CURE Epilepsy Webinar
Cutting Edge Technologies for Treating Nano-Rare Epilepsies
(Transcript)

Dr. Laura Lubbers: I want to thank you for joining us today. Rare Disease Day is Tuesday, February 28th and in recognition of it, today's webinar is entitled Cutting Edge Technologies for Treating Nano Rare Epilepsies, and it is intended for everyone, including persons with epilepsy and their caregivers. Rare diseases are defined as those that affect fewer than 200,000 people in the United States. However, there are many diseases that are caused by genetic mutations that only impact a handful of individuals worldwide. In these cases, the small number of people present a variety of challenges to identifying and developing effective treatment options, including navigating a long diagnostic journey, often with misdiagnosis and the high cost of clinical trials. This webinar is the second installment of the 2023 Cure Epilepsy Webinar series where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the Cure Epilepsy website.

You can also download transcripts of all of our webinars for reading. Cure Epilepsy is proud to celebrate our 25th anniversary this year. Since our founding in 1998, we've raised millions of dollars to fund epilepsy research that supports our mission, which has defined a cure for epilepsy by promoting and funding patient-focused research. Cure Epilepsy provides grants that support novel research projects and that advance the search for cures and more effective treatments. Included in our research portfolio is a new funding mechanism we launched last year called the Rare Epilepsy Partnership Award. This award supports the development of the necessary tools, techniques, models, and data collection platforms to stimulate and accelerate research on rare epilepsies. Each award is co-funded by Cure Epilepsy and one or more rare epilepsy partner organizations. If you are a researcher, please check out our website in the coming months for updates on this funding mechanism.

Today's webinar will highlight the work of n-Lorem Foundation. The n-Lorem Foundation is focused on creating free individual treatments for people with what are termed nano-rare diseases caused by genetic mutations that affect 30 or fewer people in the world. 40% of n-Lorem Foundation's patients suffer from epilepsy, and these people may benefit from more individualized treatments that meet the unique needs of each person. This webinar will also discuss the use of individualized antisense oligonucleotides or ASOs for treatment of these nano-rare epilepsies. ASOs are short strands of modified deoxyribonucleic acids or D N A that can be developed rapidly and inexpensively and can specifically target and potentially halt the development of disease-causing proteins, thus attempting to change the course of the disease. This webinar is presented by Dr. Sarah Glass, the Chief Operating Officer at the n-Lorem Foundation. She leads the implementation of the foundation's mission to discover, develop and provide personalized experimental medicines for people with diseases caused by genetic mutations affecting fewer than 30 individuals worldwide.

Dr. Glass is passionate about forging partnerships to increase our collective ability to provide hope for people in need. She combines her professional

experience as a geneticist, drug developer and clinical trialist with the urgency she has felt as the parent of a nano-rare child. Before Dr. Glass begins. I'd like to encourage everyone to ask questions. We'll address the questions during the Q and A portion of the webinar. Keep in mind you may submit your questions anytime during the presentation by typing them into the Q and A tab located on your WebEx panel and clicking send. We'll do our best to get through as many of the questions as we can. We do want this webinar to be as interactive and informative as possible, however, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. So with that, I'll turn it over to Dr. Glass.

Dr. Sarah Glass: Great, thank you so much Laura. I'm really happy to be here with you today. I really appreciate the opportunity to talk with you today about the work that we're doing at the n-Lorem Foundation as Laura so kindly introduced is a nonprofit organization that is really focused on the mission of applying the efficiency, versatility and specificity of antisense technology. And we really apply this to be able to offer treatments to patients who otherwise do not have an opportunity for treatments in today's drug development environment for rare diseases. And ultimately these are the patients that are affected by mutations that are seen only in a handful up to 30 patients worldwide. And I think ultimately what we've already heard, many of these patients are either not diagnosed or have taken many, many years to even get to the place of having a diagnosis. And what we've learned through our couple of years, since being established in 2020, is that ultimately there are so many individuals actually, even though each patient is unique, and there are so many though that really need this help.

