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ALNY - 2018 RNAi Roundtable: Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

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CORPORATE PARTICIPANTS

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Pritesh Gandhi *Alynlam Pharmaceuticals, Inc. - VP of Medical Affairs*

PRESENTATION

Joshua Brodsky

Okay. I think we are live. Good morning, everyone. Thank you for joining us today for RNAi let down table 40 will be discussing the massive influx in RNA therapeutic and development for the treatment of primary hyperoxaluria Type 1.

I am Josh Brodsky, Director of Investor Relations and corporate communications at Alynlam. With me today are Pritesh Gandhi, Vice President and General Manager of the lumasiran program; Dr. Sally-Anne Hulton of the Birmingham Children's Hospital at the NHS trust; Kim Hollander, Executive Director of the oxalosis and Hyperoxaluria foundation; and Richard Riese, Vice President of clinical development at Alynlam.

Today's RNAi roundtable is part of a series of roundtables that we have been hosting this summer focused on our R&D efforts.

Today's event is expected to run for approximately one hour.

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.

And 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 will now turn it over to Pritesh. Pritesh?

Pritesh Gandhi - *Alynlam Pharmaceuticals, Inc. - VP of Medical Affairs*

Thank you, Josh. I will provide a brief overview and then pass the presentation to Dr. Hulton.

For well over a decade, Alynlam 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 have consistently demonstrated potent and durable reduction of disease causing proteins or toxic metabolites across our pipeline and now we are transitioning from an R&D company to an R&D as well as a global, commercial organization.

Last week, we were very excited to announce FDA approval of the first RNAi therapeutic ONPATTRO for the treatment of polyneuropathy among adult patients with hereditary transthyretin-mediated amyloidosis.

ONPATTRO is the first FDA approved treatment for patients with polyneuropathy caused by hATTR amyloidosis, a rare, debilitating and often fatal disease.

We are grateful to the patient community, health care professionals worldwide and to the FDA for bringing this important medicine forward for patients with this particular condition.

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In addition to our commercial drug ONPATTRO, we have a robust and sustainable pipeline. Our pipeline is focused on 4 strategic therapeutic areas or stars.

The first is genetic medicines, which is the most advanced. We also have investigational medicines in cardio metabolic diseases, hepatic infectious diseases and we are now venturing into CNS diseases as well.

We're going to focus our discussion today on one of our genetic investigational medicines, lumasiran, currently in development for primary hyperoxaluria Type 1 or PH1.

Lumasiran has received a Breakthrough Designation from the FDA, PRIME designations from the EMA and we have global development and commercial rights to this particular program.

Our overall key development strategy at Alnylam has been to identify genetically validated liver express target genes to leverage a biomarker to establish proof of concept in a Phase I/II study and also to have a definable regulatory pathway for approval and to ensure global market access.

As it pertains to lumasiran, the mechanism of action of lumasiran is that it works upstream of the causative enzyme defect.

Lumasiran targets glycolate oxidase or GO and depletes the substrate necessary for oxalate production.

We know that oxalate is the toxic metabolite that directly contributes to the pathophysiology and the clinical manifestations of patients with PH1.

We've also established proof of concept in a Phase I/II study and my colleague Richard Riese will go through some of the data where we have shown that lumasiran has demonstrated to have a favorable -- an acceptable safety profile as well as shown a reduction of [urinary] oxalate by more than 50%.

Lastly, we have shown that we have aligned with the FDA with respect to our pivotal clinical trial design, specifically, we have aligned with the FDA on the eligibility criteria, on the dosing regimen as well as the time to follow-up in our primary endpoint being reduction in urinary oxalate compared to placebo at 6 months.

So with that background, I am pleased to introduce you to Dr. Hulton. Dr. Hulton is the president of the British Association of Pediatric Nephrology and is a consultant pediatric nephrologist at Birmingham Children's Hospital NHS Trust in the United Kingdom.

She is going to provide an overview of primary hyperoxaluria Type 1. Dr. Hulton?

Unidentified Company Representative

Thank you. Thank you for inviting me and good morning to everyone.

So primary hyperoxalurias are inborn errors of metabolism of which 3 types have been described at the molecular level and I will focus on PH1 for this presentation.

So next slide. The PH1 is caused by mutations in a gene that results in dysfunction of the enzyme AGT, which is found specifically in the liver.

This is a Vitamin B6 or paradoxine dependent enzyme. The liver is the only organ responsible for glyoxylate detoxification through this enzyme AGT.

Thus, the liver is the key and responsible organ and a liver transplant would be a cure for PH1 but the native liver must be removed in order that excessive oxalate production is to be avoided.



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So this slide shows here that the kidneys are the main oxalate excreting organism and is the key factor so there's the key link between liver and kidney taking place.

Oxalate deposits in the kidney as a result of the insolubility of oxalate and stones are formed within the tubules in the kidney and they internalized into the cells -- the oxalate is internalized into the cells and moves into the interstitial space where it causes an inflammatory reaction and subsequent calcification of the kidneys, which is termed nephrocalcinosis and I will be referring to this again in the future.

Next slide. As the kidneys fail, the oxalate accumulates in all the blood vessels to all organs in the body with a result [interfect] known as systemic oxalosis, again, something I will refer to in more detail.

