10-Oct-2019

Alnylam Pharmaceuticals, Inc. (ALNY)

Investor Meeting - Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

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MANAGEMENT DISCUSSION SECTION

Operator: Good day and welcome to the Alnylam Pharmaceuticals RNAi Roundtable. Today's conference is being recorded. At this time I would like to turn the conference over to Mr. Josh Brodsky Director of Investor Relations and Corporate Communications. Please go ahead, sir.

Joshua Brodsky

Director-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Good morning, everyone. Thank you for joining us for today's 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; Dr. Kenji Fujita, Vice President of Clinical Development; Dr. Elaine Worcester of the University of Chicago; and Andrew, a patient diagnosed with PH 1, who is joining us along with his wife and caregiver, Nicole.

Today's RNAi Roundtable is part of a series of roundtables that we are hosting this year. Today's event is expected to run for 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 and we encourage you to read our most recent SEC filings for a more complete discussion of risk factors.

And so with that, I'll now turn it over to Pritesh.

Pritesh Gandhi

Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

Thank you, Josh, and hello to all of our listeners.

I will provide a brief overview of Alnylam and then pass the presentation to Dr. Worcester. For well over a decade, Alnylam has focused its efforts on our Nobel Prize-winning technology of RNA interference therapeutics. This new class of innovative medicines can essentially silence any gene in the genome via a natural mechanism. We've consistently demonstrated potent and durable reduction of disease causing proteins or toxic metabolites across our sustainable pipeline.

Our pipeline is focused on four strategic therapeutic areas. These four strategic therapeutic areas include genetic medicines, cardio-metabolic diseases, hepatic infectious diseases, and CNS and ocular disease. We are going to focus our discussion today on one of our genetic investigational medicines, lumasiran, currently in late stage clinical development for the treatment of primary hyperoxaluria type 1 or PH1. Lumasiran has achieved Breakthrough Designation from the FDA and PRIME designation from the EMA.

From a disease background perspective, PH1 is a rare autosomal recessive disease that is characterized by pathological overproduction of oxalate by the liver. Oxalate combines with calcium to form calcium oxalate crystals leading to urolithiasis, nephrocalcinosis and kidney failure. Once patients experience renal insufficiency, the calcium oxalate crystals will deposit in other tissues resulting in systemic oxalosis. Specifically, they can deposit in the eye resulting in potential vision loss, they can deposit in the heart potential resulting in cardiomyopathy and/or arrhythmias, and they can also deposit in the bone resulting in pathologic and painful fractures.

The diagnosed prevalence of PH1 is noted to be about 1 per million to about 3 per million in North America and Europe. The disease is more prevalent in areas [indiscernible] (00:03:41) mutations especially in the Middle East and North Africa. Presently, there are no approved therapies for the treatment of PH1.

With that background, I'm delighted to introduce you to Dr. Elaine Worcester. Dr. Worcester received her undergraduate degree from Augustana College and her medical degree from the University of Illinois. She completed a residency in Internal Medicine at Loyola University Medical Center and a nephrology fellowship at the University of Chicago where she has worked extensively on calcium oxalate crystallization. Currently, she's Professor of Medicine in the Section of Nephrology at the University of Chicago and is also on the Scientific Advisory Council of the Oxalosis and Hyperoxaluria Foundation or the OHF. Dr. Worcester?

Elaine M. Worcester

Nephrologist & Professor of Medicine, University of Chicago Medicine

Thank you very much, Pritesh. I'd like today to talk a little bit more about primary hyperoxaluria. Next slide, please, with the figure.

So primary hyperoxaluria, as you have heard, is a disease that primarily affects the liver. There are two ways for oxalate to get into the body. One is through the food that we eat and that accounts for a modest amount of oxalate absorption. The other is from production in the liver and normally that is a very modest amount. Both sources of oxalate eventually wind up in the bloodstream and are filtered by the kidney. Oxalate doesn't have any function in the body and it can't be broken down; so it's only fate is to get excreted by the kidney.

Under normal circumstances, this can happen safely, but in the case of primary hyperoxaluria, so much oxalate is produced that it tends to crystallize in the form of calcium oxalate crystals and this can cause kidney stones, which are very painful and will eventually pass, and it could also occur in the tissue itself where crystals form in the tubules and in the tissue and this is called nephrocalcinosis; and this is very, very damaging to the kidney and can lead to kidney failure. Next slide, please.

There are actually three kinds of primary hyperoxaluria and each of them is due to a mutation in an enzyme in the liver that leads to increased oxalate production. Primary hyperoxaluria type 1 is the most common and accounts for about 80% of cases. And this is due to decrease – it's either absence or decreased activity of AGT, alanine-glyoxylate aminotransferase. So AGT is found in the peroxisome and it normally converts glyoxylate to glycine,

which is very soluble. But when this enzyme has mutated, glyoxylate builds up and eventually it will follow another pathway to production of oxalate.

PH2 accounts for about 10% of cases of primary hyperoxaluria. And this is caused by mutation of a second enzyme, GRHPR, glyoxylate reductase/hydroxypyruvate reductase. And again, this mutates a gene that would normally convert glyoxylate to glycolate, which again is quite soluble. But in the absence of this activity, the glyoxylate builds up and again tends to convert to oxalate, which has to be excreted by the kidney.

The final form of PH3 is due to mutation of HOGA, 4-hydroxy-2-oxoglutarate aldolase. And this again leads to increased production of oxalate. Next slide, please.