And really that's why we are focused on this mutation-directed drug discovery and development for this patient population. And I think what the premise behind n-Lorem being founded in January of 2020 is really because of the gap in healthcare for this patient population. And ultimately we know that there is not a path for commercial approval for patients with these types of mutations for these particular treatments as well. We also know that we have four F D A guidance documents that were released in January, April and December of 2021 specific to these antisense oligonucleotides for individual patients. This is exceptional. These are F D A guidance documents specific to this technology that really provides this really wonderful and robust roadmap for n-Lorem to be able to ensure that we are discovering and developing quality ASOs for every single patient.

So, I guess, if we just start for a moment, what is antisense technology? Laura introduced it at a very high level and really what is the importance of quality and experience? So ASOs are these single-stranded synthetic R N A sequences. They're designed to selectively bind via this complementary-based pairing to the R N A of encoding the gene of interest. And really what n-Lorem is focused on is really enabling and applying this technology in a way that can work towards scaling to help many, many patients and as many patients as we can that are in need. And the technology here is a really important focus and this technology is

the reason that an organization like n-Lorem is actually even feasible. The question is how in the world does an organization be able to say specifically that we're going to actually discover, develop, and offer a drug for free for life and then actually be able to stand behind that, really and truly.

And it's because of these specific characteristics that you can see here. Now it's rapid, it's efficient, it's versatile so there's multiple different routes of administration, a number of different organs that we can target. It's validated and it's well understood and I think that, for myself, joining n-Lorem and was so exceptional to talk to Dr. Stan Crook who is our C E O who also pioneered R N A Therapeutics over 35 years ago. Really understanding this down to every single chem chemical modification and having all of this experience to be able to understand the consequences of making these minor modifications, which perhaps might seemingly be minimal and not have significant outcomes, but they actually do. And so having that experience is so important for every single patient. And I think that for free for life, so what does that really mean in the context of drug discovery and development?

This technology is we're able to manufacture in a very cost effective manner. And so we have really worked over the last couple of years to continue to optimize and refine this very precise drug discovery and development process and that enables us to really have this scalable approach that is going to enable us to help many more patients in the future. So I think it's important just to touch on really what is the process. And so for every single patient that n-Lorem ultimately brings into the program applies this three decades, of really advances, in the medicinal chemistry through massive parallel screening for every single patient looking across typically around thousand sites in the R N A, many, many ultimately thousands of chemistries that have been studied over the past years. Ultimately designing typically in the order of 500 ASOs for each patient as the start of that funnel, then we go through this rigorous drug discovery and development process to ultimately lead us to the optimal ASO that we move through the clinic.

And underpinning all of this is really the knowledge around the molecular mechanisms and again, what are these factors that affect the ASO activity? And some of these listed here, but there are many others and that's why it's so important that we really work together, understand the knowledge. There are hundreds of publications out there, many safety databases that have been published and really putting all of this together and to do this for every single patient that we make this commitment to really working towards that optimal ASO for each patient. This slide is very busy, but I think it's important also to highlight, again, being very transparent about the process that we are following in order to achieve the milestones that will get us to that optimal ASO. And given our experience, we really have become so specific and rigorous in what each step is in order to ensure that we can be efficient but what's more important than being efficient is being high quality.

And so really working from the place of ensuring that every single step is performed at very high quality with then the ability to have criteria that enables us to move to the next step, to continue to progress ASOs that are behaving in a favorable manner, exhibiting the characteristics of an optimal ASO, and then ultimately getting rid of those that are not. And so we're ultimately continuing along this path as you can see, to go from really starting with hundreds of ASOs down to what that single lead ASO that will then take us into the I N D enabling talk study and to manufacturing in the finish to enable that clinical treatment.

Now there's a number of different optional screening steps. Interestingly to just call out one specifically allele-selective ASOs have become a requirement for actually the majority of patients who have been accepted into the n-Lorem program. What this is either the option is to be either non-allele selective or allele selective. And so non allele selective means that you can ultimately target anywhere along that R N A in order to produce the desired effect, whereas the allele selective means that we are targeting only the pathogenic allele, therefore we need to understand very specifically the genetics and the differences between the wild type and the pathogenic allele in the context of normal variation to be able to tease those apart and target only the pathogenic allele. And this is very important when we start to think about what is the loss of function liability for some of these different targets that we are really working on in this portfolio.

