

19-Aug-2021

# Alnylam Pharmaceuticals, Inc. (ALNY)

**Lumasiran Update Call** 

### CORPORATE PARTICIPANTS

#### Joshua Brodsky

Senior Director-Investor Relations & Corporate Communication, Alnylam Pharmaceuticals, Inc.

#### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

#### Jeffrey M. Saland

Professor - Icahn School of Medicine at Mount Sinai, Alnylam Pharmaceuticals, Inc.

#### John Gansner

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

# MANAGEMENT DISCUSSION SECTION

#### Joshua Brodsky

Senior Director-Investor Relations & Corporate Communication, Alnylam Pharmaceuticals, Inc.

All right. Good morning, everyone, and thank you for joining us for this RNAi Roundtable. Today, we're going to be discussing our lumasiran franchise, which is now largely focused on OXLUMO, which is indicated for the treatment of primary hyperoxaluria type 1, but we're also excited to briefly discuss our plans for lumasiran in to the recurrent stone formers with our new phase 2 program.

Hi, everyone. My name is Josh Brodsky. I'm Senior Director of Investor Relations and Corporate Communication at Alnylam. And with me today, I am pleased to have Jeroen Valkenburg, Senior Director, Iumasiran Franchise Lead; John Gansner, Director of Clinical Research and Clinical Lead for the Iumasiran franchise. And also Dr. Jeffrey Saland, Professor at the Icon School of Medicine at Mount Sinai in New York and a key opinion leader in the treatment of PH1.

Today's RNAi roundtable is the fourth in a series of roundtable webinars that we're hosting over the next few months to review progress across our various programs. Today's event is expected to run approximately 75 minutes. Jeroen will moderate the Q&A session at the conclusion of the presentations. And as always, 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, which is located to the upper right of the slide window.

And finally as a reminder, we will be making forward-looking statements during this webinar and we encourage you to read our most recent SEC filings for a more complete discussion of our risk factors. And now with that, I will turn it over to Jeroen.

#### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you, Josh, and for all of those dialing in now or listening to the recording later. We're very excited that you're joining us to learn more about our lumasiran franchise and I also want to specifically thank Dr. Saland for joining us today to share his experience with managing patients with PH1.

Now as many of you know, Alnylam is the leading RNAi therapeutic company committed to advancing a whole new class of medicines for the treatment of a wide range of diseases. Based on Nobel Prize-winning technology, we can essentially silence any gene in the human genome. And with this elegant and natural mechanism, we can

Lumasiran Update Call



significantly reduce the production of disease-causing proteins or toxic metabolites that contribute to the clinical manifestations of various conditions.

At Alnylam, we've successfully harnessed the RNAi mechanism to build our organic product engine, deliver sustainable innovation and to bring medicines to patients with high unmet medical need around the globe. We truly believe this underscores the transformational potential of this modality as a whole new class of medicines.

And earlier this year, we announced [indiscernible] (00:03:00) new plan to guide Alnylam forward over the next five years called Alnylam P5x25. Alnylam P5x25 is aimed at bringing transformative medicines to patients around the world while advancing a robust and high-yielding pipeline of first and/or best-in-class clinical programs from our organic product engine and delivering exceptional performance.

Our lumasiran franchise for PH1 and for patients with recurrent stones is poised with the potential to make a significant contribution to Alnylam's vision. One of the P5x25 goals is to achieve six or more marketed products by the end of 2025. And we presently have four approved products: ONPATTRO, GIVLAARI, OXLUMO and with our partner Novartis, Leqvio.

Now turning to Alnylam's full clinical development pipeline, you will see that we have over a dozen programs in the clinic spanning Phase 1 to Phase 4 studies. And we are very proud that we built this pipeline organically. And we look forward to advancing these programs and bringing potentially transformative medicines to patients in the future.

Of course today, we'll focus on the lumasiran franchise and the key activities for the programs highlighted here on this slide.

OXLUMO is the first and only approved therapy for the treatment of primary hyperoxaluria type 1 in the EU and US since November 2020. And recently also we achieved regulatory approval in Brazil, with more geographic expansion ongoing, which I will talk to more later. And with that background, it's my pleasure to turn over to Dr. Saland, who is a Professor of Medicine at the Icahn School of Medicine at Mount Sinai in New York. And he's also a key opinion leader in the treatment of primary hyperoxaluria type 1. Dr. Saland?

#### Jeffrey M. Saland

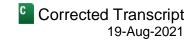
Professor - Icahn School of Medicine at Mount Sinai, Alnylam Pharmaceuticals, Inc.

Well, thank you very much for inviting me to speak. And you should all be where the blue background slide start. Just denotes upfront conflicts of interest. Again this program is sponsored by Alnylam Pharmaceuticals, and I'm presenting on their behalf and I've worked with them in various ways including as a consultant. And there's a Q&A at the end of this presentation as well.

Overall, what I'm hoping to do is, give you a context of kidney stone disease in general and how as physicians we distinguish patients with kidney stones from one another and determine whether or not they may or may not have hyperoxaluria and then moving into primary hyperoxaluria type 1, which I'll just say PH1, because it's so much shorter and easier, talk about that obviously in much more detail.

So, for the next slide with this table in orange just as a background kidney stones are really common. And before we talk about PH1, which is a rare kidney stone disease, it's really important to understand that we are starting with a very big set of patients with kidney stones. It's more common in men, about 1 in 10 10 men will suffer a stone during their lifetime, about 1 in 15 women. But the rate really varies by not only by sex, but by age. So the older a person is the higher the risk. Children rarely have kidney stones, and by race and by race, this is from a

Lumasiran Update Call



national study of self-recorded race. So there's important differences, but basically kidney stones themselves are common.

What about kidney stone recurrence, meaning the fact when a kidney stone it happens once it's just not a recurrent stone, more than once is recurrent. So, this happens on average every seven years on an individual basis. And epidemiologically that would be about 15 per 100 person years. But the rates are really skewed like all statistics, the devil is in the details, right?

So if you, if you're not a person who's really had a recurrent stone, yet your risk is essentially one every 17 years. But if a person has already had at least more than one stone, then that person's risk of having recurrence becomes one every six years. And the upshot of that is that, if an adult has one stone as physicians we often say well, that could be just bad luck maybe poor hydration, combination of factors, but two or more stones that really is probably not bad luck or at least becomes likely enough to be a preventable condition for recurrence that we would start to evaluate it. And none of that applies to children, any stone in a child can be considered abnormal and my joke on the slide is that not just the kids being abnormal, but the stones also.