The prevalence of primary hyperoxaluria, as you heard, is about 1 to 3 cases per 1 million people. So it's a very rare disease prevalent in the United States is not accurately known. But our data of primary hyperoxaluria is largely due to two large consortia. In the United States, it's the Rare Kidney Stone Consortium and in Europe it's OxalEurope; and so a lot of the data I'm going to be sharing with you today comes from these two groups.

The prevalence for our primary hyperoxaluria type 1 is increased in countries that have high rates of consanguineous marriages such as in the Middle East, Pakistan and North Africa. And to give you some idea, primary hyperoxaluria type 1 is thought to cause about 1% to 2% of end-stage renal disease in children in Europe and in the United States. But in Tunisia, it causes 17% of end-stage renal failure in children. So that gives you some idea of how much more common it is there. Next slide, please.

People with primary hyperoxaluria type 1 tend to progress through several stages of the disease. Under normal circumstances, as we said, oxalate will be excreted in the kidney without any complications or symptom. But in people with primary hyperoxaluria, the oxalate can build up in the kidney in the form of crystals in the tissue or as kidney stones, and these crystals eventually cause damage to the kidney, and you gradually lose kidney function.

We grade kidney function on a scale of 1 to 5, 1 being the mildest and 5 being the most severe, which usually requires dialysis. So as the kidney failure progresses, gradually the kidney is not able to excrete the daily production of oxalate. And at that point, oxalate begins to build up in the blood and eventually the kidney completely fails requiring dialysis, and oxalate in the blood can now deposit in many tissues as Pritesh said. Next slide, please.

So primary hyperoxaluria is actually can be caused by many different mutations. There are thought to be at least 178 different mutations that can result in primary hyperoxaluria, but they don't all cause the same type of damage to the enzyme. In some cases, the enzyme is completely absent. In other cases, it's prevalent, but it's mistargeted to the wrong part of the cell. And in some cases, there's at least partial enzyme activity. And this might be at least somewhat the reason that the presentation for primary hyperoxaluria can be so variable and there are thought to be perhaps five general presentations for PH1 now; and in fact, that would probably be true for all forms of primary hyperoxaluria.

In some cases, the disease presents very early in life, in infancy, in children under the age of one year who [ph] can present (00:11:04) with kidney stone or who may present with less easily diagnosed symptoms like failure to thrive, urinary tract infection, abdominal pain, and in these children, can quickly develop nephrocalcinosis or deposition of crystals in their kidneys, and they may wind up with kidney failure as early as ages two to three.

Then, there are children – probably a more common pattern is children who begin forming kidney stones at an early age and form kidney stones throughout childhood. And in those cases, they develop chronic kidney disease and may progress to dialysis at a somewhat later age in the adolescence or early adulthood.

Some people actually don't begin forming stones until later in life, until adolescence or adulthood, and they may progress to kidney failure more slowly, in later adulthood. In some cases, the diagnosis of primary hyperoxaluria is not made when the person presents with kidney failure. The kidney failure is not realized to be due to primary hyperoxaluria and it's only after they get a transplant and then the transplant fails because of oxalate deposition that the diagnosis is made.

And finally, in the current era, there were now people who are [ph] being made – (00:12:28) the diagnosis being made, because of screening of family members, asymptomatic relatives of people with PH1 will be identified because of genetic screening. And this is optimal, because it allows early treatment. The figure here is from OxalEurope and it shows you the relative ages at which first symptoms occur. The front row of blue bars shows you the percentage of people who presented various ages. And it's also interesting looking at the orange bars that diagnosis is often delayed even when symptoms are present. The appropriate diagnosis may not be made until several years later. And you can also see that there are some people in whom symptoms only appear later in life in adulthood. The same pattern is generally true for PH2. And so this variation in presentation may be due to the type of gene mutation. And there may also be other disease modifying genes that are not yet identified that may also affect how PH1 manifests in certain people. Next slide, please.

Here you see an example of how variable the urine oxalate excretion can be in people with primary hyperoxaluria type 1. In this figure, these are 27 different patients, each of whom collected four 24-hour urine, and what you're seeing is the mean for each person and the bar show you the standard deviation around that mean. And the triangle show people who have a specific type of mutation that makes the patient responsive to pyridoxine. In these patients, administration of vitamin B6 or pyridoxine can greatly improve the function of the enzyme and so urine oxalate excretion will drop. And so you can see that in these people with the triangle, the urine oxalate excretion are somewhat lower. The open squares are people who do not have a pyridoxine-sensitive mutation and you can see that their oxalates are higher, but you can see the enormous variability of oxalate excretion from about 0.75 millimole up to over 3 millimole. I should say that normal would be less than 0.5 millimole per day. Next slide, please.

This slide again shows, to some extent, the variability in oxalate excretion. You can see here that these bars, the dot is the mean excretion for the groups, for example PH1, PH2 and PH3 patient, and the line is the median. And you can see that the box for PH1 is much larger than any of the other, which gives you some idea of how variable the excretion of oxalate can be in this particular disease as compared to PH2 and PH3. And also that excretion tends to be somewhat higher in PH1 than in the other two forms of primary hyperoxaluria. Next slide, please.

The data here is from OxalEurope and, in general, the most common presenting symptom for any form of primary hyperoxaluria is kidney stones. You can see the blue bar is PH1, red bar is PH2, and the green bar is PH3; and for all three, kidney stones would be the most common presentation. Unfortunately, kidney stones are very, very common in America, in Europe and in other parts of the world. And so, by far, the majority of people who make kidney stones will not have PH1. And so passage to a kidney stone may not be seen as an event that could be linked to this dangerous disease but may be thought of as simply a more common ordinary occurrence.