I think what we've shown here and what we're seeing is that ASOs can reduce, either be used to reduce the protein or also be used to increase the target protein. And the majority of the patients that have been accepted into the program do have the need to reduce the protein. You can see here that the potency of the modern ASOs is shown in multiple different organs. What this enables, again, is we are not in the n-Lorem context, we are not paving a new path as far as what organs are we targeting. We are leveraging validated routes of administration and validated and well-understood chemistries that we have a lot of knowledge and experience in historically to be able to confidently move into discover and develop ASOs for patients. And these really allow for this very low dose and a long duration of the effect. And this translates into the manufacturing costs as well.

I think it's important to pause for a moment and acknowledge that this is still drug discovery and development. So drug discovery and development typically takes what? 10, 15, 20 years, often tens to hundreds of millions of dollars for some of these very large drugs and populations. And so we are very much honing in on a very short timeline compared to that in just the couple of years and ultimately the cost being so much less. And so one could really envision that there might be a compromise in quality and that's really important to n-Lorem at this stage is to really move forward leading with the quality that is our really and truly our highest priority.

So what we're doing really is focused on industrializing our ability to discover and develop these experimental ASOs. So the goal is to treat patients that can

be treated today. These patients each are being treated under investigator initiated research, INDs with their own individualized ASO. We've worked really to maximize the quality of every step, and that's not only in the discovery and development of the drug itself, but also in how are we actually evaluating the performance of that particular drug as well. And all of this connected to that drug discovery process that I just mentioned previously is all brought together that really ensures us to be able to behave in this very professional and drug discovery pharmaceutical rigor level of development that we're working towards for these patients.

I mentioned this professional management. I think that's a really important element, especially in the context of these individualized ASOs. Ultimately we want to be sure that we are very much aware of what is going on around us outside of n-Lorem in the context of this technology and especially in the context of the regulatory processes. And so that really enables us and ensures and is a really strict requirement for our organization to ensure that we're aware of what is going on around us and most importantly to really then translate that to how that affects how we're working on discovering, developing the ASOs, how our physicians that we're working with, treating and dosing the patients and just collectively how are we ensuring that we're really aware of the implications on these patients today and also in the future.

I think importantly the data collection and maximizing learnings is really, really important. And so ultimately one could ask what is the value of data on a single patient? Well, there is significant value, not only for that specific patient in that collecting data for that patient from the point of acceptance or before, into the n-Lorem program on their natural history data and then collecting the same outcome assessments during treatment enables that comparison. And ultimately that comparison is going to translate into a treatment decision, into that benefit risk assessment for that physician to be able to make that decision on whether we want to continue treatment with this ASO for that patient.

And in addition, not only within each patient, but the goal is in our commitment is to look across patients as well and to really be able to aggregate the experience of patients who may have common manifestations or if we want to look at common characteristics of ASOs and the effects on some of these clinical manifestations. There's so many different ways that we want to make sure that we're collecting data in a way that can really enable as much learning as possible. I mentioned before really about scaling to meet the need. And the last piece that is so important and this is becoming increasingly important, is really on the patient support. And so I think, we all in the rare disease community and myself as a parent of an [inaudible 00:17:51] of one child, even in the context of a rare disease group that may have a couple of hundred or 50, a hundred, a few thousand patients, many of what we're finding is these patients with the individual mutations are often even more isolated. And so we want to really work to continue to support them to the best of our ability.

I think one piece that's really important in that as well is really thinking about timelines. And I mentioned before, what does the n-Lorem timeline look like when compared to traditional drug discovery and development? But when one is waiting for a treatment, we fully acknowledge every day is an eternity. And so really working on how to ensure some of this additional transparency, and really knowledge sharing on the complexity of drug discovery and development, on the fact that this is still science and ultimately every single target is unique, every patient is unique and even within two patients that have the exact same mutation can have different variation around those mutations, which means that they still need their own unique ASOs. And I think that is just really important lesson with regards to this scientific variability that we will expect in the discovery and development of these treatments. And that's important to continue with that transparency on what the timeline could look like.