The next slide shows the clinical presentation and diagnosis and this is highly variable from no symptoms at all through to single kidney stones, the calcification I described and kidney failure.

Sibling and family screening is particularly beneficial as it can identify [ascent masa] cases, which allow the institution of appropriate therapy before symptoms arise.

If a patient presents with renal stones then this must be sent to the laboratory for analysis where calcium oxalate is found and then specific tests can be arranged.

The next slide shows photographs of stones; the top left indicating stones passed from a patient of mine and the figure below showing a large stone removed by a urologist from one of our patients.

On the right-hand side is an x-ray and ultrasound scan demonstrating the calcification of the kidneys known as the nephrocalcinosis.

The next slide is a diagrammatic representation of the enzyme defect, particularly showing here a liver cell, which is the sight of the defect for AGT.

I have identified this in blue, which is the paroxizone, the small organ now in which this enzyme is featuring in this particular PH1 condition.

This slide also shows the enzyme defect for PH2 and PH3, all of which are responsible for high oxalate production but I'm not going to go into that in further detail, I'm only going to focus on PH1.

Next slide. The gene mutations and diagnosis related to them have been identified and specific genes can be identified and targeted or as well we can also test whole gene or exome sequencing for all 3 types, which those exome sequences are now available in developed countries.

Next slide demonstrates that urine oxalate itself cannot confirm which type of PH is present in a patient.

You will see the blue bar indicates the PH1 patients but note the significant overlap in urinary oxalate excretion in all the different types, so this is why genetic testing needs to be performed.

The next slide shows the wide range of onset in primary hyperoxaluria with all the different groups being affected at all ages but note the preponderance of effect in the younger population. The format of these slides I will use in this talk and you will see that the PH1 is demonstrated in dark blue throughout this talk.

The next slide shows data that we've collected through the [OxalEurope registry,] which now has a large number of patients but demonstrates here the preponderance of PH1 patients.

The blue box indicates the incidence that has been reported in most of the literature that you will see in the red box what we have highlighted now is the prevalence as demonstrated through our information obtained through the [OxalEurope registry] indicating a higher prevalence than previously published.

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Next slide. In my view, primary hyperoxaluria is underdiagnosed worldwide but particularly underdiagnosed in Asia and the Middle East.

I have been working with colleagues in Pakistan to demonstrate the increased incidence in prevalence in this area, as this is profoundly related to consanguinity in these regions, so a high genetic frequency of certain gene mutations.

And I've highlighted in the map with the red stars the areas particularly associated with higher incidence in prevalence of PH1, so note North Africa and the Middle East.

Next slide. This slide shows that PH1 is diagnosed at all ages but is most commonly diagnosed in children and young adults, which is the key focus of our care.

The next slide shows that PH1 is a life limiting condition. This is demonstrated by the survival curve and little has changed to the survival curve over the last 10 years.

And death in these patients with PH1 is primarily related to kidney impairment and this is important in relation to how we look after and our future care for these patients.

Next slide. I want to draw attention to the particular importance of renal failure in children with PH1 where again the prevalence of this disease is very high in the Middle East and North Africa, and this accounts for a high proportion of deaths from kidney failure in childhood.

This is different from the causes of death and kidney failure from other associations but particularly, PH1 is not recorded so frequently in the United Kingdom and USA in comparison with, for example, Tunisia and Kuwait as recorded here.

The next slide demonstrates the age at the time of kidney failure in PH1 shown again in blue bars where children and babies under 1, note the number of children being affected under 1 year of age with renal failure in that group. This is a particularly difficult group to care for, the infantile oxalosis group.

Next slide. The factors that we believe impact on renal survival relate to the amount of oxalate present in the urine, that's [times] the degree of hyperoxaluria and also the amount of nephrocalcinosis, that's calcification of the kidneys. This is shown graphically on the left-hand side of the panel.

On the right-hand side, I have a graph showing the cumulative survival curve in patients with a specific gene mutation, namely the glia 170 arch mutation. This mutation is more likely to respond to large doses of Vitamin B6 or pyridoxine and these patients are predicted to have a better long-term outcome. This is an important reason to perform genetic analysis as this identifies perhaps a better prognosis.

In the next slide, I have created a chart, which shows the progression of kidney disease towards dialysis in green with a decline in renal function, which is marked against the stages recognized of chronic kidney disease, stages 1 to stages 5. Stage 5 is -- [that's termed the "old term"] in stage renal failure.

I have related this to show how the increase in plasma-oxalate is demonstrated in red on the top and then the development of systemic oxalosis, which is clearly linked to the plasma oxalate levels.

And the systemic oxalosis is the key factor in early death.

If a patient can remain in CKD Stage 1 to Stage 3 then their prognosis is better and our aim is trying to preserve those.

The next slide demonstrates the consequences of PH1. There is great variability in patients, signs and symptoms but as the kidneys fail and oxalate builds up in all organs in the body resulting in systemic oxalosis and I have listed some of the organs there but I have a few slides to illustrate this.



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Though showing on the next slide features in the eye with a calcification in the retina of the eye and deposits within the retina shown on the left. And on the right an x-ray of a 9 year-old patient of mine with calcification of the kidneys. And you will note very slim bones and marked osteopenia. This young girl has had fractures of her limbs and you will note the pin in the femur of her leg demonstrating where she had a fracture.

