the course of the disease. In adult patients specifically, there is a median delay of approximately 6 years between onset of clinical manifestations and definitive diagnosis. And as Dr. Somers mentioned, up to 2/3 of the patients will receive their diagnosis after reaching end-stage kidney disease. This truly highlights the tremendous disease burden, suffering and associated economic impact to the overall health care system.

With progression of disease and as the kidneys begin to fail, intensive dialysis up to 6 days of the week is needed as a bridge to a dual liver kidney transplant, with the average cost of transplantation and accompanying lifelong immunosuppression, exceeding $1 million. Thus, there is an urgent unmet need for alternative treatment options that adequately reduce oxalate production at its source, preserve kidney function and have the potential to change the natural course of the disease.

Based on the data from ILLUMINATE-A, we believe that lumasiran has the potential to be a first-in-class, best-in-class medicine that substantially curbs the production of oxalate, the insoluble toxic metabolite responsible for the clinical manifestations of PH1 and has the potential to have a favorable impact on kidney function and disease progression. With our comprehensive clinical development strategy, we hope to make lumasiran available to all patients across the spectrum of PH1 regardless of age and regardless of disease severity.

Given the epidemiology of the disease, lack of approved therapies and Alnylam's approach towards disease education, we view the market opportunity to be over $500 million, representing the potential for a new and significant revenue source to Alnylam.

Next slide, please. As we prepare for the potential commercial launch of our third wholly-owned RNAi therapeutic, we are working on a number of initiatives to enhance disease education and awareness, leading to earlier diagnosis and improved diagnosis rates, focusing on disease education for both pediatric and adult urology and nephrology specialties. On that front, we are continuing to leverage our health care professional facing disease state awareness campaign referred to as Behind The Stone. This campaign urges physicians and health care professionals to look

beyond acute stone events and provides tools and resources, including aboutph1.com, a disease education website that details the web slides of the disease, highlights its unpredictable rate of progression and navigates the path to an accurate diagnosis.

An important goal of this campaign is to increase suspicion of PH1 in any pediatric patient who presents with even a single kidney stone or any adult patient with recurring stone events and to include PH1 as part of the differential diagnosis. This should then prompt genetic screening to help confirm or rule out a diagnosis. This campaign also emphasizes the importance of early intervention and disease management, given the devastating consequences of progressive renal dysfunction. To that end, we are working to ensure tools exist to accelerate the time to an accurate diagnosis.

Lastly, in partnership with the Oxalosis and Hyperoxaluria Foundation, or the OHF, we have developed PH1 of a kind video animation series, designed for children living with PH1 and their caregivers. With many patients diagnosed in early childhood, this award-winning video series fills a significant gap in educational content for young patients and their families and continues to demonstrate Alnylam's commitment to the needs of the community.

Next slide. In terms of upcoming milestones, we are on track to report top line data from ILLUMINATE-B. And at Alnylam, this means Q2, Q3 of this year and potential approval of lumasiran by year-end. We are very excited to launch lumasiran at the end of this year and bring forward a medicine that will positively impact the lives of patients and caregivers.

Thank you for attending, and now we will go to the questions.

QUESTIONS AND ANSWERS

Answer – Pritesh J. Gandhi: The first question is for Tracy McGregor. Tracy, can you describe in terms of the baseline demographics of patients and load in ILLUMINATE-A, what their genetics were in terms of the specific mutations? And what proportion of them were pyridoxine or Vitamin B6-sensitive?

Answer – Tracy McGregor: Sure. So just as a reminder, in ILLUMINAtE-A at baseline, 9 of the 13 placebo patients and 13 of the 26 lumasiran patients were taking pyridoxine. We do know the genetics, patients either had genetics coming into the study or they were genetically tested as part of the eligibility criteria. Not all of the patients on pyridoxine had the classic G170R mutation. So clinically, patients are tried on the pyridoxine if they could potentially have a response. And if there's observation of a response, these patients are continued on therapy.

During the double-blind, placebo-controlled period, all the patients who entered the study with pyridoxine were instructed to continue pyridoxine. And those not on pyridoxine were instructed not to start pyridoxine to remove confounding to the primary endpoint. And then in the subgroup analysis, it showed that both groups, those who started the trial on pyridoxine and those who were not on pyridoxine at the start of the trial, both experienced clinically meaningful declines in their urinary oxalate levels.

Answer – Pritesh J. Gandhi: The next question is for Dr. Somers. Dr. Somers, based on your presentation and your clinical experience, how do you associate oxalate levels in the urine and renal stone events and nephrocalcinosis and the impact of quality of life across the entire PH1 disease spectrum?

Answer – Michael Somers: Yes. So certainly, the more oxalate you have in your urine, the more likely you are to have precipitation of the oxalate to form kidney stones or nephrocalcinosis. So it's very much linked together and this is the whole reason why the individuals with hyperoxaluria have such issues with nephrolithiasis and nephrocalcinosis. I can't underscore how horrible it is for their quality of life to have all of these urinary tract events going on. And many of the patients I take care of with PH1, they can never remember a time when they're not in some sort of pain from stones or several weeks going by without them having some urgent medical visit related to their stones. So finding a way to decrease levels of nephrolithiasis and nephrocalcinosis can make a remarkable difference in individual's quality of life.