So this slide really walks you through what is the n-Lorem process, initially starting with the treating physicians, submitting an application to n-Lorem on behalf of a patient and ultimately this application includes information about the genotype, the phenotype, ultimately really working towards our internal organization and our scientific reviewers to be able to do a very deep dive. First on the mutation, do we understand what the functional consequence of the mutation is sufficient to be able to understand if that ASO strategy to knock it down or to up-regulate, to have a splice modification would have the desired impact? So we're actually, interestingly, finding there are many submissions that the mutation, the functional consequence may be partially understood but not significantly understood that will be sufficient to actually determine what that ASO strategy might be. And so really working as another effort is to really think about how can we support those patients, how can we support those physicians to suggest that if we have this additional amount of research evidence, this would enable that ASO strategy.

Ultimately, we then after internal really rigorous review, really focused on the technology, the ability and the amenability of the technology, the ASO technology, to target this patient's mutation in addition to the clinical manifestations and understanding from a physician and what the physician has shared based on the patient's treatment goals to be able to, again, this benefit risk decision. Does this patient seem that, do we feel that we can help this patient? In which case if we feel that we can, they're accepted into the program and ultimately their mutation becomes a drug target in our discovery and development pipeline.

So moving forward, the drug discovery and development is internal and we also work with a number of CROs as it's done in traditional drug discovery and development. And then typically what we're working to do and what we've established in our process is that we really do every activity as concurrent as possible in order to ensure that we are not waiting when we don't have to because back to we know every day is so important. So for example, once we have our lead ASO, you typically would go into that larger top study, wait for the results, then move to the next step of manufacturing. Instead what we do is go

straight into tox in manufacturing concurrently. This saves multiple weeks and months and then we can ultimately be able to accelerate and get all of the information we need for that I N D as efficiently as possible for each patient.

And as I mentioned before, the patients are treated under the investigator initiated research INDs. And so these research INDs are held by the treating physician who submits the application. Typically it's the person who submits that application and ultimately after that's approved and we work through the institutional I R B review, then the initiation of treatment begins.

I wanted to highlight something that's really become increasingly important. I mean, it's been important from the beginning, but even today is acknowledging that really across the patients, even in the n-Lorem portfolio, we're working with over 30 institutions and this is new, this is new. And so what we're really trying to do is to navigate and understand what are the key barriers at each institution? What are the key concerns? What are the risks? What are the opportunities? How can we further refine and optimize our partnership with each institution and really focus on the mission? Because really and truly, at the end of the day, n-Lorem, as a non-profit, who is working towards a only treatment for this patient and for this institution, for their physician to hold this I N D, really that's a powerful message. And institutions have been very compelled to want to collaborate and to come on board and we're really putting a lot of solutions in place with regards to defining comparable systems across all the institutions, whether it be protocol templates, I N D templates and really providing all of the support that we possibly can.

So n-Lorem has put into place the clinical operations, data collection and especially that regulatory support. So our team essentially drafts 90% of these INDs because this is new and most individuals have not drafted a 1200 page regulatory document, nor would we have expected them to. And so that's really our commitment to the physicians and especially to be able to encourage new physicians to be interested and open and willing to try this and to help a patient and to know that n-Lorem's going to really support them through that process as well.

So where we are today is we have received over 160 applications. I'm sure this is actually probably even increased in the last couple of days since finishing the slides, but the majority, about two-thirds are pediatrics. A very large majority are C N S and we do have around 80 patients that have been accepted into the program. And so, again, every single patient translates into a drug discovery and development program. We have seen that around 40% of these patients do come in and the physicians come in with seizures with epilepsy and have seizure reduction as the primary or secondary treatment goal. And so really that is a really important element of working with these physicians is to assess how are they managing, how are they planning to measure progress towards their treatment goals? And although one could envision that may be very straightforward, it's not always that straightforward and I think even in some of

these areas such as epilepsy, it's not entirely as consistent across the board as one might expect.