You can see that people can also present with nephrocalcinosis, which is crystallization in the kidney tissue. And the figure above the nephrocalcinosis bar is actually an ultrasound and what you see is the white densities are reflecting crystallization deposition in the kidney.

You can also see that in PH1, a very large number of people actually present with end-stage renal failure, meaning that the first time the diagnosis is made is when the person presents with kidneys that have permanently failed. In this disease, about 34% of people below the age of 18 year old will present with kidney failure as their first manifestation of this disease. And over the age of 18 years, up to 74% will present with kidney failure as their very first symptom.

One example would be this person. This is a 25-year-old man and he was healthy. [ph] And he had (00:17:55) normal kidney function three months prior to this event and had been engaged in very strenuous exercise and was found to have what was thought to be acute kidney failure. He had no clinical history of any stone. What you see here is a CT scan and what it shows is that the kidneys have these bright white deposits. Though that's mineral, that's calcium oxalate that's been deposited in the kidney leading to kidney failure. You can also see in the left kidney a very large stone that is just leaving the kidney and which was probably silent prior to this diagnosis. On the right, you see the kidney biopsy that was done and the little bright speckles are all the deposits of calcium oxalate in the tissue. And so this young man is now going to have to go on dialysis and get a kidney transplant after this presentation. Next slide, please.

So the most feared complication of primary hyperoxaluria obviously is end-stage renal failure. And this is data taken from the American Rare Kidney Stone Consortium and they have records for 409 patients with primary hyperoxaluria, 73% of them with PH1. And among those patients, 112 presented with end-stage renal failure including 35% of the PH1 patients. And of those who presented with still functioning kidneys, you can see what happened. On the left, you can see how many went into renal failure over the next 30 years; and by 30 years out over a 50% had reached dialysis. But on the right, you can see how different the outcome is for those with PH1 compared to PH2 or PH3. You can see that many more people with PH1 wind up on dialysis compared to the other two forms of primary hyperoxaluria. Next slide, please.

And it appears that the prognosis for renal failure is very much connected to how much oxalate is being excreted every day. And we saw the oxalate burden can vary dramatically from one person to another. And this shows the number of patients who went on to require dialysis; and it groups them by the amount of oxalate they were excreting per day. And you can see that in those who were excreting under 1.6 millimole of oxalate per day, their risk of dialysis was actually very low; whereas the more oxalate that needed to be excreted; the higher the risk of dialysis. And in those who are putting out more than 2.4 millimoles per day, almost all of them eventually required dialysis. And mortality is much higher in those patients who require dialysis than in others. Next slide, please.

This is data from OxalEurope. And on the left, you can see patient survival in that cohort of 526 patients. And on the right, you see the progression to end-stage renal failure over ages 0 to 70, but they've broken it out by the type of mutation, the commonest mutation. And what you see is that in the brown line, the arrow is pointing to it, are those people who have mutations in the G170AR allele and this is one of the alleles that means that the patient will be sensitive to pyridoxine, in which treatment with B6 can improve urine oxalate. And people with at least one allele, which was a G170R mutation, do better than those with any of the other mutations. If you've got at least one G170R allele, your prognosis is better than if you have any other type of mutation. Next slide, please.

When people are close to or at the point of needing dialysis, they're also at risk of developing oxalosis. And that is when actually oxalate begins to deposit in other organs. And the kidney is the organ most frequently involved, in fact, always involved; there will always be calcifications in the kidney with primary hyperoxaluria, but other organs can be involved including the bones where, if they're children, they may grow poorly and they can have painful bones and bones that fracture easily. They can deposit in the eyes and lead to vision loss. They can deposit in various arteries, which will then cause decreased blood flow to the hands and feet for example. It can deposit in

the heart and lead to heart failure; and it can also cause abnormal heart rhythm, which can lead to cardiac arrest and sudden death. But essentially, almost any organ in the body can be involved.

This is what involvement of the kidney looks like. What you're seeing here is a kidney that was removed from a patient with PH1 and it was removed at the time of kidney transplant. And this is a CT scan of that removed kidney and you see many forms of calcifications. The very bright dense calcifications are kidney stone. The more speckled calcifications that are marked by double white arrows, this is nephrocalcinosis. This is deposition of calcium oxalate in the papillae of the kidney. But you also see, surrounding it, sort of a halo of sort of grey and that's calcification in almost all of the kidney.

Just to fill in the detail, this is a 56-year-old man. He had his first kidney stone at age 37, but he wasn't diagnosed with PH1 until age 47, and he went on dialysis at age 56. He had a history of about 20 stone. The lower panel is showing you a progression of the calcification over three years in a 34-year-old woman with PH1. On the left, you can see that one kidney has a lot of dense calcification and kidney stones, whereas the other kidney is very minimally involved. But over the next two to three years, you can see progression where increasing amounts of calcium are deposited and eventually the kidneys become very small and almost entirely filled with crystals. Next slide, please.

Other organs that can be involved, you can see here an X-ray. These are two X-rays, one from a three-year-old child. The femur looks almost normal; well, not really normal, but there is no break on the left hand. But on the right hand panel, three days later with minimal trauma, there is a hip fracture in this three-year-old child. The other picture, the CT scan of the heart shows deposits of calcium oxalate in the heart muscle and this really affects the ability of the heart muscle to function properly. And at the bottom you can see gangrene in the fingers of a woman with PH1 because of decreased blood flow to the fingers because of the deposits in the artery. Next slide, please.