Answer – Pritesh J. Gandhi: The next question is, how do we think about GO and how does it compare to LDHA as a target?

Let me take that question. Both GO and LDHA are viable targets to decrease oxalate. We at Alnylam studied both and elected to focus on GO because of the uncertain potentially long-term impacts of LDHA. We wanted to exquisitely develop a drug that is going to be specific for PH1, and that's why we selected a target that was working upstream in the metabolic defect or pathway and that's why we selected to go with GO as the target and pursue lumasiran for patients with PH1.

Let me ask the next question to Dr. Somers. What could help improve the time to accurate diagnosis?

Answer – Michael Somers: I think what can improve the time to accurate diagnosis is really increasing clinician education about PH1, how these individuals present. The data I shared with you showed that many of these patients

have had their symptoms for some period of time before they actually get diagnosed. And oftentimes, in the world of pediatrics, there are a limited number of pediatric specialists. So there limited pediatric nephrologists or pediatric urologists who may think of inborn errors of metabolism, quicker than adult clinicians who are dealing with larger numbers of more run of the mill reasons for kidney stones or potentially even calcifications in the kidney.

So I think increasing education makes huge, huge sort of difference. Also, making sure that the diagnostic evaluation is easy to do. And I think that can be part and parcel education in terms of telling people or teaching people what's involved urine collections or genetic testing. But if someone knows how to do it, they're more likely to do it, especially if they know that think about the clinical entity is being top on the list of a differential given certain clinical situations.

Answer – Pritesh J. Gandhi: Thank you. The next question is for Tracy. Tracy, do you expect to see similar decreases in renal stone events and ILLUMINATE-A that are rolling over into the open-label extension study?

Answer – Tracy McGregor: So the reduction of the 24-hour urinary oxalate that we've seen in ILLUMINATE-A is very similar to what we saw in the patients in the Phase II open-label extension study. I presented the data of what happened with the patients historically and then during initial dosing. And it was when they got to that long-term open-label extension study that we saw the lack of reported adverse events in renal stones. However, in ILLUMINATE-A, these are the data from the first 6 months, and we await additional information from the urinary -- sorry, the renal stone events over time. This is a prespecified endpoint in our trial, and we'll be reporting this out with the extension phase of the study.

Answer – Pritesh J. Gandhi: Thanks, Tracy. The next question is that is there a consideration for studying lumasiran for PH2 and 3 in the future?

As I mentioned, lumasiran is exclusively developed for patients with PH1. Of course, there's an unmet medical need for patients with PH2 and PH3 as well. But the burden of illness for PH1, of course, is pretty high, as we have seen today from the comprehensive disease overview that Dr. Somers has provided. And so we wanted to, in essence, really develop a drug that was specific for PH1, and that's why targeted glycolate oxidase or GO.

The next question is for Dr. Somers. Dr. Somers, in your experience, what are the possible drivers of variability in terms of disease manifestation and clinical presentation for patients with PH1?

Answer – Michael Somers: Yes. The drivers of variation, so they can vary. Certainly, the underlying genetic mutation, as we alluded to, so if someone has a mutation that is amenable to pyridoxine therapy, and especially if you're a particularly lucky individual that pyridoxine can blunt your oxalate production so significantly that you can have few oxalate-mediated supply going forward, then this is of prime import.

Where the delay to diagnosis though often is pretty key because that will often change where your GFR is, where you first manifest. And as I alluded to in my presentation, as your GFR falls, as you have more systemic oxalate deposition, then you have extra renal injury happening. And certainly, this complicate your medical management and complicates your long term outcome.

Answer – Pritesh J. Gandhi: Thank you, Dr. Somers. The next question is, do you plan to provide periodic data updates for ILLUMINATE-B, considering it's an open-label study or wait until top line results once the study has been completed?

Let me take that question. We will plan to report the top line results from ILLUMINATE-B in the middle of 2020, as I mentioned. And with Alnylam Lexicon terminology, mid-2020, for us means Q2, Q3 of this year. And the study incorporates a long-term extension period, and we'll plan to provide periodic updates over the course of the study.

I believe that was the last question that we had in the Q, I guess we can go to the next slide. In terms of the upcoming RNAi roundtable that I think that we're also on the top of the hour, so we should probably go to the upcoming RNAi roundtable. And of course, we are very excited about lumarisan, and we have an upcoming RNAi roundtable for patisiran and vutrisiran in development for treatment of ATTR amyloidosis. This will happen on Thursday, September 3, at 11 a.m. Eastern Daylight Time. And then in September, again, we have givosiran RNAi roundtable for the treatment of acute hepatic porphyria, and that's on Monday, September 14.

So with that, I'm going to conclude and let me end the call by saying thank you to everybody for joining us today. We are very excited with our progress to date. And we now look forward to a collaborative review process with the regulatory body and are excited by the prospect of this investigational medicine, lumasiran, having a meaningful impact on patients and families living with PH1.

Please be safe and stay healthy. Thank you very much.