And so that's a real opportunity for us to ensure that consistency, even in patients and physicians and institutions that are seemingly working independently as n-Lorem is able to bring some of those things together and to introduce some of those consistencies across the board. Also, we touched on the different A S O strategies and so, apologies, this slide seem to have gotten a little bit mixed up here, but like I mentioned before, most of these patients have gain of function and so the A S O strategy is to knock them down. We do have a few that have loss of function that we're working to increase and also really have a number that we're working on that I mentioned earlier that do have some additional evidence in the proof of concept stage that will enable us to move from that research stage to being able to make a definitive decision about whether we feel that we can help this patient or not.

So when we look where these A D patients are, ultimately when the organization started, I think the vision is really interesting to hear Dr. Crook talk about it, just that maybe in a couple of years we'd had a handful of patients, maybe we'd be working on three to five ASOs at this point and ultimately we have really had the opportunity to grow and scale and to meet the needs of these patients and the obligation to do so. And so what this progress slide really shows you is that we do not have everyone just waiting at the door to get in, that we have really enabled scaling all the way from the point of application all the way through. And we're planning on submitting 10 INDs this year at a minimum and very likely more. And again, with the way that these programs go, some tend to, you find something very straightforward and others end up being maybe perhaps more difficult R N A to target.

And so we do anticipate that some may move ahead and some may fall behind. And so ultimately we'll continue on a path with multiple programs going at all times. Just want to briefly share one of our first patients who was dosed last fall. This is Susanna, who she was accepted in November of 2021. And you can see from these photos really had a very standard early childhood and ultimately began to really regress after being diagnosed with a [inaudible 00:28:30] mutation. And ultimately after being accepted into the n-Lorem program, really as we've done with all of the patient's programs, it's working to very feverishly target, do what we can to ultimately accelerate all of the elements that are required to have an successful drug discovery and development program. We need patient cells, whole genome sequencing, all of the nonclinical and clinical data and then C M C data as well, the manufacturing data to be able to file this I N D and the treatment began for her last October.

Just share this brief video. So this is Luke and Sally Rosen, I don't know if you can hear this, but ultimately Susanna over the last couple years has really declined in her mobility and her time in a wheelchair has become more and more frequent. She had very frequent falls, was unable to stand up by herself and this was just a huge accomplishment to see Susanna stand up and not only does she

stand up, but ultimately her walking over to her dad after a big high five and offering to him, let me show you how to stand up. So this is the reason why I love just what I have the privilege to do and just why I love to be able to have the opportunity to talk with all of you today. It's just so incredibly meaningful. And I think the question is how, how can actually an organization be able to scale to meet the needs of these patients?

Well, it's because of all of you, it's because of all of these organizations and this slide will just become explosion, I'm sure, over time way too many groups that we will not be able to include on this slide. And it's just contagious. It's so powerful and so inspiring to be able to be a part of this. We found that you can see all of the different types of organizations that are involved and interestingly, some of the organizations that are the most passionate are the ones that typically are the least connected to patients in their daily work. But even some of our manufacturing partners. I mean this is very, very inspiring for them to be able to have to their organizational town halls discussions about, wow, so they literally took this drug powder and put it in a vial and they can have a patient, an eight-year-old girl, an adult who is affected by seizures daily. I mean, they can have a specific person in mind when they're doing their work, which typically they don't have the opportunity to do and that's really exciting for them.

So we're really at a position now where we know we can do this, we know how to do this. And like any startup, essentially, is what n-Lorem was, is really working to establish what are the processes, what are the systems we need to put in place? And I think what's so interesting is that pretty much every couple months we are saying, "Well here's what we put in place a quarter ago, let's take another look and see how that's working for us today. And you know what, let's make some adjustments and continue to modify and grow." And so we've really, we've grown our team, we've opened a new lab recently in San Diego and that's been able to triple our discovery capacity. We have some exceptional scientists and just individuals across the board who have joined our organization that is just really, really creating this very strong fabric upon which we can really grow.