This is a slide that shows the typical diagnostic procedure for people with primary hyperoxaluria. If primary hyperoxaluria should be suspected in people who have stones or nephrocalcinosis in childhood and also in people who have recurrent [ph] ca-ox (00:26:17) stones or nephrocalcinosis in adulthood or who have a family history of primary hyperoxaluria; and typically, the diagnosis is made when a 24-hour urine shows an elevated urine oxalate.

There are a few other causes for elevated urine oxalate that needs to be ruled out, mostly GI diseases and malabsorption, which can usually be done by history. And in some cases, you can assay for urine glycolate or L-glycerate which will be elevated in PH1 or PH2. If patients are suspected to have PH1 or PH2 or PH3, the next step would be genetic testing to confirm the diagnosis and the type of PH that they have. And in some cases, liver biopsy may be needed to look for enzyme activity. However, in these days with good genetic testing, that's not usually required.

The complication can come when people present with chronic kidney disease because at that point, urine oxalate may not be severely elevated. The kidney is no longer able to excrete the load of oxalate and so urine oxalate may not be a good diagnostic test. And in that case, you may need do plasma oxalate and see how elevated that is. Next slide, please.

This is the slide showing plasma oxalate levels in patients with primary hyperoxaluria in the blue dots. And people who had kidney stones from other causes in the gray squares or yellow triangles and in people who had no kidney stones at all. And you can see that in all blue, as the eGFR gets lower, which means that as kidney function gets poorer and poorer, the blood oxalate level will increase. But at any level of kidney function, the blood

oxalate will be much higher in the people with primary hyperoxaluria. And this, of course, is why they are so prone to getting oxalosis.

And on the small inset on the right, you can see the effect of dialysis on serum oxalate. Dialysis will remove serum oxalate. The two left panels are pre- and post-dialysis in people with renal failure from other causes. And the right is people with primary hyperoxaluria. You can remove oxalate with dialysis but unfortunately the removal is not adequate, and so these patients need much more intensive dialysis to keep them from building up a lot of oxalate levels in oxalosis and they should be transplanted as soon as possible.

The current treatment for these patients if they are detected early is primarily very good hydration to achieve fluid intake that will keep the oxalate in solution and minimize the deposition in tissue or kidney stone formation and to avoid any situation where they would get volume depleted; very prompt treatment for vomiting or diarrhea, avoidance of dehydration. Crystallization inhibitors can also be helpful including citrate and orthophosphate. These can somewhat prevent calcium oxalate crystals from forming. And pyridoxine is helpful in patients who have the type of mutations where pyridoxine maybe helpful and the trial of pyridoxine is often recommended.

In terms of patients who need stone removal, we recommend that they have endoscopic techniques as opposed to open surgery or lithotripsy, extracorporeal lithotripsy, which can cause real damage. We really want to minimize anything that could cause further damage to the kidney. But at the point where renal failure occurred, the patients need dialysis and then they need transplant. And the typical treatment for primary hyperoxaluria type 1 currently would be a combined liver-kidney transplant. You need to replace the kidney, but you also replace the liver, so that the patients now have a normal enzyme. The liver will work fine in every other respect, but if you don't replace the liver, the transplanted kidney is vulnerable to oxalate deposition. Last slide, please.

So currently, we have so many problems in treating our patients. First of all to improve awareness of primary hyperoxaluria, so that patients are detected early enough to allow treatment; although treatment that's currently available is not curative, it can delay onset of renal failure and improve prognosis. We also need to make sure that our patients are getting appropriate management so that they have a better long-term outcome. But we certainly need many better treatments to prevent renal failure and to avoid systemic oxalosis, so that we can give our patients a future without dialysis.

Thank you very much.

Pritesh Gandhi

Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

Thank you, Dr. Worcester for that very instructive presentation that demonstrates the heterogeneity in clinical presentation of patients with PH1 and the unpredictable rate of progression of the disease that requires aggressive management.

Next, we have the opportunity to hear from Andrew, who was diagnosed with PH1 at the age of 37, and his wife and caregiver, Nicole. Andrew and Nicole?

Unverified Participant

How are you doing?

Unverified Participant

Thank you for having us and given us the chance to share Andrew's story. Since Andrew was diagnosed as an adult, we've shared this journey together along with our two children, [indiscernible] (00:32:21), age seven, and [ph] Sophia (00:32:21), age four. Andrew was diagnosed with PH1 at the age of 37 as previously stated. And with his late onset of the disease, we wanted to take this time to share some unique challenges and experiences that he's had during his journey with PH1.

Unverified Participant

Growing up, I was pretty healthy most of my life, played several sports, and I never had any issues with any stones or any pain or anything like that. Then at age 30, I was diagnosed with gout and that was kind of the precursor to everything. And several months later, I had my first kidney stone event where I had to be admitted to the ER and had to have the stone surgically removed. And then they blame that originally on my diet and my lifestyle and just told me to lose weight and follow up with them, after like six months, but [ph] my issue was (00:33:13) I lost the weight, but never followed up with them. Then about three to four years later, I had my second bout with a kidney stone, again, had to be admitted, and I have it surgically removed. And again, same thing, blamed it on lifestyle; and then I've lost some more weight, never followed up.

And then once I turned 37, I had my bout with my third kidney stone and I passed several kidney stones at home, and I knew something was wrong because I could feel something blocking the ureter and the urine wasn't coming out [ph] strong (00:33:48). And I tried to tough it out, waited like 14 hours before I went to the hospital. And finally, I decided to go in and luckily I did, because they told me if I would have waited any longer, I could have died, and I think that kind of hit me harder than actually finding out I had kidney failure. Next slide.

And then I was on dialysis for almost a year and half. I started daily in the hospital for a few days, but eventually moved to a center undergoing dialysis three times a week from 5:45 AM to 9:45 AM. During this time, I had little-to-no discussion about PH1. My physician has renewed the plan for me; it was eventually to have a transplant. Dialysis came with challenges: extreme fatigue, low blood pressure, dizziness, anemia, mood changes and additional surgeries; and [indiscernible] (00:34:50) replaced and had two fistulas put in. My first fistula didn't work or mature because the artery was too small. During this time, I felt like I lost the most precious time with my family, friends and myself. I filed for disability and was unable to work and this was taxing on my family. We almost lost our home due to the lack of income and faced increasing medical debt. At times, I contemplated was dialysis worth it due to how I felt and the challenges I faced, but I knew I couldn't give up. My hope was in knowing that I will have the opportunity for a combined liver and kidney transplant. Next slide.

Unverified Participant

Unfortunately, the battle to get Andrew listed for transplant as well waiting for the right organ match was another challenge we encountered. We encountered delays with his listing as his genetic testing was not done at the time of his original diagnosis. And originally, when he was hospitalized, when he mentioned that he had kidney failure, they had treated it as an acute kidney injury, expecting his kidneys to recover after several weeks of running more blood work; and realizing that the kidneys weren't recovering, they readmitted him. He had a pretty severe case of

gouts that was all over his body, which was rare for him as he used to only have it in his feet. And at that time, they realized that this was something bigger than just an acute kidney injury.

And we were lucky that a nephrologist on the hospitalization route just going through the different doctors week-by-week came by and visited him and realized that this was more genetic versus just a kidney injury. And at that time, he diagnosed him, but didn't put him through the genetic testing. So, during his transplant evaluation at Nebraska Medical Center, the transplant team really saw him as a patient with a very healthy liver, not with liver cancer like most patients that they [indiscernible] (00:36:42) disease. So, they wouldn't list him for a liver transplant until the tests confirmed that he had PH1.

So he had to wait over a month for his genetic test results to come back. When they did, it was official. He had PH1 and he was listed for a combined liver and kidney transplant.

As we mentioned earlier, since they viewed his liver as healthy, his MELD score which determined his placement on the UNOS list was much, much lower than most. And unfortunately, it wasn't [ph] favor (00:37:08) enough for him to be able to get a transplant as soon as possible. But thank goodness, UNOS has a policy to add points to those with PH1, so they can be moved up the list, as a need for transplant can't be determined just by that liver function score. Unfortunately, at that time, he had another snag. Someone forgot to file his exception points at UNOS. And another two months passed with him still very, very low on the list due to that MELD score.

Finally, that was all settled after a lot of advocacy and follow up on our part. Once he was officially listed at the right score, he received a total of four calls for possible organ matches. His fourth call occurred on August 8 and resulted in his transplant surgery. The transplant surgery and recovery were a miracle, but an experience that I felt I could never truly be prepared for as a caregiver. He has a fighting spirit and after 13 days in the hospital, Andrew was discharged and he is now recovering at home.

Unverified Participant

[indiscernible] (00:38:09) the transplant has its ups and downs. I consider myself someone who had PH1. I still faced new world of medical appointments treatment and medications. My liver is doing great, but due to the timing and the combined transplant, the kidney is still taking time to work on its own. After transplant, I was placed on 24-hour dialysis in the hospital. This aggressive approach was to remove as much possibly from my blood as possible to allow the kidney to thrive. After nine days of consecutive dialysis, they ran my blood oxalate level and I was relieved to hear that there was little to no oxalate in my system.

[ph] With all the experience and (00:38:49) issues as adult, for those that are younger, I highly encourage anyone to seek or follow up care, to keep your appointments. When a serious medical event happens, maintain a close relationship with your physician, so many factors aren't missed and the condition doesn't worsen before the treatment can begin. If I could have made life-changing steps before my kidneys failed, I would have done so in a heartbeat to preserve those organs and avoid transplant. The more people know about PH1, the better. Awareness is key to advocating for yourself as a patient.

Thank you again for hearing my story and for any help that can be provided to patients facing this terrible disease.

Unverified Participant

Thank you.

Unverified Participant

Thank you.

Pritesh Gandhi

Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

Thank you, Andrew and Nicole, for sharing your journey with us. It really inspires us all to work incredibly hard to bring forward a medicine that can make a meaningful impact amongst patients with PH1.

Next, I want to introduce you to Kenji Fujita, our Vice President of Clinical Development, who will describe our early-stage clinical data and the ILLUMINATE studies. Kenji?

Kenji Fujita

Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

Okay. Hello, everyone. Thanks for having me on. I'm going to start with an overview of the clinical development program that's underway at Alnylam.

So lumasiran is an investigational RNAi therapeutic targeted towards glycolate oxidase or GO enzyme, which is in development for the treatment of PH1. Lumasiran is designed to reduce hepatic levels of the GO enzyme thereby depleting the substrate necessary for oxalate production. Healthy individuals convert glycolate into glyoxylate which is then converted to glycine by the AGT enzyme. However, as Dr. Worcester reviewed previously, patients with PH1 had insufficient activity of their AGT enzyme, which leads to build up of glyoxylate and consequently of oxalate. So by decreasing the activity of the GO enzyme, lumasiran aims to move the block in the pathway further upstream, which will result in decreased glyoxylate and subsequently a reduction in build-up of toxic oxalate.