The next slide. So, in terms of guidelines, there are extensive guidelines and I'm just going to cite a couple of those here, but I would say most clear guidelines among them are American Urological Association guidelines.

So, at a first stone, our physician would essentially review your history, dietary history, family history, get some basic labs most likely. And if a person has managed to essentially have the stone be able to bring it into the office and I'll leave it to your imaginations, but people use things like coffee filters or sort of just scoop them to give you an image of that. But if the person has a stone it can be analyzed chemically.

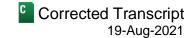
And if a person has two or more stones, then the evaluation should be expanded and become a full-diagnostic evaluation. And here I highlight, again, if a person has the current stones or a childhood stones or these risk factors. So, again, even after the first stone if someone has a family history or presents with a lot of stones or an uncommon stone type or any of these really should be clues that a full evaluation is needed.

Next slide. So, this is a picture of a particular type of kidney stone formed of pure calcium oxalate, a monohydrate, that's the chemical composition. This is quite uncommon in terms of general kidney stones. And if a person brings in a stone that gets a report back that its calcium oxalate monohydrate, that's a pretty good indication that they most likely have primary hyperoxaluria. And that should again lead physician down that road.

At the same time, and this is a picture for the next slide – and you're not meant to sort of be able to read this. Kidney stones, they often look like stones and we're not geologists. It's often hard to tell them apart. This is useful, but it's not really reliable enough just looking at the stone or finding it's composition to really determine if a person does or does not have primary hyperoxaluria and even a calcium oxalate stone can form. That's the most common type of stone regardless of whether a person has primary hyperoxaluria or not the monohydrate being the exception.

So the next type of evaluation we do is, called the timed urine collection. And I joke with my patients that we can really tell a lot by what is in your urine, the same way if you're walking down the street at least in New York, this is true by what you see on the sidewalk before the garbage gets picked up. And the first sort of cartoons are what the way archaeologists go through, ancient trash you can figure out a lot. You can go through current trash and figure out a lot, the last two I guess being manifestations of our current pandemic.

Lumasiran Update Call



The timed urine collection, it's usually over 24 hours. This is the next slide showing that the big brown jug. And as you can guess this is not really a popular activity. It needs a lot of good instruction and patients really it's something that takes a little practice in some cases, but it's possible to do and it gives us good information. When we send this test, we get reports back. These are just two types of examples and I just for the purpose of being able to show them, because they're both from commercial labs. This is from a published paper. So, this is not particular patient, but the table on the left showing sort of color coded risk factors where green is sort of no or low risk factor and yellow and then orange sort of color coded in terms of what's higher risk and lower risk.

And on the right is a different labs interpretation and the graphical form, where depending on the composition of the urine you get essentially a sort of where that patient's risk on the perimeter of that target is and what type of stones are likely to form. These are kind of recommended types of lab reports to guide physicians towards what are the relevant risk factors. But you can see especially in the table, we get a really rich view of what minerals and metabolites are in the urine from this type of analysis. And this defines the risk factors for kidney stone disease.

Highlighting this column oxalate, and again this is just an example, the normal range of oxalate is in this lab's units is 20 to 40. So if a person has 40 or more that defines hyperoxaluria. So that's what we've been talking about. It's nothing more, nothing less than a 24-hour urine sample showing high oxalate. And if a person is over 40, that's high. Over 80, so double the upper limit of normal suggest primary hyperoxaluria pretty strongly.

So, what is oxalic acid or oxalate, it's a pretty insoluble chemical. It combines with calcium very nicely. You can see it – can imagine how nerdy I am at the hardware store, but wood bleach not being something you would probably want in your urine. But that's what oxalate is. It's how insoluble is it, if it were just in water that upper limit of normal. So the 0.44 millimoles corresponds to the upper limit of normal. That would take almost one gallon of water to dissolve. That's not quite true of urine, because we have naturally form – we have naturally occurring stone inhibitors like citrate and other minerals that can make it more soluble. And you know urine is this amazingly evolved solvent for – so that we don't have to drink that much. But, again, if you were to double that amount meaning primary hyperoxaluria, you begin to get an idea of why patients with PH1 do develop stones.

So here we are. We've covered the overall view of kidney stone disease, again, and we've gotten to the point of how we determine a patient has hyperoxaluria in the first place and now we're going to talk about hyperoxaluria itself.

And to simplify it somewhat, this is the next slide showing sort of the simple view of secondary and primary hyperoxaluria. There are basically these two types. Secondary is a way of saying that it comes from the absorption from the intestines. And that can happen essentially in two ways. A person can be eating so much oxalate containing foods that they just absorb a lot of it. And that's I would say less common than you would think.

Most high oxalate foods have a [ph] heart to consume in (00:14:37) the kind of quantities it would take unless you happen to have another risk factor. Other things that are probably more common, so intestinal diseases such as Crohn's disease or other diseases that result in fat malabsorption can cause a person to hyper absorb the oxalate they do eat.

And low calcium intake, that's not a typo, the lower amount of calcium a person takes can actually increase the amount of oxalate they absorb because the calcium is not binding that oxalate in the intestines. So typically patients and many primary care doctors get that reversed. And unfortunately a lot of patients with stones are told to avoid calcium completely. And that's really in about 90% of the time bad advice.

Lumasiran Update Call



Finally, and just to highlight in yellow there genetic testing for PH is really quite useful and has become really the best way to identify patients with hyperoxaluria as having a form of primary hyperoxaluria. And then the Rare Kidney Stone Consortium, and I'll abbreviate that is our RKSC, genetic testing identifies about 90% of cases in the that consortium is a large study that's been going a long time funded by the NIH.

So in PH1, again, about 90% of the patients can be genetically identified. What happens is person overproduces oxalate and the kidney is really the only way that that oxalate can get out of the body that actually cannot go anywhere else. And so, this again is what leads to kidney stones or nephrocalcinosis. I'll talk more about that in a second and can eventually lead to kidney failure, because that oxalate can damage the kidneys.

This is a rare disease. Historically the prevalence is estimated to be 1 to 10 per million with some regions being higher and it's probably underdiagnosed. I'll talk a bit more about that in a second. The median diagnosis of PH1 is during childhood, but a diagnosis is possible at any age. Genetically, and again genetics being probably the most accurate way of diagnosing this condition. Shows that the prevalence is really about one in 150,000. So, the difference between that and historical prevalence is pretty significant. And that's why we understand that it's underdiagnosed not just the fact that it tends to be diagnosed late and we see missed diagnosis, not infrequently. But again the genetic prevalence indicates that there's a range of disease severity as well.

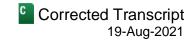
What is the nature of this disease and I believe there's some more slides about this and I'm not going to go through it in great detail, but starting from the end, on the lower right of that white box [ph] as an autosomal recessive disease (00:17:29) genetically you have to have both [indiscernible] (00:17:33) of your gene affected. The bottom-right corner of that box shows calcium oxalate kidney stones, but working back from that that results from an overproduction of oxalate from glyoxylate this product of metabolism. And if you look where that red arrow is the enzyme AGT is defective, normally it converts these to completely benign products of metabolism alanine to pyruvate, but within the absence of that it leads to this cascade that ends up being oxalate. So, normally humans really don't produce much oxalate at all.

One of the signs symptoms and I would say outcomes what happens from PH1. Well, infants and children can really present quite severely ranging from poor growth to kidney failure, which I've seen. And that can happen as young as a few months of age. Nephrocalcinosis is something to highlight. This is not exactly a kidney stone. This is the equivalent of sort of a whiteout if it were a snowstorm where the entire kidney becomes sort of essentially crystallized with calcium oxalate as opposed to as discrete kidney stone. It's quite uncommon condition in general. So, kidney stone formers don't usually have nephrocalcinosis. If they do, it's a sign of PH1 or there are a couple of other rare kidney stones diseases. So this should be a big red flag when that seems. Anybody, who already has progressive chronic kidney disease and kidney stones, it should be considered to have high risk. And that's a sign of PH1.

As kidney disease develops, and again the oxalate deposition and the stone formation itself can cause kidney function to decline another related condition begins to happen systemic oxalosis. And this happens as the kidney fails. It can no longer get rid of oxalate effectively. And so it deposits in other organs and it can damage the bone, bone marrow, heart skin, eye many other parts. And this can really be quite devastating. And it's a disease I hope, I never see again.

Unfortunately, the unmet need here is that, 90% of patients with PH1 progress to kidney failure by the time they're 60 and by 35 about half of them already have. So this is a really, really bad disease to have. And this is something that again. It's historical rates, but these are patients that are studied and that are diagnosed. And so the actual rates in the real world may be different, but this is the best data we have. It's a really significant disease.

Lumasiran Update Call



Also just to point out, again statistically this is starting with about 250 patients, and it looks like a pretty slow decline. So, you could imagine a person's kidney function slowly declining. That's actually not quite the case. Each little sort of vertical line here is someone losing their kidney. And that can happen suddenly even from a very high function, because kidney stones are these sort of rapid events sometimes, a person can have pretty good function and suddenly be blocked by a couple of large kidney stones and lose their kidneys abruptly and there's reports about that. And unfortunately that is not necessarily uncommon.

The progression to kidney failure does vary even among patients with primary hyperoxaluria, and it essentially this is a complex slide to walk you through it in great detail. But the amount of oxalate matters. So how much oxalate is in the urine determines the risk of kidney failure. And those highlighted numbers by the curves you can see that the worst quartiles, meaning the people with the highest amounts of oxalates, those are the patients who are going to progress. And you can see just 30 years after diagnosis 80% of the patients in the worst quartile have lost their kidneys as opposed to those less than 1.6%, which is sort of still a little bit high, but not terrible that – that kidney survival is much better.

So, this really shows that if you can lower the urine oxalates and the hope is that you can affect this disease. And this is a really – historically, this is a slide that has really caught the – caught the eye of investigators. And so, this slide then talking about diagnosis delays is important, because there are so many. In adults, about 50% of the time – by the time they're diagnosed, they already have significant kidney disease. And the delays are really measured in years, not months. And it's so extreme that about 10% of the patients who are diagnosed are diagnosed only after they've actually lost their kidney.

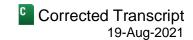
So, these are patients that might have seen doctors for a considerable amount of time and the diagnosis was just not made. And to take it a step further and this is amazing to think about this. A person can have kidney failure, get a transplant and then have what we would consider recurrence and only then be diagnosed. And so it is such a difficult diagnosis to make unless one is aware about it. So this is a really important aspect of this disease.

So what's done and really I'm talking about historically – historically and currently really the most important aspect of all kidney stone diseases, but especially PH1 is hydration. And by hydration, I don't mean a little bit, I mean a lot. When I was training the, you know it really was a huge impact on me to understand that to get young kids to take this amount of water, we had to put in a feeding tube to enable fluid, just water to be given overnight, because there weren't enough hours in the day to help them drink enough. And so you can dissolve oxalate. But again because it's so insoluble, you really need a lot of liquid. Other strategies have involved inhibitors of stone and crystallization. Vitamin B6 is an important aspect of kidney disease management and PH1 about 30% to 50% of patients will have some reduction in urinary oxalate. And that's important to remember. There is at least one mutation that's associated with a good B6 response. But, again, remember that even with all of these things, on the slide 90% of patients progressed to kidney failure. So, none of these things have really done the trick for patients with PH1 historically.

Other treatments and then by treatments I really mean treatments of the disease complications in this case. Stones, you know stones are stones, and urologist is surgeons, who may need to remove or otherwise take out kidney stones and those approaches are pretty routine with the exception being that if they're done many, many times, they can, they can by themselves be damaging things like lithotripsy can damage the kidneys especially if done many, many times.

Chronic kidney disease which can develop really the management is pretty routine for as it would be done for other types of kidney disease. In terms of kidney failure, what's not routine is if a patient ends up on dialysis with

Lumasiran Update Call



PH1 dialysis actually doesn't remove oxalate very well, because again it's just such an insoluble product even with dialysis it's hard to remove, and so we're in a standard patient might need dialysis in the United States 3 times a week. These types of patients will need it daily or even better yet nightly prolonged, prolonged dialysis and sometimes even sort of what we call double dialysis.

Kidney transplants can cure kidney disease in most patients, but they don't really work in patients with PH1 very well and I'll show you that in just one second, because the oxalate that may have deposited in all this other parts of the body can be remobilized once a new kidney is round and come out start to be excreted and essentially ruin a new kidney. So, another strategy that's been done is to replace the liver [ph] as a form of (00:26:15) genetic therapy. So, literally do a liver transplant or a liver kidney transplant. And as you can imagine, that's a whole different level of risk. And these are the outcomes and now coming to towards the end of my talk, but just to highlight the results of transplant, again this is being the most extreme result of PH1 win in the top two boxes of this graph, which I've tried to highlight.

And, again, I know it's a little bit small, but essentially the graphed outcomes for kidney only are pretty poor. And when you do a combined transplant, which is the bottom two panels, the outcomes are a little bit better, but they're still not great. And there's not that many studies of this as you can imagine, but again the transplant outcomes are not ideal. So, this is again historical data, we want to avoid the need for transplant. And I'm not aware of a study that shows the results of dialysis patients, but whatever they would be — they would be much worse than transplant, because dialysis really doesn't cure this disease in patients suffer systemic oxalosis.

So, in summary, PH1 usually presents as a kidney stone disease, kidney stone disease itself being very common and PH1 being very uncommon. So, high index of suspicion is needed, but it's also – PH1 is rare but underdiagnosed and metabolic and genetic evaluation is very easy to combine relatively inexpensive and very good at diagnosing PH1.

PH1 itself is a pretty significant disease untreated or unrecognized, it can be devastating. And when leading to kidney failure systemic oxalis this is one of the worst diseases I've seen. Traditional treatments are okay, but they really have a lot of unmet need left to traditional treatments, we will see about 90% of patients lose their kidneys over time. So that's the end of my section and I'm going to turn it over to the next speaker, I believe, John Gansner.

#### John Gansner

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

Thank you Dr. Saland for that great presentation. I'll now present some recent highlights from the Lumasiran Program, both in the PH1 population and in a new opportunity. We're really excited about recurrent stone formers.

Next slide, please. So lumasiran is a marketed RNAi therapeutic for primary hyperoxaluria type 1. It's subcutaneously administered, small interfering RNA that harnesses the natural RNA interference mechanism of the body. It targets the mRNA for HAO1 which includes glycolate oxidase or GO in the liver and decrease production of GO, reduces hepatic oxalate production and as shown in the figure.

Next slide, please. The ILLUMINATE, Phase 3 program is the largest clinical development program in PH1 to evaluate lumasiran across all ages in the full PH1 disease spectrum. ILLUMINATE-A is a double-blind placebo-controlled trial in PH1 patients six years and older with in eGFR of at least 30. The primary endpoints results have been published in the New England Journal of Medicine, a premier medical journal.

Lumasiran Update Call



ILLUMINATE-B is a single-arm open-label study in PH1 patients less than 60 years old with an eGFR greater than 45. Primary endpoint results were presented last year at the American Society of Nephrology and publication is expected this year.

ILLUMINATE-C is a single-arm open-label study in PH1 patients with severe renal impairment, including those on hemodialysis. Top-line results were released last month and top-line results for systemic oxalosis are expected in 2023. In addition, to the ILLUMINATE studies, we, have a Phase 2 study in recurrent calcium oxalate kidney stone formers that is expected to initiate in 2021.

Next slide. This is a summary of the ILLUMINATE-A Phase 3 study design. We enrolled 39 patients with PH1 and elevated urinary oxalate levels who are randomized [ph] 2 to 1 (00:30:45) to receive lumasiran or placebo. After the six month double-blind period all patients received lumasiran.

Next slide. This shows the percent change in 24-hour urinary oxalate in ILLUMINATE-A. The mean baseline UOx in both the lumasiran group in blue and the placebo group in red was high at 1.8. This is about 3 time to 4 times the upper limit of normal. Patients in the lumasiran group had a rapid and sustained reduction in UOx during the double-blind period. The primary endpoint was positive with a 53.5% reduction in UOx for lumasiran relative to placebo from baseline to month six.

In the extension period, the reduction in UOx was sustained in lumasiran group the blue line. In the placebo group that started lumasiran dosing in the extension period, the red line, the reduction in UOx after starting lumasiran and the extension period was 57.3% versus baseline similar to the lumasiran group in the double-blind period.

Next slide. I want to highlight the proportion of patients with 24-hour urinary oxalate levels less than or equal to 1.5 times the upper limit of normal in ILLUMINATE-A. As you can see in the graph on the right, 84% of patients treated with lumasiran achieved near normalization or normalization at month six compared to the 0% of patients treated with placebo. This response was sustained at month 12. You see the 88% and the extension period and 77% of patients who crossed over from placebo to lumasiran in blue achieved near normalization or normalization at month 12.

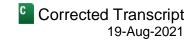
Next slide. In terms of safety in ILLUMINATE-A, the profile remained consistent at months 12 with what had been observed during the double-blind period. The majority of adverse events were mild in severity. Most were common – the most common related adverse events in at least 10% of patients were injection site reactions which were mild and transient. One patient with a serious adverse events of zero sepsis, which was graded severe was considered not related to study drug.

Next slide. This is a summary of the ILLUMINATE-B Phase 3 study design. We enrolled 18 patients with PH1 and elevated urinary oxalate to creatinine ratios to receive lumasiran with dosing according to weight.

Next slide. This shows the percent change in urinary oxalate excretion from baseline to month six for ILLUMINATE-B. Remember that in this young patient population 24-hour urine collections are generally not feasible. And that is why spot urine collections were used for the primary endpoint. As you can see, there is a rapid and sustained reduction in spot urinary oxalate to creatinine ratios across all weight groups. It's a 72% reduction versus baseline for the overall population as shown on the right.

Next slide. In terms of safety results for ILLUMINATE-B, one serious adverse event occurred which was considered not related to the lumasiran. This was a viral infection. Most common drug-related adverse event was injection site reactions in three – the 17% of patients all were mild and transient.

Lumasiran Update Call



Next slide. This is a summary of the ILLUMINATE-C Phase 3 study design. And this open-label multi-center single-arm study we enrolled 21 patients of all ages with advanced PH1. These patients had to have elevated plasma oxalate levels and impaired renal function. In cohort A, patients were not on hemodialysis. In cohort B, patients were on hemodialysis. Top line results for the six month primary analysis period were released in July, and I'll review them on the next slide. All results are expected to be presented at a medical meeting later this year.

Next slide. So for the top line results for ILLUMINATE-C, lumasiran achieved substantial reductions in plasma oxalate relative to baseline in both, dialysis-independent and dialysis-dependent patients. lumasiran administrated and encouraging safety and tolerability profile, there were no deaths or drug related SAEs most common AEs where ISRs injection site reactions in five patients for 23.8%, all of which were mild. There were two discontinuations due to adverse events both occurring during the extension period and neither related to study drug. And I want to note that supplemental regulatory filings are expected to be submitted to the FDA and EMA in late 2021.

Next slide please. I'd like to make a transition now and spend some time discussing clinical endpoints. I'm going to start with eGFR, which is a measure of kidney function and it's very important for patients with PH1 they are at risk of developing kidney failure as discussed by Dr. Saland. The results on this slide are from ILLUMINATE-A and ILLUMINATE-B and what you can see is that eGFR has remained stable through the treatment period in both studies.

Next slide please. On this slide, we're looking at an exploratory analysis of kidney stone event rates. I'll start with ILLUMINATE-A on the left where the results are broken out by treatment group, because the historical rates of kidney stone events were different between the groups. As you can see patients initially randomized to lumasiran, in the left lumasiran – lumasiran panel, the historical rate was 3.19.

During the first six months of the lumasiran treatment, the rate was lower at 1.09. And during the next six months of treatment from months 6 through months 12, the rate was 0.85. In the placebo the lumasiran panel in the center the historical rate was 0.54 for the rate on study with placebo was similar at 0.66, and the rate from months six through month 12, which represents the first six months of lumasiran treatment was lower at 0.17.

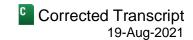
So for ILLUMINATE-A, in both groups, we're seeing a lower kidney stone event rate after the start of lumasiran treatment. In ILLUMINATE-B, on the right, the historical rate was low at 0.24. And after six months of treatment, the rate was also 0.24. So, no change to-date, but relatively low event rates.

Next slide, please? To wrap up the discussion of clinical endpoints, I'd like to review our data on something called medullary nephrocalcinosis, which Dr. Saland also briefly mentioned. And this is caused by calcium oxalate deposits in the kidneys. The development in nephrocalcinosis has been shown to increase the risk of developing kidney failure.

In ILLUMINATE-A, we found that medullary nephrocalcinosis upgrade was mostly stable or improved. On the left, we have the placebo group. And you can see that 85% of patients were stable, no patients had improvement, and 8% had worsening nephrocalcinosis.

In the center panel, after six months of lumasiran treatment, most patients had stable nephrocalcinosis, 11% had improvement, including bilateral improvement and 3% had worsening. On the right, for the subset of patients who have been treated with lumasiran for 12 months, 46% had improvement including a large proportion with bilateral

Lumasiran Update Call



improvement, 17% were stable and 13% had worsening, including a small proportion with bilateral worsening. We did have a higher percentage of missing data in month 12 in part due to COVID-19.

Next slide please? This is data for ILLUMINATE-B, where we saw that medullary nephrocalcinosis grade was stable or improved. After six months of lumasiran treatment, 56% of patients were stable and 44% showed improvement, including bilateral improvement.

Next slide please. To conclude this section, Alnylam's Lumasiran Program is the largest clinical development program in PH1 across all patient types. We have demonstrated significant and sustained lowering of UOx in infants, children and adults with preserved renal function in the ILLUMINATE-A and ILLUMINATE-B, we've demonstrated substantial reduction of POx in patients with severe renal impairment including dose on hemodialysis and ILLUMINATE-C, we've seen encouraging signs of improved clinical outcomes and measures in an otherwise progressive disease with stable eGFR, reduction in kidney stones and improvement in nephrocalcinosis grade, we've seen an encouraging safety and tolerability profile and we're excited about the ILLUMINATE-C top line results on systemic oxalosis endpoints that are expected in 2023.

Next slide please. At this point, I'd like to spend my last few minutes discussing the new opportunity that we're very excited about lumasiran for recurrent kidney stones.

Next slide please. So, recurrent calcium oxalate kidney stone disease is associated with significant clinical burden including pain, infection, sepsis, hospitalizations and a greater risk for developing chronic kidney disease and end stage kidney disease. There are limited effective treatment options and despite best standard of care, recurrent stones still occur. Approximately 80% of kidney stones in adults are performed from calcium oxalate crystals with up to 2.5 million Americans having recurrent calcium oxalate stone disease with elevated urinary oxalate by our estimates.

Next slide please. We're expecting to initiate a proof of concept Phase 2 study in recurrent calcium oxalate stone formers with elevated urinary oxalate levels by the end of the year. We believe there is a strong rationale for using lumasiran in this population. And as you can see from the figure on the right, endogenous synthesis of oxalate makes up over 50% of the total oxalate excreted in the urine in healthy volunteers. We do plan to exclude patients with secondary elevation of urinary oxalate and recurrent kidney stones from our Phase 2 study. The primary endpoint in the study will be the percent change in urinary oxalate from baseline to months six.

Next slide please. And with that, I'll turn it back over to Jeroen for final thoughts on the future of the franchise. Thank you.

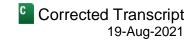
### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you. So much, John, and also thank you Dr. Saland, we really appreciate it. And those were great presentations. Let's now turn to the program opportunity and commercial progress.

So, at this stage ahead of our Phase 2 study for lumasiran and recurrent stone formers as John just showed, it's too early to discuss the market opportunity for the lumasiran in detail, but of the 3 million to 5 million Americans with recurrent calcium oxalate stones, approximately up to 2.5 million have elevated urinary oxalate. And based on that, lumasiran has the potential to grow into a specialty franchise. And our primary focus over the next couple of months is to initiate our Phase 2 program by the end of this year as highlighted by John previously.

Lumasiran Update Call



So, I'll now turn to lumasiran's market opportunity for PH1, which as you know is a rare progressive genetic disease with debilitating and life-threatening clinical manifestations. PH1 one has a low index of suspicion as illustrated by Dr. Saland earlier with many patients who believe as many as 50% remaining undiagnosed. Patient diagnosis can often occur late in the course of the disease and in adult patients specifically, there's a median delay of approximately six years between onset of clinical manifestations and a definitive diagnosis.

Up to two-thirds of the patients will receive their diagnosis after reaching end stage kidney disease. And this is also why we're excited about ILLUMINATE-C data, which included exactly those patients. With progression of disease and as the kidneys begin to fail, intensive dialysis up to six days of the week is needed as a bridge to dual liver kidney transplant with the average cost of transplantation and accompanying lifelong immunosuppression exceeding \$1 million. Thus there is an urgent unmet need for alternative treatment options that adequately reduce oxalate production at its source preserve kidney function and have the potential to change the natural course of the disease.

As per John's update OXLUMO has the largest clinical development program across all patient types, including infants, children and adults with severe renal impairment, including those on dialysis.

Across these patient types OXLUMO has accumulated the longest clinical trial experience of any PH1 treatment with an encouraging safety and tolerability profile and has shown reductions in urinary oxalate and plasma oxalate along with encouraging signs of improved clinical outcomes that we believe ultimately matter most to treating [ph] HCPs and their (00:44:57) patients.

With our comprehensive clinical development strategy, we hope to make OXLUMO available to all patients across the spectrum of PH1 regardless of age and regardless of disease severity. Now given the etymology of the disease and the lack of other approved therapies and Alnylam's approach towards disease education which I'll talk to more shortly, we [indiscernible] (00:45:19) the market opportunity to be over \$500,000, representing the potential or significant revenue source to Alnylam. And our commercial team is working hard to achieve that goal and therefore we'll take a look at OXLUMO's global commercialization progress next.

As I mentioned OXLUMO was already approved since late 2020 in the US and EU and also now approved in Brazil. We have successfully launched in the USA and Germany, and we have named patient sales in France and other markets. The commercial team is working hard on additional launches in the Netherlands and Luxemburg in 2021. And Italy, Spain, and Belgium are expected in 2022.

We also have partnerships in place in Turkey and Israel aiming to have access to OXLUMO in also 2021 and 2022. And finally, we continue to expand our footprint for OXLUMO globally with continued global regulatory filings and launch plans across regions. I'll speak to our regulatory filings in more detail shortly, but now let's look at OXLUMO commercial Q2 and year-to-date performance approximately eight months after approvals in the USA and Europe as we disclosed at our Q2 earnings call recently.

And what we see is continued demand strengths in OXLUMO's second full quarter of launch and we achieved \$16 million in global net product revenues in the second quarter and attained approximately 100 patients on commercial OXLUMO treatment in the US and EU as of June 30.

Our market efforts are progressing very well with no [ph] access headwinds and confirmed (00:46:53) medical policy inclusions for over 80% of covered US lives and seven value-based agreements finalized to-date with commercial payers. And it's important to put into context that OXLUMO is Alnylam's third successful RNAi launch. And because of that, we can leverage the infrastructure that has been built and continues to be expanded upon

Lumasiran Update Call



from ONPATTRO and GIVLAARI as shown on this slide. Like ONPATTRO and GIVLAARI, OXLUMO's playbook with a strong product profile backed up by the largest clinical development program in PH1 today with our ILLUMINATE-A study recently published in the New England Journal of Medicine and our publication for ILLUMINATE-B in infants and young children expected this year and ILLUMINATE-C top-line results just presented and full data to be released at an upcoming medical congress.

Now, first and foremost the main commercial focus right now is to help those patients that have already been diagnosed with PH1 and they're treating healthcare professionals to get access to OXLUMO as soon as possible. In addition to our societal engagement with both medical and patient communities we partner to enhance disease awareness leading to early diagnosis and improve diagnosis rates and we focus specifically on pediatric and adult nephrology and urology specialties.

And on that front, we are continuing to leverage our healthcare professional facing disease state awareness campaign that we referred to us Behind The Stone and this campaign urges physicians and healthcare professionals to look beyond acute stone events and provide tools and resources including about PH1.com which is a disease education website that highlights PH1 unpredictable rate of progression and navigates the path to an accurate diagnosis.

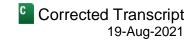
Now an important goal of this campaign is to increase suspicion help PH1 in any pediatric patient who presents would even a single kidney stone or any adult patients with recurring stone events and to include PH1 as part of the differential diagnosis. Now this campaign also emphasizes the importance of early intervention and disease management given the devastating consequences of progressive renal dysfunction as presented by Dr. Saland earlier today. To-date this website for healthcare professionals has had over 44,000 unique visitors with over a 1,000 [indiscernible] (00:49:15) and over 300 materials downloaded highlighting the interest in the medical community.

Now, staying in a digital space with COVID, we've also further expanded our digital disease educational programs with well-established digital educational companies shown here on the slide such as Medscape, Medthority and PeerVoice. And through these online programs, we've already reached thousands of positions around the globe and expect to reach thousands more over the next coming months.

Now, improving disease awareness is of course ultimately driving diagnosis of PH1 and we support that through our Alnylam Act Program, which is a sponsored no chart third-party genetic testing and counseling program for patients with a family history or suspected diagnosis PH1. We've already received over 500 tests for PH1 year-to-date. And we've also expanded this program into parts of our CEMEA region or it's called Gene Act. And this will further support physicians with making a rapid and accurate diagnosis of PH1. And also Alnylam Act and Gene Act are great examples of where the TTR and acute hepatic porphyria infrastructure has successfully paved the way for PH1.

Of course diagnosis needs to come hand-in-hand with access. And at Alnylam we've developed innovative solutions to ensure our patients have access to the therapeutics that they desperately need. And we've been successful in negotiating value-based agreements or VBAs that link payment to real world outcomes. And we've introduced prevalence-based and patient need adjustments within the framework of our VBAs for OXLUMO to mitigate the risk of escalating our variable costs for payers. And this approach is working. As I've shown on our Q2 results, we successfully negotiated seven value-based agreements and have realized greater than 80% of US lives covered for OXLUMO.

Lumasiran Update Call



We've also built our own bespoke patient assist hub called Alnylam Assist to guide and support US patients throughout their treatment. And using Alnylam Assist patients can be connected with dedicated case manager who provide supportive services including benefit verification and coverage explanation.

Given the complexities of US healthcare system, this level of personalized support can make a world of difference for patients seeking or undergoing treatment with OXLUMO. Now in terms of the next steps for lumasiran, we are excited to have just released a top-line data from ILLUMINATE-C and are aiming for full data release at a Medical Congress later this year and through ILLUMINATE-C clinical program together with ILLUMINATE-A and ILLUMINATE-B, we aim to establish lumasiran as the therapeutic option for PH1 regardless of age or disease severity including patients on hemodialysis.

Now towards that goal we intend to file supplemental regulatory applications within the US Food and Drug Administration and the European Medicines Agency in late 2021. Furthermore as John outlined, the 24-month we sold on systemic oxalosis from ILLUMINATE-C are expected in 2023. And if possible we plan to submit supplemental regulatory applications with the FDA and EMA thereafter, further strengthening our already strong label. Then more in the near-term, we're also expecting regulatory approvals in Switzerland, Israel and Canada and continue to expand our regulatory approvals around the globe over the next couple of years.

And as discussed earlier by the end of this year we're also initiating a Phase 2 trial to explore lumasiran's potential for recurrent stone formers. And finally, we are proud to show our commitment to the PH1 community with approvals now when the US, EU and Brazil and upcoming expected label expansions and approvals around the globe to grow our franchise further to positively impact the lives of patients with PH1 and their caregivers.

And with that I want to thank you for your attention and we'll now turn to the Q&A with the questions.

# **QUESTION AND ANSWER SECTION**

#### Jeroen J. Valkenburg

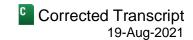
General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

And the first question let me just hold this up. The first question is how is OXLUMO's launch progressing and what has contributed to the initial launch strength. And I'll take this question first and for other questions, I'll ask Doctors Gansner and Saland to join in as well.

So, as I mentioned earlier, we've achieved a global net product revenues of \$60 million, which is a 79% quarterover-quarter growth with approximately 100 patients on commercial drug.. And the drivers for that strong launch uptake is a couple of things. First, we see very smooth and seamless transition from our EAP program our early access program in Europe. Thanks to the collaboration between our local medical affairs team, the access team and the commercial team and so when physicians opt and choose for the treatment to continue, these patients are now transitioning to a commercial drug.

As I mentioned the access part of it, we have no headwinds on the access side with over [indiscernible] (00:54:27) now already in the US. and over 80% of lives covered for OXLUMO to-date. And I think when I just listened to Dr. Saland's presentation, we also should put into context that this is a terrible disease and there is a high unmet need and physicians and patients are looking for ways to rapidly lower urinary oxalate in a sustainable manner and they're also looking for ways to lower plasma oxalate with the ultimate goal to, of course, prevent

Lumasiran Update Call



progressive kidney disease and I think this high unmet need in infants, young children, adults is also driving the fast uptake that we're seeing.

With that, I think I have a question, John, for you. It's about recurrent renal stones. And it's very simple one, what are the next steps in recurrent renal stones?

John Gansner

be eligible.

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

Sure. Thanks, Jeroen. So, as mentioned earlier week we plan to initiate a Phase 2 study in late 2021 to investigate whether lumasiran can reduce the risk of renal stone occurrence in patients suffering specifically from calcium oxalate – recurrent calcium oxalate stones and they will have to have an elevated urinary oxalate level to

Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you, John. I will now turn to some questions on ILLUMINATE-C and John and Dr. Saland, I'll ask you to comment both. But John, first for you, what's the significance of the top line results and what do they add to what has already been shared from the ILLUMINATE-A and ILLUMINATE-B studies?

John Gansner

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

Okay. Well, maybe I can take a step back first and just sort of frame this again. So, ILLUMINATE-C studied patients with advanced PH1. And so, those patients have severely impaired kidney function including end stage kidney disease and once they reach end stage kidney disease, they've historically been treated with intensive hemodialysis and required potentially dual liver kidney transplant which is a procedure that Dr. Saland highlighted is associated with high morbidity and also lifelong immunosuppression potentially.

So, there's a lot of morbidity associated with advanced PH1 and this morbidity is really related to elevated plasma oxalate levels. And the elevated plasma oxalate can cause systemic oxalosis, which is deposition of oxalate and in multiple tissues leading to things like bone fractures, cardiomyopathy, impaired red blood cell production, vision loss, all sorts of serious manifestations.

And so, the top line data from the ILLUMINATE-C study show that treatment with lumasiran can reduce elevated levels of plasma oxalate in patients with advanced PH1 compared to baseline. And so combined with the findings from ILLUMINATE-A and ILLUMINATE-B, we believe the results demonstrate the potential for the lumasiran to provide a therapeutic option across the spectrum of PH1 regardless of age, regardless of disease severity, including in patients on hemodialysis and the safety and tolerability profile of the mass rand. Following six months of treatment in ILLUMINATE-C is encouraging with a safety profile that essentially matches what is observed in ILLUMINATE-A and ILLUMINATE-B and ILLUMINATE-C there were no drug related serious adverse events and an injection site reactions were the most common drug related AEs reported in more than 10% of patients or at least 10% of patients. And all of the injection site reactions were mild. So that's sort of a I think that answered your question.

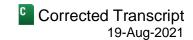
Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thanks, John. Yes it did. And maybe I can invite Dr. Saland to give a clinical perspective on what ILLUMINATE-C means for patients with advanced hyperoxaluria type 1 Dr. Saland.

FACTSET: callstreet
1-877-FACTSET www.callstreet.com

Lumasiran Update Call



#### Jeffrey M. Saland

Professor - Icahn School of Medicine at Mount Sinai, Alnylam Pharmaceuticals, Inc.

Sure. Yeah. Again, this is the group of patients that have already suffered such kidney damage that the oxalate that's being produced in their liver simply cannot get out of their body fast enough. And it's building up their eyes and their heart. They're getting heart failure. They're breaking bones. It's you know – it's really devastating to see patients affected like this, even children you know I've had teenage patients with multiple fractures and heart failure from this condition. And you know I'd like to make up silly metaphors and sort of imagery. But if you can imagine having a flood in your, in your bathroom from a bathtub that's overflowing, because the drain is clogged and the faucet is turned on as fast as it can be, because in this case it's the oxalate. It's filling up, filling up this patient with oxalate and the faucets wide open. So the hope right is that this disease can be stopped by turning off the faucet and at least not having it flood, right.

You've already flooded. Patient's kidneys are failed. Turning off the oxalate production, if that's possible, and again this is what the top line results seem to show. You know this is really important. There's very little hope of helping a patient in this the age of the disease without stopping oxalate production. And that's what historically would drive us to do something. I mean, if you think about it as radical as taking out their liver completely taking it out and replacing it with somebody else's liver as a form of genetic therapy. So we're taking a very blunt type of treatment, a very blunt instrument and using very precise RNA interference to silence the gene instead of taking someone's liver to do that. It's just, it's a – it's something that as a clinician you hope you get a treatment like this.

#### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you so much Dr. Saland, and staying with you, we have another question that just came through which is about recurrent stone formers and the question is does it require chronic treatment and what treatment duration do you think is required.

#### Jeffrey M. Saland

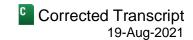
Professor - Icahn School of Medicine at Mount Sinai, Alnylam Pharmaceuticals, Inc.

Well, this is a broader question. So again stone formation in general is a very common thing, 10% of — approximately 10% of the population mainly adults will have stones and then some subpopulation of them will have recurrent stones. It's very important to understand that that analysis is has to be done to figure out why is a person having stones.

And if you were to narrow that down to the group of patients that has hyperoxaluria. You're not in this case necessarily primary hyperoxaluria, but recurrent calcium oxalate stones. That group of patients tends to have multiple recurrences over time. And again that that one slide that I showed the statistics ends up being about one every six years. But some of those patients actually have considerably more frequently. So again – and if you're talking about a bell curve as you go out further once the patients had two or more stones their time median time recurrence would be even less. And certainly there are patients I've seen that have incredibly frequent stones and lots of complications even though they don't have PH1. And we don't always necessarily find why a patient is having that.

So the exact number of those patients is probably unclear. But it's a large number compared to PH1. And if you can reduce the production of oxalate in addition to addressing dietary and other potential risk factors I think that could be a significant contributor to helping those patients. But again that's a study that's yet to be done and just have to wait and see.

Lumasiran Update Call



#### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you so much Dr. Saland. John any additional thoughts from your side on that?

Д

#### John Gansner

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

No. I think Dr. Saland covered it nicely. I mean, again if you're a recurrent stone former. I think if you look at the guidelines, most of these patients are asked to follow chronic and sort of take what you would considered a chronic treatment approach, which stay hydrated and do various things like that. So I would – yeah, so I think we can leave it at that.

••

#### Jeroen J. Valkenburg

General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thanks John and Dr. Saland. And question that just came in is I think John this is for you, the first part and I'll take the second part. And it's why wouldn't you consider PH2 and PH3 as a potential indication and what do you think of Dicerna's recently published Phase 2 trial date off for PH2 patients. Thank you. John?

Δ

#### John Gansner

Director - Clinical Research, Alnylam Pharmaceuticals, Inc.

Yeah. Okay. So, we have a targeted therapy for PH1 with lumasiran. And, obviously we thought about PH2 and PH3. I think what I can say about them is that the biochemistry is complex. And I think that's illustrated by the recent Dicerna results. And so I guess I can't give a definitive. But we certainly feel comfortable with PH1 and having a targeted therapy for PH1. I know Jeroen you said you'll address the Dicerna results, so I mean I'll turn it over to you for that.

Δ

#### Jeroen J. Valkenburg

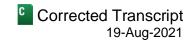
General Manager - Lumasiran, Alnylam Pharmaceuticals, Inc.

Thank you, John. And I think first and foremost, you have to take one step back and the PH community is a very small community of passionate physicians and patient advocates and patients, their families and caregivers, including companies like Alnylam, Dicerna and other companies. And we're all routing for a positive outcome for patients with PH2.

Unfortunately, the results from givosiran were not positive and it showed mixed results, especially for patients with PH2. And so, for patients with primary hyperoxaluria type 1, it's also important to look at that there's no head-to-head studies done. So, any comparisons here need to be done with that caveat and with that disclaimer, but the data that was included in the top line results basically gave us even more confidence in the opportunity for OXLUMO. And that's because of the data that that John had shared with you on the most comprehensive clinical program for PH1, where we have data for patients across all patient types and all ages. And, yeah, these data builds us – makes us believe that that OXLUMO is best positioned and that it will be very difficult for givosiran to overcome that that have start, right. And outside of the of the data results, I think what I spoke to earlier is that this is Alnylam's third RNAi launch and we have a global footprint established. We have playbooks that we've learned from ONPATTRO that we've learned from GIVLAARI. And I think that's also an element where we – that benefit will be very difficult if not impossible without a different shading product to overcome.

So, I hope that answers that question.

Lumasiran Update Call



And I think with that, we are – we have no further questions. So, Josh, I think I'm going to turn over to you for final thoughts and closing remarks.

noughts and closing remarks.

#### Joshua Brodsky

Senior Director-Investor Relations & Corporate Communication, Alnylam Pharmaceuticals, Inc.

All right. Thank you very much, Jeroen, and thanks to all of our speakers. So, that does it for today's RNAi roundtable. As always, you can access the replay of the webinar. You can download the slides on the Capella section of Alnylam's website. And once it becomes available, we'll plan to post the transcript of this event there as well.

Now, we want to remind you that we have two more upcoming roundtables in the series. The next one will be on Monday, September 20. And we'll focus on our earlier stage liver-directed RNAi therapeutics pipeline programs. And then a couple of weeks later, we'll conclude the 2021 series with an RNAi roundtable on our CNS and extra hepatic delivery efforts. So, we hope you can join us for both of these events.

So, that concludes this event. Thank you all for joining and hope you have a great day. Bye-bye now.

**Operator:** Ladies and gentlemen, this concludes today's conference call. Thank you for your participation. You may now disconnect.

#### Disclaimer

The information herein is based on sources we believe to be reliable but is not guaranteed by us and does not purport to be a complete or error-free statement or summary of the available data. As such, we do not warrant, endorse or guarantee the completeness, accuracy, integrity, or timeliness of the information. You must evaluate, and bear all risks associated with, the use of any information provided hereunder, including any reliance on the accuracy, completeness, safety or usefulness of such information. This information is not intended to be used as the primary basis of investment decisions. It should not be construed as advice designed to meet the particular investment needs of any investor. This report is published solely for information purposes, and is not to be construed as financial or other advice or as an offer to sell or the solicitation of an offer to buy any security in any state where such an offer or solicitation would be illegal. Any information expressed herein on this date is subject to change without notice. Any opinions or assertions contained in this information do not represent the opinions or beliefs of FactSet CallStreet, LLC, or one or more of its employees, including the writer of this report, may have a position in any of the securities discussed herein.

THE INFORMATION PROVIDED TO YOU HEREUNDER IS PROVIDED "AS IS," AND TO THE MAXIMUM EXTENT PERMITTED BY APPLICABLE LAW, FactSet Calistreet, LLC AND ITS LICENSORS, BUSINESS ASSOCIATES AND SUPPLIERS DISCLAIM ALL WARRANTIES WITH RESPECT TO THE SAME, EXPRESS, IMPLIED AND STATUTORY, INCLUDING WITHOUT LIMITATION ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, ACCURACY, COMPLETENESS, AND NON-INFRINGEMENT. TO THE MAXIMUM EXTENT PERMITTED BY APPLICABLE LAW, NEITHER FACTSET CALLSTREET, LLC NOR ITS OFFICERS, MEMBERS, DIRECTORS, PARTNERS, AFFILIATES, BUSINESS ASSOCIATES, LICENSORS OR SUPPLIERS WILL BE LIABLE FOR ANY INDIRECT, INCIDENTAL, SPECIAL, CONSEQUENTIAL OR PUNITIVE DAMAGES, INCLUDING WITHOUT LIMITATION DAMAGES FOR LOST PROFITS OR REVENUES, GOODWILL, WORK STOPPAGE, SECURITY BREACHES, VIRUSES, COMPUTER FAILURE OR MALFUNCTION, USE, DATA OR OTHER INTANGIBLE LOSSES OR COMMERCIAL DAMAGES, EVEN IF ANY OF SUCH PARTIES IS ADVISED OF THE POSSIBILITY OF SUCH LOSSES, ARISING UNDER OR IN CONNECTION WITH THE INFORMATION PROVIDED HEREIN OR ANY OTHER SUBJECT MATTER HEREOF.

The contents and appearance of this report are Copyrighted FactSet CallStreet, LLC 2021 CallStreet and FactSet CallStreet, LLC are trademarks and service marks of FactSet CallStreet, LLC. All other trademarks mentioned are trademarks of their respective companies. All rights reserved.