We're also working to establish a data platform. I mentioned earlier the importance of collecting data. Working on creating this community for the nano rare, the patient empowerment program. And I think it's really important also to highlight that there is a lot going on around us as well. So being engaged with Office of Science Technology is really working towards, broadly speaking, what is the community doing to be able to support these patients? And a lot of what we do at n-Lorem is going to be able to be extrapolated and extend far beyond [inaudible 00:33:06] ones. So if you think the needle swings pretty far all the way over to these individual patients, but the individual patients will ultimately turn into ends of few to an N of 20 to an N of 50, it's still not necessarily commercially tractable. And so we are really being able to shape what this can look like for generally these smaller populations of rare disease patients as well.

I think another area that we're really focused on as well is trying to have this sequencing, whole genome sequencing earlier. I think you hear many, many people talk about this all the time, I think we are seeing it on a daily basis in the applications we receive. And this is in part that we see patients who, again, have had many years of diagnostic odyssey and are very far along in their disease progression and it's difficult to not think, "Oh, we can try to help them today, but imagine if we could have reached them three years ago." And I think that's what really, when we talk again in a year or in three years or five years, I hope we can say that this amount of time is shrinking. Can we continue to really work on optimizing what the process looks like? And this is not only from before diagnosis, diagnosis to discovery initiation. Again that's a requirement for additional, this long-read sequencing that's required for the ASO design as well as to abstain patient cells.

Some of those, that a lot of us in our patient communities you think about how can we be ready for a clinical trial? These are some areas. So really thinking about how can we proactively work with patient communities to be very specific on if we have this in place, we can move much more rapidly because some of those elements are taking up to a year, literally up to a year sometimes to be able to get that, the sequencing in cells. I think, just mentioning before about the regulatory alignment, that is going to continue to grow, I think ultimately with each I N D that we submit and are able for the investigators to have approved, I think we continue to earn the trust of the F D A and that's really, and vice versa, we want to very much maintain this very open and transparent engagement with the F D A to ensure that they can learn as much as they want from what we're doing if it will be helpful for whatever they have in mind in the future.

And I think the last two pieces here, obviously the costs are a critical concern and then the other question about what's happening beyond antisense. So we know ASOs are only able to help a small proportion of patients and this is very much something that we try to acknowledge and that's why we want to be very specific and definitive on the decision on whether we feel we can help or not because there are many other potential paths for therapeutics and antisense is only one that we're really focused on right now. But I think, ultimately, other modalities will come along eventually and so that's something that'll be very exciting in the future as well.

Oh, there we go. So in conclusion, I think just wanted to really highlight, I mean we're really working, we've had a lot of success so far with regards to industrializing the discovery and development of these mutation-directed treatments. And even though we are in a really spectacular place today, there are many, many challenges ahead and I think we want to continue to acknowledge that. This is a continuing day, hour and hour, every single day. Honestly, half my day today is spent talking about things that we can do different and better and continuing to work towards improving our processes, expanding our partnerships, all of these things. And ultimately these partnerships are so critical at every single step. And I think it's just important to

acknowledge the reality. The demand has been probably more than 20 fold, actually, greater than we expected. And so we do have a lot of support and we need additional support. And so we would just love to partner with any of you if there's an opportunity and just happy to be here today and Laura would be happy to chat with you a little bit about a few questions.

Dr. Laura Lubbers: Wonderful.

Dr. Sarah Glass: I just want to, sorry, just really quickly, I just want to thank everyone. I think I'm speaking on behalf of many, many individuals who have contributed to n-Lorem so far today and we're just so grateful and especially to the patients for whom we're working today.

Dr. Laura Lubbers: Thank you Sarah. What an amazing story. What an amazing effort this is to see it come to life not that long ago. I remember when it was announced and I thought, how is this going to work? And to see how you have advanced this area and continue to refine and develop new methods to make this all happen at the level of urgency that patients need is truly remarkable. Congratulate you all for that mindset and for moving this forward. We do have a number of questions that have been queued up, so I'd love to get to those and I have questions as well. So the first question we have is, you've been talking about targeting specific mutations, but you've also been pretty practical about where it's helpful and where it's not. Can you speak to families that have a diagnosis of L G S or Jevens or infantile spasms? How do they think about this technology? Is it right for them or not yet?

Dr. Sarah Glass: Honestly, it is very specific to every single mutation and I think that's the unfortunate reality. And as much as that doesn't help broadly speaking, and I think that's what we're really finding, especially in some of these cross patient groups, is like how can we actually give you a much more informative answer than that? What we have started to put in place is almost even a, we started pre-submission type of assessment, if you will, is almost even just like a triaging because we do have a lot of questions like that. So for my patient community, we have this type of mutation or this type of mutation or we have here these two which are affecting three people or five people, and what do we do? Should we find a physician? Should we submit an application? And so I think that's the best that I can offer is that I think what we found is typically, first of all, the prevalence of the mutations is very important, obviously.

The functional consequence of the mutation. If we understand the functional consequence and if there is a realistic ability to affect the consequence of that mutation. So ultimately, for example, null mutations, ASOs aren't able to help, those are typically going to move into the gene therapy space to some extent. We do know a hundred percent for as far as the organ system, obviously these are all C N S, but I think we get those questions a lot as, so if we want to target the muscle or if we want to target lung and things like that, those are also areas that we cannot target. So I think part of it is understanding what ASOs cannot target. So some of that also is really focused on the mutation but focused a little

bit broader than that. And so I think that would be my suggestion is really in thinking about those questions is to say, the first question is what does the mutational spectrum look like for each of those areas that you mentioned, those patient groups and to say, okay, do we have some functional consequences that are well understood?

Are the prevalences in these regions that would apply here? And all this is really driven by what these F D A guidance documents provide. They're very specific, actually, refreshingly specific on the type of patients that actually qualify for these because this is a different drug discovery and development path than a commercial program. So it's a much abbreviated path. And that's very important for all of the patient communities to know is that these go specifically from a single G L P animal talk study right into the patient. Whereas in traditional clinical trials you go multiple animal talks, phase 1, 2, 3, et cetera. And so that's why the F D A is very specific on what are the characteristics of patients that are actually suitable for this path. And some of those characteristics are in the genetics, it's in the clinical manifestations, it's in what is the other treatment landscape.

So that's another element as well, is really just do we have a sense of, well, there are all these other treatments that are already really targeting these patient populations. So this is really focused on patients who just really and truly don't have any other options.

Dr. Laura Lubbers: Wow. The F D A also needs to be recognized for their willingness to do this. I mean, they're definitely the gatekeepers and it can be hard to move things forward. And so I think it's really remarkable as well that they've put the time and the energy into really refining this and helping to guide, so kudos to them as well. I wanted to ask a question. You talk about the functional consequences of a mutation, and that can take a lot of time to sort out. How does that work get done and if it's not done by n-Lorem, sorry, how does it get funded? How does that research get accomplished so that it can perhaps inform you?

Dr. Sarah Glass: It's really variable honestly. And I think the most interesting, it's actually fascinating, sometimes you will find a mutation that will have evidence for having gained a function consequence in some circumstances and loss in others. And some you might not necessarily very clearly be able to understand it and it could just require a little bit more research in a particular lab. Most of the research that's happening is back into the lab of the submitting physician for the most part. So that's only helpful, however, if one, a patient is connected with the physician who is also a lead researcher in that particular gene. And so I think what we're working to do, and we have a couple of potential partnerships where there could enable almost a proof of concept lab to some extent, where you say, okay, this could be amenable if we have X, Y, Z data that will then get us over the ability to make that decision as far as do we have an ASO strategy or not?

And so that's very much something that we're working on now is to have a more centralized location. So as with a lot of rare diseases is how are we looking across diseases? So instead of saying we're focusing on the gene, if we're saying, well, here's a type of study, here's a type of experiment that is often missing, if we could only have this capability to do this for many different genes or for different patients in a more centralized type of location, I think that's what we're aiming to do in the future as well. That research piece is so important.