The next slide shows evidence of systemic oxalosis in the heart but the heart echo showing increased wall thickness and features also shown here of crystals within the heart muscle.

The next slide demonstrates systemic oxalosis features in the skin on the left-hand panel not only in older people but also in young infants with this mark mottling of the skin as a result of the oxalate depositing in the blood vessels to the skin.

And on the right-hand side of the panel, rather disturbing images of the effects on bones and 2 blood vessels of the fingers and toes, which can even result in gangrene in some cases.

Our aim is to try to prevent these consequences if we can.

The next slide looks at renal impairment in PH1 and our current information shows that despite instituting treatments, kidney failure, which is shown here in red, is not being prevented significantly over time.

And you will recall my earlier point that death is related to kidney failure, so this finding at the end-stage renal disease as indicated here in red is not a good one.

The next slide shows again graphically with a survival curve demonstrated here with a blue line is the patients who have renal failure showing their significant reduction in survival in comparison with the patients who do not have renal failure and are shown in the red line at the top of the graph.

The next slide focuses a bit on infantile oxalosis, which is invariably associated with systemic oxalosis.

Because of the high rate of kidney failure, there is a high death rate in this group.

The only effect of treatment option in this group is the combined liver and kidney transplant and I will focus a little bit more on that in the next few slides but before we do that, we need to look at why we need to treat and diagnose early in order to prevent the requirement for liver and kidney transplantation if that is at all possible.

So the next slide just focuses a bit on early diagnosis and therapy. It's important for us to document the genetics in patients in order to allow us time to reflect whether the gene is more likely to respond to Vitamin B6 and less likely to require transplantation.

Though the conservative treatment as shown in the next slide is listed here and all the patients get dietary advice and all the patients are placed on a high fluid intake.

And then those who are particularly responsive to Vitamin B6 are monitored for this and the gene mutations are listed there as those which are the key ones responsive, the most patients tend to be started on pyridoxine and see whether they respond or not.

The next slide demonstrates the importance of ongoing management for kidney function.

Here, we measure the glomerular filtration rate, which is a marker of kidney function, which is calculated through either a test -- a formal test or looking at the plasma creatinine. And when the GFR falls below [60 mL] body surface area, then assessment for transplantation needs to take place.

Initially, considering either an isolated liver transplant to be advised if the GFR continues to fall progressively below 60 but to try to avoid a significant decline in kidney function and thus a need for dialysis.



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The next slide looks at the features of the effectiveness and in fact ineffectiveness of dialysis in PH.

The problem with dialysis is that it cannot clear oxalate effectively and in essence, a full week of dialysis will clear only the equivalent of 2 days of the endogenous oxalate production.

So I have children who are on dialysis 6 days a week for 4 to 5 hours of dialysis on hemodialysis sessions in our hospital and they are in essence only clearing 2 days of oxalate production thus resulting in an inexorable rise in oxalate and the deposition of oxalate in organs in the body with systemic oxalosis developing.

The next slide shows the effect of liver transplantation, isolated liver transplantation at the start. This is when the kidney function is still acceptable. But don't forget that the drugs that are used to prevent rejection from a liver transplant actually can compromise kidney function.

So the isolated liver transplant is performed when the kidneys are still functioning successfully but may need a kidney transplant later.

You will note here that despite we -- the fact that we have had technical improvements, having a liver transplant in this condition is not without risk. So look at the number of patients who died, though this shows despite effectivity in replacing the enzyme is not without risk.

The next slide looks at the combined transplantation. This is when kidneys are impaired, so you need both a liver and kidney transplant requirement.

And this can be done either at the same time when it's time to combine transplant or in stages where the liver is done first and then the kidney transplant some months afterwards or even years later.

As the oxalate, which is stored in the bones can block out a kidney transplant within hours of the transplant if the levels are very high. Though, sometimes patients are required to continue dialysis until those levels are lowered.

After liver and kidney transplantation, the urine oxalate can remain elevated for many years due to the very slow resublimization of the systematic calcium oxalate.

The next slide shows the product transplant survival for a kidney transplant alone in PH1 patients. This is shown in the dotted line at the bottom of the graph and look how much worse this is in comparison with a combined transplant above it in the solid line that they're all much worse than the transplantation of kidney transplants alone for other conditions, non-PH conditions at the top.

It just shows the effect of oxalate in impairing function over time.

And the next slide shows the survival curve here for combined liver and kidney transplants. And even though this is effective, it's still a high-risk procedure with a significant number of deaths.

Though we need to remember that long term, there are all the other attended problems such as rejection of the transplants and increased cancer rates from the immunosuppression. These all still exist even if we have resolved the original problem with the enzyme and we now have a functioning kidney.

So finally, the last slide demonstrates the current problems and to end, I believe that the PH patients face very many ongoing problems not only with the high mortality and morbidity associated with the liver and kidney transplantation but also in relation to inequity of care across different countries.

The difficulties in treating recurrent stones and most importantly, our current inability to prevent a decline in kidney function, which is associated with the high oxalate.

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So hence I believe the need is required for a very different approach to treatment, which is where the novel therapeutic approach using the RNA interference currently being investigated by Alnylam is so important in this group. Thank you.

Pritesh Gandhi - *Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs*

Dr. Hulton, thank you very much for that overview including the epidemiology, the clinical presentation and the significant unmet medical need for this particular patient population.

To put Dr. Hulton's presentation into further clinical perspective, I'd like to introduce our next speaker, Kim Hollander. Kim is the Executive Director of the oxalosis and Hyperoxaluria foundation or OHF. Kim?

Unidentified Company Representative

Thank you for that kind introduction.

Next slide. OHF is the only non-profit in the world, solely dedicated to finding treatment and a cure for the life threatening rare disease, primary and enteric Hyperoxaluria and related hyperoxaluria conditions.

We do this through promoting research, education, advocacy, compassion and awareness on a global level.

We are the largest private funder of hyperoxaluria research in the world.

For close to 30 years, we have invested more than [\$90] million in basic and clinical research, fellowships, tuition and scientific meetings with a simple goal, to discover and deliver treatment and a cure for hyperoxaluria.

Our hope is that one day no one will separate the full effects of primary and enteric hyperoxaluria and other related conditions.

Next slide. Rare diseases are not so rare. Approximately 7,000 rare disorders are known to exist and new ones are discovered each year.

Rare diseases often referred to as an orphan disease, and effect between 25 million to 30 million people in the United States and approximately 30 million in the European Union.

A disease or disorder is defined as rare in Europe when it affects fewer than 1 in 2,000 people.

A disease or disorder is defined as rare in the United States when it affects fewer than 200,000 Americans at any given time.

Actually, there is a 1 in 10 chance you know someone living with a rare disease. That is 1 person on every crowded elevator.

Children represent the vast majority of those afflicted with rare disease.

Approximately 80% of rare diseases are not acquired, they are inherited like primary hyperoxaluria.

They are caused by mutation or a defect in genes.

It is common that primary care physicians either do not recognize specific symptoms or don't make the link between common symptoms and rare disease. As a result, the patient journey to an accurate diagnosis can be long and difficult.



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For people living with a rare disease, their quality of life is typically, greatly affected by the chronic progression and frequently life-threatening nature of the disease.

People with rare diseases have tremendous unmet needs including misdiagnosis, a long time to finally receive a correct diagnosis, and when they do, 95% have no treatment, with 0 cures.

With limited information, patients often feel alone and isolated.

Next slide. Meet the Skinner family. Natalie and Jared who reside in Colorado where their beautiful children, Benson who is turning 13, Claire who is 11, Mabel, 7; and Lucy, 3.

Their journey started in 2007 when Natalie took Claire for her scheduled 8 week old checkup. At the time, Claire's pediatrician noticed that Claire was not getting a lot of weight, although not overly worried, the doctors drew some blood just to be sure that there was nothing else going on.

The next day, young parents Natalie and Jared received a call that would change their lives forever.

The doctor said they needed to take Claire to the hospital immediately. He urged them to pack an overnight bag as he explained that their little baby girl was in kidney failure.

Silence was coupled with disbelief by both Natalie and Jared.

The Skinners spent the next 6 weeks at Children's Hospital in Aurora, Colorado.

Claire started a rigorous hemodialysis program to help remove toxic waste and extra chemicals and fluid from her blood.

In the process, the doctor discovered her kidneys were completely filled with oxalate crystals.

It was then that Claire received a diagnosis that she had a rare disease called primary hyperoxaluria Type 1.

Claire would need a combined liver and kidney transplant to survive but first, needed to gain more weight because she could -- she couldn't even qualify to go on the transplant waiting list.

Claire continued on hemodialysis 6 days a week to help her body filter out all the bad stuff her body was making; however, the doctor quickly realized that the oxalate crystals caused from her disease were taking over little Claire's body and that they would need to go to extreme measures to help Claire survive.

It was then that Natalie and Jared had to provide additional relief to their daughter's tiny body, which was stricken with oxalate overload.

A very experienced nurse taught Natalie and Jared how to perform peritoneal dialysis, which is done at bedtime at home.

The baby's room, which was once filled with stuffed animals and toys was immediately converted into a hospital room.

Natalie, with limited medical experience, became a skilled nurse overnight so that she could create a sterile environment and hook her newborn up to a machine 12 hours every night, in addition to the 6 days a week that Claire was receiving hemodialysis.

With the inherent loss of blood that comes with doing so much dialysis, Claire needed frequent blood transfusions. Not wanting to expose her to blood from multiple donors, Natalie and Jared's 2 closest friends with her same blood type donated blood each month to help mitigate some of the risk from the many transfusions Claire needed.



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Complications are always lurking around the corner. Doing a routine placement of an essential line dialysis catheter, the right atrium of Claire's heart was inadvertently punctured and blood began to pool near her tiny heart.

Emergency open heart surgery was quickly put into action. With a [partition] of steady hands, the [sap stack] was repaired and her failing heart was going to be strong again.

The doctors restored a steady beat necessary for life.

2 years after diagnosis and dialysis began, Claire who is now a toddler had gained enough weight and was ready for a combined kidney, liver transplant.

The Skinner family moved to Rochester Minnesota so that Claire could be placed on the transplant waiting list at Mayo Clinic under the watchful eye of Mayo Clinic Hyperoxaluria Center, a specialized point of care facility that was opened by the OHF.

95 days later, the call that had been anticipated since she was 2 months old finally came. An unknown family suffering the unimaginable news of the death of their young son said yes to give his organs for transplantation.

The surgeons who performed this miracle studied new and performed with exactness an operation beyond the families comprehension.

Claire received a new kidney, a new liver and a second chance at life.

They freed Claire from spending 15 to 18 hours a day connected to a tube. Her transplant and recovery went well and she was dismissed from the hospital 2 weeks later.

However, the story does not end there.

The Skinners found out that their older son Benson and their youngest daughter Lucy, also were diagnosed with primary hyperoxaluria Type 1.

They live with the daily reminders of what the future could be like when their kidneys can't take the overload of oxalate anymore.

All they have to do is look to their sister's scars to remind them of the tragedy of this disease.

Claire is beyond a doubt a walking, talking, dancing, singing, life-loving miracle girl.

She has overcome the odd medically numerous times and has persevered through unexpected bumps in the road.

She continues to benefit from the advancement of medicine and shows them all that even posttransplant, she is thriving. However, Claire's medical journey will continue for the rest of her life. She will be faced with a lifelong medication and managing complications that can arise from her transplants.

Next slide. I leave you with a statement from Natalie and her family. She said, "we are so grateful for scientists who were enlightened to discover, doctors who knew how to diagnose and treat, nurses who knew how to teach, friends who knew how to aid, a team who knew how to act. OHF knew how to become a beacon of hope, a family who knew it was right to say yes and 4 strong children who came into this world knowing how to face the challenge.

The Skinner family works closely with the OHF on all projects while trying to keep their lives as normal as possible. They have hope that through the efforts of the OHF and the work of Alnylam, one day, the burdens of this life altering, life-threatening disease will victoriously be lifted.

I asked Natalie what drives her each day to get back to the OHF community. Her response was "I give because someone else gave to me first."



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Although this disease is unknown to the majority of the general public and is vaguely known to many to the medical community, it is no longer unknown to the Skinner family. It is their everyday.

On behalf of the Oxalosis and Hyperoxaluria Foundation Community, we thank you.

Pritesh Gandhi - *Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs*

Thank you very much, Kim, that was just incredible, and big thank you to you for everything that you do for the community and for patients and for families.

The patient's story that you presented was just incredibly moving. Understanding the patient experience and what patients and families go through is just central to any organization, any academic center, any company that is going to be engaging in any sort of research for this particular patient population and sharing that patient story was incredibly insightful and very special.

So thank you so much Kim. We appreciate that.

Thanks, Kim. Next, I'd like to introduce you to my colleague, Richard Riese, who is Vice President of Clinical Development at Alnylam. Richard will go through our Phase I/II data with lumasiran. Richard?

Unidentified Company Representative

Thank you, Pritish.

Next slide please. Lumasiran is an investigational RNAi therapeutic targeting glycolate oxidase GO enzyme, in development for treatment of primary hyperoxaluria Type 1, PH1.

Lumasiran is designed to reduce hepatic levels of the GO enzyme, thereby depleting the substrate necessary for oxalate production, which directly contributes to the pathophysiology of PH1 as shown on the next slide.

Typical individuals who do not have PH1 convert glycolate into glyoxylate, which is then used to produce glycine within the peroxisomes of their hepatocytes.

Next. Patients with PH1 have insufficient activity of their AGT enzyme as previously described by Dr. Hulton, leading to a buildup of glyoxylate and most importantly, oxalates.

Next. Lumasiran decreases the activity of the GO enzyme. In patients with PH1, this moves the block in the pathway further upstream, resulting in decreased glyoxylate.

Since glyoxylate is a required substrate for the production of oxalate, the amount of oxalate produced by the liver is decreased.

Hence, lumasiran is designed to significantly reduce and potentially abrogate hepatic oxalate overproduction which is a primary cause of the morbidities associated with PH1.

One pharmacodynamic effect of blocking the GO enzyme is an increase in glycolate levels as shown on the next slide.

This slide shows the plasma glycolate levels in healthy volunteers in our Phase I Part A study, single ascending dose study.



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Healthy volunteers receive doses ranging from [0.3 to 6 mgs per kgs]. As expected, we saw dose-dependent increases in plasma glycolate levels in these healthy volunteers after dosing with lumasiran.

Importantly, glycolate unlike oxalate is highly soluble and efficiently excreted in the urine without crystallization.

It is worth noting that many patients with PH1 already have elevated glycolate levels as part of their disease pathophysiology.

And that there is no known negative impact of elevated glycolate levels, as shown on the next slide.

This slide highlights four reports of patients with either confirmed or presumed deleterious mutations in the gene encoding glycolate [oxidase] who do not have PH1. Three of these patients showed marked elevations of urinary glycolate excretion, while the urinary glycolate levels were not measured in the fourth patient. There were no clinical disorders attributable to the elevated glycolate levels in these patients, including no metabolic, liver or kidney conditions. These findings are further supported by a nonclinical study results in rat and markets, which indicate that for prolonged glycolate elevation, resulting from knockdown of the glycolate oxidase protein levels by lumasiran is not associated with toxicity.

In our lumasiran Phase I, Part B study, 20 PH1 patients were dosed with lumasiran in a multiple ascending dose design.

Inclusion criteria included ages 6 to 64, estimated glomerular filtration rate of greater than 45 and urinary oxalate excretion greater than 0.7 [milli mo] per day [corrected] by body surface area.

3 initial cohorts were dosed at [1 mg] per monthly for 3 doses, and 3 [mgs] per [kg] quarterly for 2 doses.

In addition, 2 expansion cohorts were added at 1 [mg] per kg and 3 mg per kg monthly for 3 doses.

All 20 patients have completed their dosing in this part of their study.

These patients are also eligible to enroll into an open-label extension study.

Next slide. Baseline demographics for these studies included an age range of 6 to 43 years of age with 80% less than 18 years old.

65% of patients were females and there was a wide range of weights, ranging from 21 to 110 kilograms.

EGFR on these patients at baseline ranged from 42 to 131.

Let's first talk about safety and tolerability.

Multiple doses of lumasiran were well-tolerated in patients with PH1.

75% of patients, that is 15 out of 20 reported at least 1 adverse event, AE.

There are no AEs that led to study discontinuation.

Most adverse events were mild or moderate in severity and unrelated to study drug.

2 patients reported severe AEs; 1 placebo patient with pyelonephritis and 1 lumasiran patient with renal, colic and kidney stone and was deemed unrelated to study drug.

The most common AEs were abdominal pain, headache, nasal pharyngitis, pyrexia and vomiting, all deemed unrelated to study drug.



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Injection site reactions or ISR's were reported in 2 patients. These ISR's were mild, transient and self-limiting.

One placebo patient had an FAE of nephrolithiasis and pyelonephritis. There are 3 lumasiran patients with FAEs, 1 patient with nephrolithiasis or kidney stone, 1 patient with gastroenteritis and 1 patient with abdominal pain and pyrexia.

There are no SAEs that were considered related to study drug.

Importantly, there were no clinically significant laboratory or hematologic findings.

Next slide. Moving onto efficacy. Lumasiran had robust and sustained decreases in urinary oxalate excretion.

Mean urinary oxalate levels at baseline in all 3 cohorts ranged from approximately [1.25] to [1.7].

Treatment with lumasiran resulted in a 64% mean maximum production in urinary oxalate across all dose regimens, including a 63% reduction relative to baseline at study Day 85.

This robust reduction in urinary oxalate is clinically relevant.

As shown above, the risk of end stage renal disease, patients with primary hyperoxaluria was directly related to the level of urinary oxalate.

Patients with urinary oxalate levels above 1.6% had an increased risk of end stage renal disease over time.

Whereas patients with oxalate levels below 1.1 had a lower risk.

Lumasiran lowered urinary oxalate levels below 1.1 in all patients with baseline levels above 1.6.

To summarize, lumasiran is a subcutaneously administered investigational RNAi therapeutic designed to reduce hepatic production of oxalate in patients with PH1.

Multiple doses of lumasiran have been well tolerated by patients with PH1 with no drug-related SAEs or no discontinuations from study.

Patients receiving lumasiran experienced substantial and sustained reductions in urinary oxalate.

Thereby supporting the therapeutic hypothesis that RNAi mediated inhibition of glyoxylate oxidase may alleviate pathologic overproduction of oxalate in this devastating disease.

These data support the continued development of lumasiran with a Phase III study planned to initiate this year.

We also plan to study additional patients of younger ages and those with more severe manifestations of PH1, including renal failure and systemic oxalosis.

I will now turn it over to Pritesh to close our presentation before we move into Q&A.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Thank you, Richard, for providing that overview of our Phase I/II clinical data.

Before we go to Q&A, let me share with you some upcoming data presentations and program milestones.



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We will present updated data including expansion cohort data from our Phase I/II study at the upcoming European Society of Pediatric Nephrology or ESPN meeting in Turkey in October.

Also in October, we'll present our Phase I/II open-label extension data at the American Society of Nephrology meeting in San Diego.

As Richard showed, we have now established proof of concept in our Phase I/II study where lumasiran has demonstrated an acceptable safety profile and a greater than 60% reduction in urinary oxalate.

This sets the foundation to initiate our pivotal trial in the middle of 2018, report top line data at the end of 2019 and submit an NDA in early 2020.

With that, we'll now go to question and answers.

For those of you who want to ask questions, please submit questions by entering question in "ask a question" field and hitting the submit button.

So let's go to question and answers. The first question is to Dr. Hulton. Dr. Hulton, what is the average time from symptom onsets to diagnosis and how does that differ amongst the adults compared to the pediatric patient population?

Unidentified Company Representative

Well I can't give a clear answer to that as there is a huge variation between all the data that we've collected all over the world, not only from the OxalEurope registry but the same for the registry from North America. So we have patients who have symptoms from a very early age. In the infantile group, the symptoms tend to be more quickly diagnosed as it were in that the infant becomes more ill more obviously and more readily and a blood test probably done sooner than in the older children and in the adults.

So those children present to be in the first year of life tend to have a diagnosis made more readily but I would say we have had patients who've had delays of up to 2 or 3, 4 months between symptoms that are recurrently presenting with failure to thrive, vomiting, feeling unwell, quite nonspecific symptoms at the beginning and then as soon as they have more obvious symptoms such as blood in the urine or passage of a stone or a urinary tract infection, which is associated with a stone, then a kidney ultrasound scan and blood test is done more readily.

For the other group, for the older population, there is such a variability and many people are misdiagnosed or don't have a diagnosis that's considered for many years despite passing kidney stones. So there are many, many patients who've had recurrent kidney stones with no thought paid to assessing urinary oxalate and certainly no thought in relation to whether there might have a primary hyperoxaluria.

Some patients have even been diagnosed after a kidney transplant, they've already presented to a kidney unit and some reputable kidney units across the world where the kidney transplant is done and then the kidney transplant fails shortly after the transplant, say within 2 to 3 weeks and then a biopsy of the kidney transplant is done and demonstrates that the kidney is full of oxalate crystals and then a retrospective diagnosis is made, this is obviously the patient where a kidney transplant shouldn't have been conducted, it should have been a liver transplant or at least a combined transplant in the first instance. And so there is this huge range and it's about trying to get to the world population educated about how these patients present and how variable the presentation can be.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Thanks, Dr. Hulton. And a similar and a related question to Kim. As Dr. Holton mentioned that there may be some patients and families that may experience a delay in diagnosis, and sometimes it's too late, where patients may have end stage renal disease or patients may be diagnosed even after a transplant. What is the OHF initiative in terms of thinking about increasing awareness of the disease and potentially accelerating the time for diagnosis? Kim?

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Unidentified Company Representative

Great question. So OHF is working around the clock to try to figure things out and best ways we can educate the urologist as well as the nephrologist about the disease.

I think as Sally pointed out, sometimes it's easier to manage children because it is not normal for any child to have a kidney stone. So if it's a calcium oxalate stone then we would urge physicians to look at primary hyperoxaluria. And so this is a population that we constantly try to educate through international workshops as well as attending the American Society of Nephrology, the -- and various workshops around the world. In addition, I think a bigger nut to crack is how do we look at adult population and people that have recurring kidney stones and it really is going to start with an awareness campaign and education teaching them that it is just not normal to have this many stones in your life and/or if we look back to the history of a lot of our adult patients, you will see that they had stones in their younger years.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Thanks, Kim. Here's another question for Dr. Hulton. Why do patients with a combined liver kidney transplant have a relatively poor prognosis compared to patients that don't have primary hyperoxaluria?

Unidentified Company Representative

Well there are -- I think it's to do with the oxalate deposition. If you compare for example the combined liver kidney transplants that we do for the autosomal recessive polycystic kidney disease, a group of patients, they get a combined liver and kidney transplant but they don't have anything else going on in the blood vessels in the rest of the body. And I think it's to do with the amount of oxalate that is circulating before we get onto the stage of transplantation. And I think this is causing subtle damage to blood vessels, to hearts, to all the organs as described. And so I think that this oxalate, which is quite toxic to cells, if you look at the oxalate effect on cells in the laboratory for example, it creates a huge amount of inflammation around the area where the oxalate deposits. So these crystals are quite inflammatory and I think that it's this type of inflammatory response that results in other complications that occur more readily in this group of patients. So they need to be considered as a higher group and I think it's about the complexity of the oxalate itself, which is why I think this research program is incredibly important because I think when we are able to progress it into the group that have the kidney failure, anything that can be reducing the oxalate to this level must be good news for the general -- for their other organs in the body as well.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Okay. Thanks. Here's one more question, I guess to both of you and we'll potentially start with Kim and then with Dr. Hulton. There was a mention that symptoms amongst patients are variable. And the person asking the question is -- can you elaborate on this further that do you characterize the disease course to be potentially be unpredictable and potentially variable amongst patients? So I guess let's start with Kim.

Kim, have you heard from different family members potentially how their symptoms could potentially be different from one sibling versus the other? And then we'll also ask Dr. Hulton the same question.

Unidentified Company Representative

Sure. I think the family that I just portrayed, the Skinner family, you can see it's quite different from child to child. You had 1 child who was in kidney failure at the age of 2 months. And then her older brother and younger sister are doing just fine. So when I'm asked this question and it's one that I'm asked often, I explain to people that primary hyperoxaluria is like a ticking time bomb and we just don't know when it's going to go off in the body. And some patients will present overnight in kidney failure and they've never even had a sign or a symptom of a kidney stones. So there is a lot of variability amongst siblings and then just the journey of the patient from one patient to another can be extremely different. And so it complicates things. But I think, again, going back to education and awareness, this is going to be critical moving forward to how we can change and educate physicians and the community, how different it can be.



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Operator

And Dr. Hulton, from your experience?

Unidentified Company Representative

I think Kim has given a superb answer and in the experience from the Skinner family is such a humbling experience and it was a very moving -- a very moving tale to hear from Kim. But this is the story of the families with PH1. And I think that's a prime example. So I have looked after twins, identical twins where the one child presented to us at 14 years of age in complete kidney failure, required a liver and kidney transplant urgently, and the other child has absolutely no signs and symptoms but has the same gene defect. So this is a child who has complete -- completely equivalent gene mutation but has not had any symptoms at all. And so this is -- makes the prediction for the future very difficult that if we are screening the patients and so if we can screen these asymptomatic children and adults, through family screening or through awareness that as soon as that happens, you can begin to start improving the potential for kidney failure, for example, with a high fluid intake with proper monitoring to look in advance and now with new drugs to potentially consider the use of new drugs, this will change the face of this presentation but it makes it very difficult for us to give long-term predictions. So you can't say clearly in advance how things are going to change. But you can begin to predict more accurately as soon as the kidney functions starts to fail then you can begin to predict that things are going to go wrong quite rapidly and that the systemic oxalosis is going to have a profound effect.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Thank you, Dr. Hulton, and Kim. The next question I'm going to ask, I'm going to ask Richard. The question is lumasiran as you mentioned works on glycolate oxidase. Has Alnylam looked at LDHA as the potential target for this particular condition?

Unidentified Company Representative

Thanks Pritesh. Yes, we have also looked at LDHA inhibition as a target and these data was presented by our collaborator, Dr. John Knight, at the University of Alabama Birmingham last year. While these results were promising in terms of demonstration of oxalate lowering in a mono PH1 in mice, we still have much to understand in terms of the overall effect of the LDHA inhibition on liver metabolism.

Pritesh Gandhi - Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs

Thank you, Richard. I guess we'll have 2 last question. First, to Dr. Hulton. Dr. Hulton, what is your -- what are your thoughts in terms of numbers of patients or the proportion of patients that do progress to kidney failure? I guess that's the first part of the question. And then the second part of the question is, based on the OxalEurope registry data you presented, how many of those patients have been transplanted?

Unidentified Company Representative

So for trying to analyze the numbers of patients going into renal failure, the only way we can do this is I think with registry data or with looking back retrospectively through other data collection. So we're -- in other countries where there is perhaps insufficient information regarding the actual presence of oxalate for example as we are looking at in Indian, Pakistan and the Middle East. There are records perhaps coming through of the patients who have kidney failure and are being transplanted. And so perhaps that group, we could link in that information to give us a better idea. Because we are still trying to collect this type of information and it's something that we are not entirely sure of. And again, with the transplantation data, I don't think we have completely accurate data despite now the awareness from the European group, trying to get all of these data in because there are some surgeons who would be doing transplantation. There are patients who have undergone for example isolated kidney transplantation and a diagnosis hasn't been accurately made or is made in retrospect and their data hasn't been entered into the registry. And I think we're still unclear on exact numbers of patients. And I think that -- and I'll have to refer to (inaudible) who has been working on the data

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completely regarding the number of transplanted patients but I certainly know that for combined transplants, we've got approximately 120 patients at least who have a combined transplant that we're looking at at the minute. But there may be more that we haven't entered into the registry.

Pritesh Gandhi - *Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs*

Okay. Thank you. One question to Richard. Richard, is [perodoxine] a Vitamin B6 expected to synergize with the lumasiran and are patients on vitamin 6 in the clinical trial?

Unidentified Company Representative

Yes. So for patients on [perodoxine], who don't have a full response, that is who don't normalize or get near-normal, we do expect lumasiran to be effective and we are allowing patients on a stable regimen in perodoxine in our clinical trials.

Pritesh Gandhi - *Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs*

Thank you, Richard. Well end with one last question and that's to Kim. Kim, of course, primary hyperoxaluria type 1 is an ultra-rare and orphan disease and as it pertains to many companies trying to work in the rare disease and based or not even the rare disease, there are many drugs that look on clinical trials and fail. What are your thoughts about the drug approval process to help this particular patient populations, especially for patients that are suffering from rare diseases like patients with primary hyperoxaluria Type 1.

Unidentified Company Representative

I think its mission critical that we include the patient voice in the process works. OHF is currently working on an initiative right now with the American Society of Nephrology kidney health initiative, which is multiple stakeholders, including the patient advocacy group, family, caregivers, professionals both on the clinical and scientific side and members of industry. By doing a collective project, we are able to develop a white paper, working with members of the FDA to find acceptable clinical endpoint so that we could help streamline moving forward and move drug to market quickly and effectively and doing so in a safe manner. And so as we look to our patients, this is going to be an integral process that we want to make sure that FDA fully understands the patient journey and the unmet need of the patients and what they go through and the risks they are willing to take.

Pritesh Gandhi - *Alnylam Pharmaceuticals, Inc. - VP of Medical Affairs*

Great. Thank you, Kim. So with that, we'll end the Q&A. First of all, I want to thank the participants and the audience who were asking some very insightful questions. A special thanks to our presenters, Kim, Dr. Hulton, to Richard, and with that, I'll pass it over to Josh.

Joshua Brodsky

Thank you, Pritesh. Thanks everyone, for listening. This concludes today's RNAi roundtable. 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. We hope you can join us for our next RNAi Roundtable on Tuesday, September 11, as we discuss ONPATTRO and ALN-TTRsc02.

For more details, please visit www.alnylam.com/capella.

Thank you, everybody. Have a great day. You can now disconnect. bye-bye.



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