So I'll move now to our Phase 1/2 study Part B. This is a completed study in which 20 PH1 patients were dosed with lumasiran in a multiple-ascending dose design. Inclusion criteria included ages 6 to 64, glomerular filtration rate or eGFR of greater than [ph] 45 (00:41:29) and urinary oxalate excretion of greater than 0.7 millimole. Three initial cohorts were dosed at 1 mg/kg monthly for three doses, 3 mg/kg monthly for three doses or 3 mg/kg quarterly for two doses. In addition, two expansion cohorts were added later at 1 mg/kg and 3 mg/kg monthly for three doses.

The baseline demographics are shown in the slide. They include an age range of 6 to 43 years of age with 80% of patients less than 18 years of age, 65% of patients were women or girls, and there was a wide range of weight ranging from 21 kilograms to 110 kilograms. The estimated eGFR baseline ranged between [ph] 42 and 131 (00:42:19).

Multiple doses of lumasiran were well tolerated in patients with PH1. All patients receiving lumasiran reported some AEs, but there were no study discontinuations. Most adverse events were mild or moderate in severity and unrelated to study drug. One patient had an SAE of nephrolithiasis and pyelonephritis during placebo dosing.

There were also four patients with SAEs after lumasiran dosing: one reported a kidney stone; one with vomiting; one with gastroenteritis; and one with abdominal pain, fever and vomiting. However, importantly, none of the SAEs were considered related to study drug and, in addition, there were no clinically significant laboratory or hematologic findings.

Moving now to efficacy. Lumasiran was associated with robust and sustained decreases in urinary oxalate excretion. The mean urinary oxalate level at baseline from the three cohorts ranged from approximately [ph] 1.3 to 1.8 (00:43:31). Treatment with lumasiran resulted in a rapid reduction in 24-hour urine oxalate excretion with a reduction of 56% one month after the last dose, and a mean maximum reduction of 75% relative to baseline. Additionally, all patients achieved urinary oxalate levels of less than or equal to 1.5 times upper limit of normal and 70% achieved urinary oxalate within the normal range.

Another way to look at these data are by the oxalate-to-creatinine ratio which adjusts for variability in 24-hour urine collection. By this measure, patients had a mean maximal reduction of 77%, comparable to what I just showed you with the 24-hour urinary oxalate excretion. Note that the patients [ph] randomized for (00:44:23) placebo at top line on the graph had a relatively stable oxalate-to-creatinine ratio during the 85 days of placebo dosing.

Patients who participated in the Phase 1/2 study were eligible to continue in a Phase 2 open-label extension study. All 20 patients elected to continue in the study and there have been no dropouts to-date. Most patients were continued on the dose they received in the Phase 1/2 study; although the protocol did allow for some dose changes to be made in consultation with the Safety Review Committee based on the availability of emerging data. The data I presented here reflects the experience of 18 patients at the February 2019 data cut-off. So as of this data cut-off, the 18 patients had been followed for median four months. The experience has been similar to that in the primary treatment period and lumasiran continues to be well tolerated. There had been no treatment discontinuations or drug-related SAEs. Long-term maintenance of efficacy has been seen with a mean maximal reduction in urine oxalate of 72% compared with the Phase 1/2 baseline.

Now, just to put these results into context, I want to point out that the robust reduction in urinary oxalate that we've demonstrated is highly clinically relevant. The risk of end-stage renal disease in patients with primary hyperoxaluria has been shown to be directly and proportionally related to the level of urinary oxalate. Patients with higher levels of urinary oxalate excretion have an increased risk of end-stage renal disease over time whereas patients with lower levels had a lower risk.

Lumasiran lower urinary oxalate levels below [ph] 1.1 (00:46:13) in all patients in the Phase 1/2 study. And as you can see from this figure, which was published recently by Zhao, patients below that level had favorable outcomes in this Natural History Study.

So to summarize, lumasiran is a subcutaneously administered investigation RNAi therapeutic designed to reduce hepatic production of oxalate in patients with PH1. Multiple doses of lumasiran had been well tolerated by patients with PH1 with no drug-related SAEs and no discontinuations from the Phase 1/2 study or its long-term extension.

Patients receiving lumasiran experienced substantial and sustained reductions in urinary oxalate, thereby supporting the therapeutic hypothesis that RNAi-mediated inhibition of glycolate oxidase may alleviate pathological overproduction of oxalate in this devastating disease. These data support the continued development of lumasiran across the spectrum of patients with PH1 with two ongoing Phase 3 studies and a third plan to initiate by end of this year.

So I'll now review the study design of our ongoing ILLUMINATE-A Phase 3 Study. This is a randomized, placebo-controlled, double-blind study of lumasiran in PH1. The enrollment criteria are similar to those in the Phase 1/2 study I just presented. Eligibility criteria include age six or older, diagnosis of PH1, urinary oxalate excretion of at least [ph] 0.7 (00:47:50) and an estimated eGFR of greater than [ph] 30 (00:47:53). Patients were randomized in a 2-to-1 ratio to receive either the lumasiran or [ph] masking (00:48:00) placebo for six months.

At the end of the six months double-blind period, all patients are given the option to roll into an open-label extension in a manner that preserves the initial blinding. The primary endpoint is percent change from baseline and urinary oxalate excretion averaged across months three through six. The study is now fully enrolled. Top line results are expected later this year, and if positive, NDA and MAA submissions are planned for early next year.

I'll now explain the other two Phase 3 studies. ILLUMINATE-B is an ongoing open-label study of lumasiran in children under the age of six living with PH1. As in ILLUMINATE-A, patients must have PH1 and elevated urinary oxalate excretion, they must have eGFR greater than [ph] 45 (00:48:52), or in the case of children under 12 months old, serum creatinine within the normal range. Enrollment of targeted at around 20 patients. Because the pain in 24-hour urine collections can be challenging in children, both the entry criteria and the primary endpoint are based on urinary oxalate-to-creatinine ratio and the sample taken from single blood collections rather than the 24-hour urine used in previous studies. We anticipate top line results in mid-2020.

Finally, ILLUMINATE-C will be an open-label study of lumasiran in PH1 patients with advanced renal disease, defined as eGFR of less than or equal to [ph] 45 (00:49:30) or as elevated creatinine in patients under 12 months of age. Patients will be divided into two cohorts with Cohort A consisting of patients not on dialysis and Cohort B, patients on dialysis. The study will aim to improve 16 total patients with at least 6 in each cohort. The primary endpoint will be changed from baseline in plasma oxalate and the study is planned to begin by the end of this year.

So in my final slide, I provide an overview of the three Phase 3 studies that comprised our registrational program. Collectively, these studies will provide valuable information on the safety and efficacy of lumasiran in patients of all ages and across the full spectrum of disease presentation. Additionally, in an effort to provide early access to patients, we will be launching an Expanded Access Program or EAP in the US for PH1 patient at least six years of age with preserved renal function.

So I'll now turn it back over to Pritesh to close our presentation before moving to Q&A.

Pritesh Gandhi

Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

Thank you, Kenji, for reviewing our clinical data with lumasiran and providing an overview of the ILLUMINATE studies. Before we go into the Q&A session, I'm going to briefly go over the Lumasiran Program opportunity and the potential to make a meaningful impact in the lives of patients with PH1.

As discussed earlier, from an epidemiology perspective, it is estimated that there are approximately 3,000 to 5,000 patients in the US and Europe. Considering that PH1 is a rare disease similar to other rare diseases, there's usually a lag time from first symptom onset to definitive diagnosis; and this could be well over 10 years. Based on the literature, between one-thirds to two-thirds of the adult patient population gets diagnosed when they're already experiencing renal failure or are hemodialysis-dependent. The only metabolic cure for PH1 is a dual transplant, specifically a kidney-liver transplant. However, transplantation is associated with significant costs to healthcare systems that could be well over $1 million. Given the epidemiology of the disease, a lack of

approved therapies and Alnylam's approach towards disease education and disease awareness, we view the market opportunity to be over $500 million.

From a disease education perspective, we've recently launched a children's animation video series for PH1. Considering that about half of the patients with PH1 are diagnosed in early childhood, we've partnered with the OHF in developing and launching PH1 of a Kind. PH1 of a Kind is a four-part animated video series to support patients and caregivers such that the community can have a tool to educate friends, extended family and teachers, as well as others in the lives of patients with PH1. Children with PH1 and the family members will be more empowered to advocate for themselves by being knowledgeable about their particular condition.

In addition to disease education tools for the PH1 community, we have developed education [ph] on (00:52:56) disease awareness initiatives geared towards healthcare professionals. The goal for disease education for healthcare professionals is two-fold. The first is to augment understanding of PH1 etiology, pathophysiology, clinical presentation and disease course. And then the second is to increase suspicion that recurring stones in adults or any stone in a child requires further metabolic work up and PH1 should be considered to be part of the differential diagnosis. To facilitate potential diagnosis, we have Alnylam Act, which is a program that's available in the United States and in Canada. This particular program offers no charge third-party genetic testing and counseling services for healthcare professionals that are evaluating patients where PH1 is a potential suspicion.

In summary, we have an exciting few months ahead of us. We are on track to report top line results from our pivotal Phase 3 study, ILLUMINATE-A, by the end of this year. Assuming positive results, we plan on filing with the FDA and EMA in early 2020 with a potential for approval by the end of 2020. This would also enable potential rest-of-world approvals in the 2022 timeframe.

With that, let's go to the Q&A session.

QUESTION AND ANSWER SECTION

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

A

So looking at the webcast questions. The first question is for Dr. Worcester. In your experience, what is the biggest hurdle to accurate diagnosis for PH1? Dr. Worcester?

Elaine M. Worcester
Nephrologist & Professor of Medicine, University of Chicago Medicine

A

Hi, I'm sorry. Yes. So I'm an adult nephrologist, so my experience is mostly with adults. I think the hurdle really is that kidney stones are such a common problem and by far the majority of them are due to a much less dangerous condition, and so they tend to get shunted. I think you heard that in the patient's story that there is a blanket assumption that it's just lifestyle or – so they don't get very much evaluation. And I think increasing appreciation that a kidney stone can signal a serious illness and so that more patients get – even just one 24-hour urine would be a big improvement. And you will see the oxalate that will be a real big signal that this patient does not have ordinary kidney stone.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

A

Thanks, Dr. Worcester. The next question is for Andrew and Nicole. Based on your experience, in addition to the impaired kidney function that you had resulting in the need for dialysis, what other symptoms did you have and what impact did that have in your health before going to dialysis?

A

Well, the first precursor obviously was gout attack in my feet, mainly the big toes, but it would spread around to other toes and even ankles. That's when I first started noticing something was wrong. And then I would get like severe back pain or [indiscernible] (00:56:36), sometimes it felt like my appendix was bursting. So I would say those are pretty much the basic symptoms.

A

And with that just to [indiscernible] (00:56:45) when he would have like the gout attack that started becoming so severe that he would have to walk with a cane or he couldn't attend a family event. There was a lot of change to his normal activity very quickly until that gout recovered. And then when it came to him having the kidney stone event, when having to be hospitalized, he would have to miss work for pretty extended periods of time. So unfortunately, that did [ph] put – hamper on also just (00:57:11) our family dynamic and him personally during those events.

A

And fatigue; especially the last battle with the kidney stone, I mean, I went from being healthy. I was in gym five days a week to I had no energy at all.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.
A

Thanks, Nicole and Andrew. The next question is for Kenji. Kenji, what's clinically relevant level of urinary oxalate lowering.

Kenji Fujita
Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.
A

Well, to elevated levels of oxalate in the urine are directly responsible for the deposits in the renal parenchyma and the recurrent calcium oxalate stones the patients develop. So it's expected that any sustained reduction in oxalate production will be beneficial to PH1 patients with preserved renal function and because there's believed to be a continuous and graded benefit for the [ph] natural (00:58:06) perspective effect of reduced oxalate production. And this principle is based on data that were published by Zhao et al. in the Natural History Study back in 2016.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.
A

Thanks, Kenji. Going back to Dr. Worcester and I can provide my two cents on this as well. Can you please clarify what aggressive treatment means in patients who still have preserved renal function today?

Elaine M. Worcester
Nephrologist & Professor of Medicine, University of Chicago Medicine
A

I think it means really close follow up and really attention to continuous good fluid intake and monitoring of renal function, avoidance of salt depletion, use of crystallization inhibitors, pyridoxine when it's helpful, and trying to prevent stones from getting so large that they're very difficult to treat without surgical intervention. Surgery can be a real stress to the kidneys of patients with PH1. Unfortunately, all of these are sort of temporizing measures, but none the less they can in fact prevent onset of renal failure at least for a period of time, which is helpful.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.
A

Yeah. And just if I can add to that, too, and this was demonstrated in the case that you had shown as well, that the rate of progression can be potentially unpredictable where it could require patients to be dehydrated or have a bout of gastroenteritis that causes the patient to be pre-renal and can potentially result in acute renal failure. And especially in the patients that may be harboring stones already, that can potentially have impact on the estimated glomerular filtration rate and the overall renal function.

The other question and, I guess, if both Dr. Worcester can answer and, Kenji, maybe you can provide your perspective is what percent of PH patients respond to vitamin B6 and how effective is B6 therapy in this population. Dr. Worcester, you can go first and then, Kenji, if you want to add.

Elaine M. Worcester
Nephrologist & Professor of Medicine, University of Chicago Medicine
A

So, I think there are thought to be, at this point, three mutations that may lead to abnormalities in the enzyme that can respond to pyridoxine. And I think overall – I've seen the statistics, that maybe a third of patients with PH1 maybe have a mutation that's pyridoxine-resistant. Nonetheless, not all of them will respond to pyridoxine. Again, there was a study that suggested that maybe 60% of them will actually get a lowering in oxalate. So it's a significant number that will respond to pyridoxine and it's certainly worth trying that therapy.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

A

Yeah. So and just to add to that, too, right, I mean I think the patients that are going to be most responsive are the patients that have the homozygous for the G170R mutation and if you take a look at all the mutations that are out there, I think it mentioned that there are over 150 mutations. There are about 5% of the patients are homozygous to G170R that would be responsive to vitamin B6. Other patients may be partially responsive to vitamin B6, but then there are a vast majority of patients that don't have the G170R mutation. Kenji, do you have any additional thoughts?

Kenji Fujita
Vice President-Clinical Development, Alnylam Pharmaceuticals, Inc.

A

Yeah, and I want to point out that pyridoxine by itself is often not sufficient. Referring back to the slide that you presented earlier, Dr. Worcester, a number of those patients where you showed the 24-hour excretion of oxalate were on B6, but had elevated degrees of excretion that are consistent with risk for progression to end-stage renal disease.

Elaine M. Worcester
Nephrologist & Professor of Medicine, University of Chicago Medicine

A

Sure. Yeah. I mean the degree of response is not the same in all patients.

Pritesh Gandhi
Vice President & General Manager-Lumasiran Program, Alnylam Pharmaceuticals, Inc.

Good. That's all we have on the webcast in terms of questions-and-answers. I'm going to pass it over to Josh Brodsky.

Joshua Brodsky
Director-Investor Relations & Corporate Communications, Alnylam Pharmaceuticals, Inc.

Oh, great. Thank you, Pritesh, and thanks to the rest of the speakers as well. And thanks to all of you for listening. This concludes our RNAi Roundtable for today.

The replay and slides will be posted on the Capella section of the Alnylam website later today at alnylam.com/capella with the transcript to follow shortly thereafter. Finally, let me also remind you and encourage you to save the date to join us for Alnylam's R&D Day in New York City on November 22.

Thank you, everyone, have a great day. Goodbye.

Operator: And again that does conclude today's conference. Thank you for joining us. You may now disconnect.