Dr. Laura Lubbers: Right. And that's remarkable because in the way we typically think about science, that's a major challenge and that would be a stopping block in many cases. And yet you're taking the perspective of, well, we need to solve this challenge instead of letting it hold you back, you're figuring out how to move it forward. So again, kudos to that kind of thinking.

Dr. Sarah Glass: Well, and there's too many conversations we're having right now, honestly, where we have one of us will connect with a patient or a family and ultimately talking through with them is like, well, here's what might be recommended and to say, we wish you well, come back to us if you have more. I mean, that doesn't feel right. I think it doesn't, even though I feel on behalf of our team, they're just working so so hard, but still everyone's commitment to these patients is just so significant. So I think, and you know, do have to start to notice what the trends are. This is clearly, this is not just one-off where this is an issue. This is becoming more and more common where there's a lot of understanding, which is exceptional, but how do you go from understanding to drug target? There's some space in between.

Dr. Laura Lubbers: Right. We do have a question that taps into this. So this person is curious to know what are some of the reasons for declining an application for an ASO? And you've talked about some of those, but can you fill in any other information? Why would you decline an application?

Dr. Sarah Glass: Yeah, so the primary reason to decline is really around the mutation itself and the consequence of the mutation. So again, whether it's ultimately a functional consequence that we can't, so if it's a null mutation, we still continue to have some of those. It also depends on the gene itself. So for example, if we're looking at trying to upregulate, well, upregulation is not the same across the board. That's going to be driven by specific characteristics of that particular gene itself. And so then it comes down to, well this particular gene has these different characteristics. So again, most of the decline is really related to the clinical or to the genetic, to the genotype. And so really trying to, from a technical perspective, address whether we feel at all antisense technology can help. Now there are a small, I think proportion as well where the physicians or the patients will ultimately be presented in a way that it isn't entirely clear.

Well, the gene is the causative gene, so that we do have a handful of patients that will have maybe two mutations or more. And ultimately these are really driven towards having single mutations in a causative gene with that being very apparent. We have a number that will then creep above the 10 bus 20, 30, 40,

50 patient range. And so I think we're not there where right now we're really stricken directly to the guidance. I think eventually over time, one could envision that there could be a path even for if it's an experimental ASO for almost like an intermediate population, if you will, that doesn't exist at this stage. So that's another reason as well. Let me think. There's a number of patients that will be, if it's again trying to target the muscle or cardiovascular, things like that where we don't have a validated route of administration that we're leveraging as part of n-Lorem.

Dr. Laura Lubbers: Okay. Thank you. Are n-Lorem applications only available for patients that reside in the US?

Dr. Sarah Glass: Yeah, it's an important question. And right now we only have F D A guidance to under which these patients can be treated. We have significant efforts at this point with Canada and the UK to really evaluate and try to really forge the path in partnership with those regulatory agencies, to define a path based on other partnerships in those countries. We do have a lot of patients actually starting to apply or physicians from other countries that were, I think, trying to assess on almost a case-by-case basis. But for the most part, and it's only if we already have an ASO for that particular mutation, which is highly unlikely, but I think the goal is to help as many patients as we can, but we have to start somewhere and that's here in the US.

Dr. Laura Lubbers: Absolutely. You're working through a lot of details for sure. I think we've got time for just one or two more questions. What is the current cost structure for patients you foresee in the future?

Dr. Sarah Glass: I'm sorry, you just broke up. What did you say, the cost structure?

Dr. Laura Lubbers: Yes, the cost structure for patients and what do you foresee for the future?

Dr. Sarah Glass: So ultimately the patients don't have any obligation for the cost of these drugs and the physicians themselves. N-Lorem covers all of the costs from the point of patient acceptance through to all of the drug discovery and development and talk studies, as well as manufacturing. The physicians and the institutions are then required and obligated to support from the treatment on, and so that's what we're working through. So typically this should not be, and most physicians are having insurance will be billed for what can be billed and institutions will cover some of the other costs. