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EDITED TRANSCRIPT

ALNY - Alnylam Pharmaceuticals Inc Reports Positive Initial Results from Ongoing Phase 1/2 Study of ALN-GO1

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PRESENTATION

Operator

Thank you, ladies and gentlemen, for joining today's RNAi Roundtable. We will be conducting a web-based question-and-answer session during the webcast. (Operator Instructions).

I would like to turn the call over to Josh Brodsky for opening remarks. Josh, you may proceed.

Josh Brodsky *- Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Good morning, everyone. Thanks for joining us for today's RNAi Roundtable to discuss our progress with ALN-GO1 in development for the treatment of primary hyperoxaluria type 1. I am Josh Brodsky, Associate Director of Investor Relations and Corporate Communications at Alnylam. With me today are David-Alexandre Gros, Senior VP, Chief Business Officer of Alnylam; Sally Hulton of Birmingham Children's Hospital NHS Trust; Jennifer Lawrence, mother of a PH1 patient; and Dave Erbe, Director of Research at Alnylam.

Before I turn the call over to DA, I just want to make a few comments. Today's RNAi Roundtable focused on PH1 is part of a series of roundtables that we have been hosting this summer and which will go into the early fall. Today's event will end at around 11:00 AM Eastern time.

DA will moderate a Q&A session at the conclusion of the presentations and if you would like to submit a question, you can do so at any time during the event by clicking the ask a question button that is located above the slide window on the webcast player.

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.

So with that I will now turn it over to DA.

David-Alexandre Gros *- Alnylam Pharmaceuticals Inc. - SVP and Chief Business Officer*

Thanks, Josh and good morning. We are very excited to host today's RNAi roundtable on our ALN-GO1 program for the treatment of primary hyperoxaluria type 1 where we believe that ALN-GO1 presents an important opportunity to bring a potentially transformative therapy to patients in a disease with enormous unmet need.

Before we dive into the program, I will start by providing some overall context to Alnylam's effort.

Alnylam is advancing RNAi therapeutics as a whole new class of innovative medicines. Largely through Alnylam's efforts, RNAi is now a clinically validated approach for the development of new medicines. Alnylam's pipeline is focused on three strategic therapeutic areas or STArs including genetic medicine, cardio metabolic disease and hepatic infectious disease.

Today we have 10 programs in active clinical development including two in Phase 3 trials. By the end of the year we will have 11 clinical stage programs and we will be advancing our hemophilia program into Phase 3 in early 2017.

Our focus this morning is on ALN-GO1, an RNAi investigational therapeutic for the treatment of primary hyperoxaluria type 1 and we are very fortunate and thankful to have two guests joining us. Dr. Sally Hulton is with us today to provide a disease overview. We are also very fortunate to have Dr. Jennifer Lawrence to provide her family's and son's perspective.

With that let me turn over the call to Dr. Hulton. Sally?

Sally-Anne Hulton - *Birmingham Children's Hospital NHS Trust - Consultant Nephrologist and Clinical Lead*

Good morning, everyone. I am focusing on primary hyperoxaluria today and will just give you an overall view on the disease specific involvement to PH1 but will also give you an overview of primary hyperoxaluria itself in the world.

So if we just look through at the clinical presentation and diagnosis, all patients with primary hyperoxaluria present with a variety of elements, mostly kidney stones but some people can be completely without symptoms and that is what makes this condition rather difficult to diagnose because you can be completely asymptomatic for many years.

A number of patients present with kidney stones, either single or recurrent stones. They can also progress on to have calcification of the kidneys and subsequent kidney failure. If a child or an adult presents with a stone in the urine that must be sent to the laboratory for analysis so that the finding of calcium oxalate can be documented and then specific urine and blood tests can be arranged.

So if we look through on the next slide I have just summarized here the genetic problems associated with the three different types of primary hyperoxaluria as we know so far. And I am not going to be dealing in much detail with the metabolic pathways today as this is far too time-consuming. But you can see in the blue box area the enzyme defect AGT, which is that specific for primary hyperoxaluria type 1, this enzyme alanine glyoxylate amino transfers is located in the peroxisome for liver and is the main problem for type 1.

The elements identified with the green, the GRHPR abnormality is the gene abnormality and enzyme defect associated for primary hyperoxaluria type 2 which is not specific to the liver and for type 3 we have HOGA indicated in the brown mitochondrial area specific for pH type 3 which has only recently been identified. So there are at the moment three different types. We will be looking in more detail at the type 1 in this presentation.

So in the next slide I just wanted to indicate that there have been new developments in identifying the different types of primary hyperoxaluria. My colleague, Gill Rumsby has been very helpful in developing a urine test that looks at the urinalysis only and is able to identify various metabolites from the different types of PH that can be identified in the urine. These urine tests will help to focus specifically on the genetic tests. So the top graph indicates the different metabolites that can be identified in the urine and if you have high glycerate acid for example, that is for primary hyperoxaluria type 2. If you have high glycolate or urinary oxalate, that is helpful for type 1 and the HOG metabolite which is a glutamate metabolite is for type 3.

So this type of urine testing which could be made more available all over the world would help us to focus further on the genetic tests that need identification for the specific disease types.

Just in summary on the next slide looking at the PH mutations, PH1 mutation is in the AGXT gene located on chromosome 2 and for this you need to have high plasma and urinary oxalate. If you are in renal failure, you will have the high plasma oxalate but otherwise you will have a high urinary oxalate and glycollate level. And then I have indicated here the different abnormalities for PH type 2 and type 3 and how you need to be specific in identifying these both with gene and urine testing in order to give greater prediction for the future. I am not going to be spending very much time on those groups today.

In the following slide, I summarize the UK data looking at PH types 1, 2 and 3 just indicating the age of onset in years to show the wide range and variability of age and onset. The PH1 patients show in the bright blue color to show that the majority of those are presenting in their first 10 to 15

years of age although there are patients presenting in later life. And I have got more detail on the European data shortly in the presentation. But just to give an overview of the numbers of patients in their age ranges presenting in the different types.

If we now focus more on PH1 for the rest of the talk, I wanted to just identify that the greatest problem for PH1 patients is the phenotypic variability. So you can have a patient who is completely asymptomatic and additionally a person with exactly the same gene mutation has recurrent kidney stones to one who is in kidney failure. We have documentation of twins, identical twins with exactly the same genetic abnormality, one of whom is completely asymptomatic and the other has kidney failure from oxalosis. So this makes our diagnosis and also our predictions for the future very, very difficult in families.

The main problem with patients who have primary hyperoxaluria type 1 is the build up of the oxalate in the body over time and eventually the deposition of oxalate in all organs in the body. This is known as systemic oxalosis. The oxalate deposition is particularly problematic in bones, it is problematic in the heart muscle and affects cardiac function by resulting in cardiac conduction defects, in the small blood vessels both to the coronary arteries and all over the body system.

And additionally, there is systemic oxalate deposition that can occur in the skin, under the nails and particularly problematic in those who aren't treated. Oxalate is deposited in the bone marrow resulting in resistant anemia so that erythropoietin cannot even be responsive in these patients. The deposition can occur in the eyes, on the retina and in the nervous system, and in the small blood vessels going to the brain and to the spinal cord.

So systemic oxalosis is a huge problem and a huge burden for patients all over the world. One of the key other areas is of course progressive renal impairment as a result of oxalate deposition within the kidney with kidney failure and its resulting problems.

Then as we move to the next slide, this shows the factors that impact on kidney function and I have divided these into two sections. So if you look at the left-hand side of the slide, there is absolute evidence that the higher your urine oxalate, the greater your chance of developing calcification in the kidney and the worse your outcome.

So the graph on the left is data taken from the North American Registry with 68 patients entered into this study. And it shows if you look at the very thick topline that the patients who have a urine oxalate level that is lower than the median have a much, much longer time to kidney survival as opposed to those who have high urine oxalate excretion.

We also now have new information that suggests that the genotype that you have so the specific mutation within the PH1 that you have may show some protections. So if you for example have the Gly170Arg mutation, then you may have greater protection from kidney failure.

This is shown here on the graph on the right-hand side where in the gray color you will note that there is a slowing down of decline in kidney function by a difference of up to 20 years in comparison with patients who don't have the Gly120Arg mutation. So these new findings have impacted on our ability to determine treatments and to be perhaps give a bit more effective information to families regarding future and outcomes.

So the next slides are a couple of picture slides indicating consequences of primary hyper hyperoxaluria and you see here the retina showing crystals in the eye on the left-hand side and again on a postmortem finding of the retina. The x-ray picture on the right is a patient of mine who has primary hyperoxaluria type 1 at nine years of age and you can see the fast calcification of the kidneys, the very, very poor bone quality and the in fact a fracture of her femur needing pinning and placing.

The next slide is a slide taken from a publication indicating the myocardial biopsy with calcification within the heart muscle and giant cell with crystals right in the heart muscle indicating how this affects cardiac function.

The next slide of fingers is one not of a patient with primary hyperoxaluria type 1 itself but of a diabetic patient who had kidney failure and then a massive deposition of oxalate all over the body and this just shows how the oxalate can be deposited in the small vessels and can cause huge bone destruction. These pictures are exactly the same as those we see in patients with untreated systemic oxalosis in the infantile group that actually gets terrible bone and cutaneous deposition of oxalate. So a phenomenally painful and difficult condition to be dealing with.

The next slide is summarizing the infantile systemic oxalosis and our difficulty in this particular group as early death is very common. And by the age of three year, 80% of children who presented in that early period of their life will have developed kidney failure. There has been some difficulty and delay in diagnosing and treating these children because the normal ranges for urinary oxalosis haven't been clearly defined in different parts of the world. And that acute kidney failure is a common problem in infancy and the development of the kidney is slow and for the first six months of age, any deposition of oxalate within the kidney may have devastating effects.

So this particular group of children presenting in the first year of life have greater problems than those presenting later and are those that suffer the most from systemic oxalosis. And in this group really the only effective treatment we have at the moment is early liver and kidney transplantation.

If we look at the PH1 population in Europe, this data now has approximately 700 patients with PH1 and we have 690 of them have documented evidence of PH1 either through a liver biopsy or their genetic abnormality. And if we look at those on whom information is available about systemic oxalosis, we can see a very high proportion of patients, 51 of 132 patients actually have systemic oxalosis and this is the group that is going to be very difficult to manage.

The next slide, courtesy of my young friend, Sander Garrelfs, who has prepared this slide for me, shows that of nearly 300 patients with PH1, their age of diagnosis is actually still quite early. So you can see that the majority of patients, more than 50% of patients present under 10 years of age. So it is an age at which the diagnosis taking place in pediatric practice but it is not limited to those and if you look, there are still a large number of patients presenting at older ages which indicates this phenotypic variability in primary hyperoxaluria type 1.

So primary hyperoxaluria is very underdiagnosed and the diagnosis may often be missed or delayed and this is a result of inadequate tools which are available to deal with the testing. I am firmly of the belief that there are a significant number of undiagnosed patients all over Asia and the Middle East. This is based on information that is coming through from the Middle East and Asia.

For example, 24% to 40% of Pakistani children who have kidney stones when you look at their urine, they have either oxalate crystals or actually hyperoxaluria. They haven't been tested and so these children will definitely have one of the types of primary hyperoxaluria. We already know now of 150 Pakistani patients who have actually had the AGXT gene analyzed and confirmed. So there is a huge burden in this population. And based on evidence of work and done by Hutchinson here in the West Midlands, if you look at the is rate in patients of Pakistani origin, this places the estimates of disease burden of primary hyperoxaluria type 1 just much higher given them an instance of 1 in about 14,000 in comparison to 1 in 200,000 elsewhere in Europe. So a high probability of more patients to be discovered around the world.

On the next slide, this is a graph that is showing the Kaplan-Meier survival curve indicating how many patients actually die and how shortened your lifespan is when you have primary hyperoxaluria type 1.

The next slide shows the importance of kidney failure when you have primary hyperoxaluria type 1. So if you have no kidney failure as shown in the line in red, then your chances of survival are high whereas if you have a kidney impairment, the slide shows the graph line in blue your greater chances of dying.

So moving on to early therapy, if you can diagnose early and treat early, you are more likely to have a better prognosis but this will depend also on what type of gene you have. As you recall, the Gly170Arg will give you a better prognosis and you may then with that group have stability in your GFR over some years.

The treatments that are currently available are conservative therapy at the start where we minimize oxalate absorption, where we try to reduce our oxalate synthesis using either Vitamin B6, which is known to enhance any residual AGT activity within the pyridoxin, but particularly in that group of Gly170Arg or (inaudible) mutation, there is a particularly sensitive and we try to reduce oxalate deposition in the kidney with a very high fluid intake. These conservative measures are only useful in some patients and then in the others, we have to consider their kidney function so for our ongoing management, we look at the GFR, measure they [gly] filtration rate on an annual basis. And if the GFR is stable, we monitor and continue with conservative therapy.

But if the GFR is falling, we have to consider whether they would benefit from a liver transplant only. This is to replace the ATT enzyme and in particular to look at what type of genotype they have, they may have delayed changes in their function over time, if they have the specific mutations and if their kidney function is declining with a TFR of less than 40, then they may need to proceed forward to combine liver and kidney transplants.

The big problem for all of the patients with primary hyperoxaluria and particularly those with PH1 is the problem with dialysis and the problem that there is no dialysis program that can offset the rate of oxalate generated by the liver in patients who have kidney failure.

So even if you were on a dialysis intensive dialysis program, your weekly clearance of oxalate through the dialysis will not actually be able to cope with anything more than two days of oxalate production. So there is always going to be oxalate accumulation once you have got kidney failure. Certainly hemodialysis is better than peritoneal dialysis but the ongoing deposition remains a remarkable issue for the physicians and the patients caring those patients with primary hyperoxaluria.

So we move on to the consideration of oxalosis liver transplantation and here the timing is important because the drugs for transplantation compromise kidney function, you may be able to do the oxalated transplant when your kidney function is good and as the graph here shows that although outcomes are quite favorable, you still have a significant number of patients who will pass away during either the surgery or subsequent to those. So although this is a good option, it is not a complete solution.

The next slide combines the liver and kidney transplantation, this can either be done as I said as a combined or sequentially where you do the liver first and then the kidney. In both cases, the liver original patient's liver needs to be removed because this is the source of oxalate production and in all of the cases, the younger you are the higher the risk factors. If you are on dialysis, more of a problem and that there is always the problem of poor graft function afterwards.

So you can either consider combined with sequential depending on the different patient characteristics if's somebody is wishing to donate a kidney or a liver portion to their child or a family member, then we may be able to consider sequential transplantation in a more advantageous fashion.

The outcome is still better than for no treatment at all but however, there is still high death rates in this group and those patient survival looking at the numbers that we had with insufficient data in our Europe registry still shows that the survival of patients with 74% at 10 years but this is still not good enough when we consider the use of patients and potential longevity so certainly we need some new therapies to be reviewed in this group.

So our current problems really are the management of patients with recurrent kidney stones and how we deal with that. Then the terrible problem of oxalate deposition systemically and how we try to prevent that to happen. The deposition of oxalate in the transplanted kidney which sometimes results in immediate kidney loss and so how we try to ameliorate those problems. The management of recurrent bone fractures which is a huge problem in those who have systemic oxalosis. And then how we try to coordinate our care for patients who have multi-systemic disease, their burden on hospital, admissions, hospital appointments is very high.

So the general care of patients with PH1 is complex and very time-consuming. Also rarely do these patients really do show the huge number of complications for which we have limited facilities of dealing with them at the moment whilst we still have this enormous burden of the systemic oxalosis building up in PH1.

So finally, my slide on current research just indicates the direction of research at the moment. There is quite a lot of research in gene therapy and also looking at ex vivo gene therapy on the pluripotential stem cells with liver cell transplant and this may be preferable to liver transplantation on its own as there are no immune consequences as so that occur with other forms of transplantation have seen improvements also in the development of genetic and the mouse knockout which can give us animal models of disease of all the different types so we can now be looking at PH1, 2 and 3. And doing further research in those areas.

And then there is this whole new field of the RNAi therapeutics for which Alnylam is now working on important products which we are just about to institute for trial certainly in Birmingham beginning shortly. And I think this is a very exciting and important new area for us and possibly the first new development that we have had for our patients in many years that may alter their future.

Thank you very much.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thank you, Sally, for that terrific overview. Jennifer, let's now turn to you for the patient perspective.

Jennifer Lawrence - - *Roundtable Participant*

Okay, thank you. Thank you to Dr. Sally-Anne Hulton for that wonderful overview of primary hyperoxaluria.

My name is Jennifer Lawrence and I am the mother of George, who has primary hyperoxaluria type 1 and I was asked to share George's story and our short journey with this diagnosis.

We feel very fortunate that George has the kidney function that he does have and he does have favorable genetics. He does have as one of his gene mutations, the Gly170Arg mutation of which Dr. Sally-Ann Hulton just spoke and his other mutation produces a truncated version which has no function. So George's story is perhaps a more fortunate story than stories of many children with this diagnosis. Next slide, please.

This is our family. Josie is on the left, she just turned 14 and George just turned 12. And there is my husband, Billy Kidmore, and I think who are both obviously carriers of this gene.

The next slide shows a picture of George and me; I am a full-time working mom. I take care of adult patients with endocrine problems in our hometown of Valdosta, Georgia and my husband Billy with whom I practice is an adult rheumatologist.

The next slide shows George in January 2013. It was actually New Year's Eve when George was just eight years old that he passed his first kidney stone. He had probably passed a couple of stones before that we had mistaken for a bout of gastroenteritis or a muscle ache after playing tennis. The stone that George passed on New Year's Eve was just one of six. The removal of the remaining five would require a series of painful surgeries and procedures.

George has always had a high pain threshold which may have proved to be a mixed blessing. It did help him through the passing of the first stone and the battery of surgeries but it may have also delayed his diagnosis. His first surgery actually occurred in Valdosta when he was unable to urinate. Just a few nights before we had been up with him throughout the night with what we thought was a stomach upset. He was uncomfortable but his abdomen was soft and he was afebrile. We were actually on vacation with some friends at the beach and we took him early in the morning to a local emergency room for evaluation. And while we were awaiting a physician, he went to the bathroom and he felt better so we returned to our vacation condo and decided we would follow up with his local pediatrician that week.

Before we had a chance to see his pediatrician after a basketball practice when he went to urinate, he was unable to pass his urine. We realized then what had been the discomfort from the previous night.

I could actually see a very dark stone at the tip of his urethral meatus, which is the tip of his penis which was blocking his ability to urinate. So we called a local adult urologist who met us at the emergency room and he tried to manually manipulate the stone which was stuck in the tip of his urethra but it was too large so his first surgery actually was cutting the urethral meatus open to be able to remove the stone.

So despite this next slide, even with his toughness recovering from these surgeries was difficult. In spite of pain though he really did try to keep a very optimistic attitude and he maintained his very thoughtful spirit throughout that. His first remark actually after awakening from that initial surgery was I'm glad this happened to me and not Josie, his older sister.

A few days after recovering from this initial surgery before we could even have the imaging which we had arranged, he had a subsequent stone and obstructions and this time it was a couple of stones, they had moved and blocked his kidney function higher up so that he presented to the emergency room with pain with bilateral kidney stones, his blood pressure was 170/110, his potassium dropped to two, dangerously low.

These metabolic disturbances occurred because of the kidney obstruction and we also learned that his kidney function was dramatically low.

We assumed initially that this kidney dysfunction was just from the acute injury to his kidneys from the obstruction and of course later with further evaluation we learned that it was from something different -- and the kidney itself in addition.

The next slide shows George doing homework before one of his surgeries. He had several surgeries with stents and then laser lithotripsy to get rid of the stones. His urethra was sore from surgery that took hours with tubes and wires that are actually made for adults being passed for the lithotripsy. And so always his first urinations after these procedures were very painful. We actually figured out that if I played him Chopin nocturns, that would sort of help him relax before he would have the painful process of urination.

But throughout this, he tried to stay positive and keep up with his homework. He actually went back to school immediately and our school allowed us to let him urinate in the faculty bathroom since his urine was full of blood. And we knew that he would scare off other children but he only missed 12 days of school. He kept his A average and he worked very hard and actually decided during his operations that instead of becoming a movie producer which was his first aspiration, he would become a pediatric nephrologist.

So the diagnosis of hyperoxaluria in the next slide, it then took several months before his urine cleared of blood so that he could formally be tested. It was then that we learned that he had primary hyperoxaluria and receiving this diagnosis seemed surreal even though his father and I are both physicians and even though we knew that hyperoxaluria was a possibility, we had thought it was very unlikely. No one else in our families had had kidney stones and we knew that primary hyperoxaluria was an exceedingly rare disorder. And we also knew that the paucity of treatment options and the possible need for a kidney liver transplantation made this diagnosis almost too frightening to consider.

Next slide. So after receiving the diagnosis, we quickly found the Oxalosis and Hyperoxaluria Foundation website which proved to be a wonderful resource for us. And within 24 hours, we contacted the offices of Dr. Dawn Milliner at the Mayo Clinic Hyperoxaluria Center in Rochester Minnesota. And even before George's first appointment with her a few weeks later, she was able to help us, she guided us on his genetic testing and his initial treatment.

So by the time we landed in Rochester a few weeks later, George's genetic testing was literally being emailed to us on our phones from the Hyperoxaluria Center and that confirmed primary hyperoxaluria type 1.

In the face of such a daunting and a frightening diagnosis, the Hyperoxaluria Center helped us in three crucial ways by giving us a treatment plan and a support system and hope. Next slide.

George has been an inspiration to us throughout this experience with his optimism and his courage. Within a couple of weeks of his diagnosis, George had progressed to drinking three liters of water and he was determined to meet this challenge. His local nephrologist said that was just not going to be possible for someone his age but he worked very hard to achieve this and he wanted to be successful and he didn't want his disease to keep them from enjoying school or sports or other activities.

But as any parent of a child with this condition with hyperoxaluria knows, drinking continuously is not an easy task.

This is a picture of George a few weeks after his diagnosis. The diagnosis of primary hyperoxaluria was made just weeks before he took an annual trip to his summer camp, Mandarin, in North Carolina and his favorite activity at this camp was mountaineering which requires spending several nights away from camp in the woods. And we wondered how would this be possible with all of the water he had to drink and the medication, how would he keep up with the water drinking without us? And luckily for us with the help of wonderful staff and nurses, George was able to take his medications, stay hydrated and he enjoyed that summer in camp.

Next slide. We view living with George's diagnosis as a journey that we all make as a family. We know that our success depends on the support we receive from others, our extended family, our friends, our church and George's wonderful physicians. He worked first with Dr. Dawn Milliner as I said, at the Mayo Clinic Hyperoxaluria Center and our wonderful pediatric urologist Dr. Charlotte Massad, who actually just retired from Scottish Rite in Atlanta.

Everyone plays an important role. Josie, George's older sister, she is a person who reminds him a lot to drink and encourages him particularly when he gets frustrated or distracted with the constant water intake. And his father and I awaken him every night to drink water. The middle school secretary reminds him to drink at school and take his medications which she holds for him.

Next slide. This is a picture on the left of George and Josie and on the right George and Josie and his cousin. Basically any picture we have of George, you will see him wearing a sling. The sling actually helps them carry his water bottle so that he can drink continuously throughout the day.

Next slide and this is a slide actually of our children wearing Camelbaks. Sometimes that is another way of porting water and Josie is wearing one as well. She tries to be supportive same thing he does.

Next slide. This is actually a picture of George reading to our church preschool on one of his days off from school and even in that picture he has got his sling, it is the little black line across him and his little water bottle on the left hanging down. So sometimes actually he seems to wear the water than drinking it but he is actually making an effort to always have it.

Next slide. So this is a picture of our cabinet in our kitchen that has a lot of water bottles. We start off with one type of bottle and then we might switch to another when he feels like he is blocked on his progress, he is challenged in accomplishing the amount of water he needs to drink. We just try to reinvent the system, do better. So we switch bottles and that has helped us keep going and so we have accumulated a variety of bottle systems. To the right is actually our drawer with all the slings in different colors. Next slide.

This is the medicine. He takes liquid potassium citrate. It is supposed to be mixed in a liquid but he prefers just to get it over with and it doesn't taste very good and he just washes it down with water or sometimes a flavored drink. He got an orthodontic appliance which gave him some mouth ulcers that potassium citrate burned and that made it challenging so we switched to temporarily to pills. These are big pills. I actually have trouble getting my adult patients to take them but luckily George doesn't complain about it. And he also takes vitamin B6 as Dr. Sally-Ann Hulton described.

When we travel, we sometimes use syringes just to make it easier to carry the potassium citrate and I always carry with him a stone emergency kit.

This is just a picture of George playing tennis. We want his childhood to be as normal as possible. He loved playing tennis before his diagnosis, actually not an ideal sport for him since it produces a lot of heat in Georgia with his kidney condition but we work hard to ensure that he is hydrated before a match and he drinks continuously and he doesn't drink from any source. We actually keep track of his drinking so he counts intake in 500 cc increments. Next slide.

That is a picture of George running. He loves cross-country. This is a little bit of a puzzle to solve because running long distance obviously it is important to have good hydration and we have to be careful about his drinking. We have also learned that he can't drink too close to a race so we have learned to awaken much earlier and to pre-hydrate so that is still a work in progress. Next slide.

This is George's kidney function. This graph shows his kidney function is estimated using the iothalamat before his body surface area. We see as I mentioned Dr. Milliner at the Mayo Clinic every six months and we usually do this and one of the issues for George is that even though he has done very well drinking and taking medications and he actually has no new stones, it is the oxalate deposition throughout his kidneys that occurred prior to his diagnosis that continues to occur and has affected his kidney function.

And his kidneys actually do not appear to be growing with him. We do ultrasounds to look at the size and we don't know exactly what that means for his future in terms of timing but we know that with maturity, puberty and increased muscle mass, his kidneys will have to work harder to keep up. And will he have enough kidney function to get him through high school? Will he need a transplant before then? What complications will he

have from that process? These are some of the questions that we keep in the back of our mind as we continue to do all we can to keep his kidney function optimal now.

So we as parents want to do everything possible to maintain George's kidney function to prevent stones, to avoid or delay a need for transplantation and we are thrilled with the possibilities of treatment options that companies such as Alnylam are investigating and we hope to be helpful partners in this process. Thank you.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thank you, Jennifer, for sharing your personal experiences as well as George's. You and George inspire us to continue working hard to move ALN-GO1 forward.

Dave, let me now turn to you for a perspective on the program.

David Erbe - *Alnylam Pharmaceuticals - Director of Research*

Thank you. Now for the listener we are on slide 60. This is an introduction to PH1. There is no need to go through this introduction considering the actual intros we have had but I just want to remind the listener that this often devastating disease is due to a specific metabolic defect in the liver peroxisomes and this is what makes it exquisitely suited for the Alnylam platform as we pursue the ALN-GO1 as an alternative to liver transplant.

So now going to slide 61 again, this is the RNAi approach that you have heard about, I won't go through the details. DA had indicated it in his introduction but I will remind you that we can see, you can see how we leverage the GalNAc conjugate platform to achieve robust, specific and sustained silencing of any gene within the liver and in fact you see that this approach has been clinically validated with human proof of concept in multiple programs and we have been able in the GO1 program to leverage all of these data that we have learned from these previous clinical programs.

So now specifically moving to PH1 then on slide 62, this summarizes just a briefly the pathophysiology. You see on the left a healthy hepatocyte peroxisome where glycolate is oxidized by the GO enzyme, glycolate oxalates into glyoxylate which is normally transaminased through the enzyme AGT to glycine.

However on the right, one sees what happens when that pathway is blocked as in PH1. Glycine is not formed but rather glyoxylate which builds up is further oxidized to oxalate which is what forms the crystals and causes the disease.

On slide 63 then, it becomes a very natural extension of the platform and of the approaches that we have been taking to similar diseases at Alnylam to imagine how one would intervene. At the top one sees what you would expect to see in a healthy volunteer and at the bottom in patients, keeping in mind that of course the difference between these two is whether they have an intact AGT enzyme for formation of glycine from glyoxalate. In a healthy volunteer by knocking down glyolate oxalate, the enzyme which is one enzyme upstream in this pathway, we expect no change in oxalate because that starts up low already but an increase in the substrate glycolate.

Once we move into patients then, we expect that same pharmacology to translate into a profound decrease in oxalate and a commensurate increase in glycolate. So that is the therapeutic hypothesis in its simplest form.

We take safety assurances from GO knockout mice who lack the enzyme that we are targeting entirely and they appear normal except for an increase in glycolate acid in their urine.

There is also a single child who was identified by one of our investigators, Dr. [Yako Fishberg], who has complete absence of GO activity but with normal kidney function in just the glycolate acid area that one sees in the knockout mice. So we take a lot of insurances from that. In addition, in our own preclinical programs with very high doses of ALN-GO1, we have seen no deleterious consequences of this knock down.

So now turning to slide 64, I want to get into the clinical update that we have just made. Dr. Dawn Milliner who was mentioned earlier, presented these data at the 17th Congress of the International Pediatric Nephrology Association. These data were very well received by the audience including many of our investigators who were present.

So on slide 64, we see the study design of this Phase 1/2 study in Part A which are the results we are going to review again today. It is single-dose, single ascending dose through four cohorts eight per cohort, randomized 6 to 2. We started at 0.3 milligrams per kilogram single-dose and went up to six milligrams per kilogram and again, it is 32 healthy volunteers here.

We will then after reviewing these data and the safety review committee has selected 1 milligram per kilogram then for the multiple ascending dose portion now in patients where we will be recruiting four patients per cohort randomized 3 to 1, they will be receiving multiple doses, three doses over monthly intervals and we will of course be monitoring safety and also the pharmacodynamic effect of oxalate lowering that we hope to see.

You can see the specifics as we go into patients that we age 6 to 64 and you can see the GFR cut off that we are requiring such that urinary oxalate will be a meaningful measure of their hepatic oxalate output.

Now going to slide 65 and summarizing these interim results from the Part A portion in healthy volunteers, we see again of the 32 subjects, they are median age, the gender mix of 50-50 and the race breakdown which reflects the London population where this study occurred.

Going to slide 66 then, a summary of some of the safety results from this. What we see is that again ALN-GO1 was generally well-tolerated in healthy volunteers, no drug related SAEs or discontinuation due to adverse events.

I won't go through the details there but you can read those. Suffice it to say that these data are very consistent with what we know from our other clinical programs with the conjugate platform and summing up there was no significant clinical finding.

Going on to slide 67, I won't go through this in detail again due to time but suffice it to say that the pharmacokinetics of ALN-GO1 is also very consistent with the profiles from our other clinical programs. We see increased exposures with those, we see rapid absorption from subcutaneous injection with elimination as we would expect.

Now on slide 68, the data that I would like to spend a bit more detail in, the glycolate data from these healthy volunteers. In brief what we see here is exactly what we would have expected based upon our published nonhuman primate results of knocking down the GO enzyme with the exception of prolonged duration. So these results are from a single injection in healthy volunteers. To achieve this profile in monkeys, we required monthly injections and that is very consistent with what we know about the platform and its translation.

What you see here is a dose-dependent increase in glycolate levels, the lowest dose which showed a pharmacodynamic effect was 1 milligram per kilogram and it goes out from there to 3 and 6. Because of these results, this was the dose 1 milligram per kilogram that the Safety Review Committee selected for transitioning to Part B.

We would predict that doses of 1 milligram per kilogram and above would have the potential to profoundly lower oxalate production in patients based upon both our preclinical data and what we know from other programs.

So then on slide 69, these are just the elevations in plasma glycolate results in these same healthy volunteers and these just reinforce the data that we saw from the plasma results, elevated glycolate. And remember that is the substrate of the enzyme glycolate oxidase that would eventually get turned into oxalate.

So in summary on slide 70, what we see is that ALN-GO1 is a novel subcutaneous administered investigational RNAi therapeutic that is designed to reduce hepatic production of oxalate in PH1 patients. These preliminary data in adult volunteers suggest that GO1 is generally well-tolerated. Again, we saw the dose dependence sustained PD activity with the expected effect of increased plasma and urine glycolate in healthy volunteers.

This starting regimen for investigation in patients will be 1 milligram per kilogram every 28 days where this increased glycolate levels that we saw in healthy volunteers is expected to translate to a reduction in urinary oxalate excretion in patients.

And so in closing this segment, I would just like to say that the GO1 team at Alnylam feels very privileged to have the opportunity to try to bring these new therapeutic patients with PH1.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Great. Thank you, Dave. Let's now turn over to Q&A. I would like to remind all of the listeners that they can submit questions online. Also when you submit your questions, let us know if you would like those questions directed to any particular individual on the call.

With that, let me start with some questions that can really apply to both you, Sally and Jennifer. So I will turn it over to both of you.

The first question is what is the biggest unmet need or challenge in the treatment of hyperoxaluria? Sally, maybe we will start with you and then we will go to Jennifer.

Sally-Anne Hulton - *Birmingham Children's Hospital NHS Trust - Consultant Nephrologist and Clinical Lead*

I think for us when you heard Jennifer speak of the journey that she has had with George, it is a very humbling experience to hear how painful the whole process is. Not only physically for George but with the ongoing issue of medication. And I think we have had no changes in treatment until the institution now of this MRNAi research. We have had nothing new that has been significant in patients with oxalosis for many years now.

The small increase in excitement over looking at gut bacteria has not really developed into anything and now we have a real problem of trying to prevent the end stage kidney failure and trying to prevent oxalate depositing in the body. And for me if we can find anything that can bypass that pathway of the increased urinary oxalate, this is important and I think that is where we now have with potentially this new improvement in looking at maybe urinary glycolates and all of the excretory products to see if there is a way we can alter the pathway is such that the urinary oxidase doesn't increase so much.

This is our way forward and this is where I think the MRNAi technology is going to be really helpful. We have nothing else up to date that can help us with this and this is the key area. You can do as much as you can putting water into infants via tube. When they grow up they have to drink it. We have heard Jennifer speak of how hard it is for George. And I think that that is really a key area for us. And if you think of a this problem in a developed world that Jennifer lives in, how much harder is this in all the areas of Third World medicine. We've got a real challenge.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thank you. Jennifer?

Jennifer Lawrence - - *Roundtable Participant*

Yes. I mean I can only echo what Dr. Anne Hulton said. It is really what we have now is supportive care and at treatment, potential that if it could replace liver transplantation would be wonderful. And of course also as I spoke in one of my slides, a way to improve kidney function or prevent loss, a lot of these kids you showed have presented already with significant kidney loss. So that is another component.

But just to reiterate really not the medication that is difficult for George, it is the amount of water drinking and you are right, we are in a -- he is probably in the best environment to be given to parents who are devoted to watching and supporting him and a whole team of folks helping him. So it is a challenging process. He would be very happy to give up even just a liter he would drink a day for an injection.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thank you. Our next question really would be helpful to get a perspective from both of you as well. The question is what are the features of an ideal treatment for PH1? Maybe this time, Jennifer, let's start with you.

Jennifer Lawrence - - *Roundtable Participant*

Well, as I said, I think George would be delighted to have anything that would help him maintain his kidney function and decrease his continuous water drinking. I think an ideal medication is a medicine that is easy to travel with, oral medicine without side effects. But he takes an injection actually every night at home and he would be willing to take an injection several times a day to replace what he does.

An ideal drug is something that doesn't have a lot of significant side effects that would help him decrease urinary oxalate levels and help him maintain preserve his kidney function and really as a parent with this, I think almost any way to do that, we would be delighted with.

Sally-Anne Hulton - *Birmingham Children's Hospital NHS Trust - Consultant Nephrologist and Clinical Lead*

Yes, I think Jennifer identifies the issue of medication that can be given daily to children and growth hormones, insulin injections, these are things that are done on a daily basis. But if we could have a medication that was for example given monthly and it could be buying injection, ideally orally is better, but a subcutaneous injection given monthly so that it can be given in the home environment. So either the parent or child can actually administer the medication themselves. At the most extended point it would be perhaps by community nurse but if this medication could be given in that form on a monthly basis, that is realistic cost and it could mean an extended to all communities. This would make a huge, huge change to the treatment because that would then result in a change so that there would be no dialysis and requirement for transplantation. It is a huge financial benefit and the economics of all the countries involved with patients with PH1. So those would be my points.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thank you. Now I've got two questions that have come in for you, Dave. The first one is are you going to explore three-month dosing intervals in Part C of the study?

David-Alexandre Gros - *Alnylam Pharmaceuticals Inc. - SVP and Chief Business Officer*

So at this point we are obviously going in with monthly dosing intervals because of what we know about the platform and what we are seeing even in our own Part A data. We won't be surprised if we are able to stretch it to quarterly dosing. Part of the design in Part B is to give three doses a month apart and then wait until the patients oscillate which we hope to go down significantly, returns to its baseline. Once that happens, they would come off study and would be eligible for the open label extension which we would anticipate would be monthly.

However as we watch those levels return, we won't be surprised if a quarterly dosing regimen would be appropriate and we will amend protocols to then follow up with that.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Next question is what is your target for oxalate lowering in PH1 patients in Part B of this study? And there's a second part to this question, is there any risk to lowering it -- to lowering oxalates too much?

David-Alexandre Gros - *Alnylam Pharmaceuticals Inc. - SVP and Chief Business Officer*

Very good question. So the PH1 community, the scientists like Dr. Hulton and her colleague, Gill Rumsby, have published that oxalate lowering of anything greater than about one-third or 30% would be significant meaning above the noise or the natural variation within patients. And so that would be the threshold that you can imagine for a drug to be required.

However, we are targeting greater than 50% decrease in hepatic oxalate production as we believe this level of oxalate lowering would be clinically meaningful for most PH1 patients.

I should note that based upon the data we have to date, we actually hope and expect to see closer to at 70% to 80% decrease in hepatic oxalate production once we get to the proper dose for our patients. And there are no known risks to lowering oxalate too much. As you get it down toward the normal range, patients would start absorbing it from their diet like a healthy person. So it is simply getting it as close to or even into the normal range but no risk of lowering it too far.

David-Alexandre Gros - *Alnylam Pharmaceuticals Inc. - SVP and Chief Business Officer*

Thank you. With that question, I think we now have to close the call. Let me begin to wrap up by thanking Sally and Jennifer for joining us today. Thank you also to all of the listeners for participating and now let me turn it over to you, Josh, for final comments.

Josh Brodsky - *Alnylam Pharmaceuticals Inc. - Associate Director, IR and Corporate Communications*

Thanks, DA. I will also echo thanks to our speakers and thanks to everyone for joining us today. The replay in flags will be posted on the Alnylam website later today at alnylam.com/roundtables with a transcript to follow shortly thereafter.

We hope that you can join us on Tuesday, October 11 at 9 AM Eastern time as we discuss our ALN-HBV program. For more details, please visit www.Alnylam.com/roundtables.

This concludes today's RNAi Roundtable. Thanks everybody and have a great day.
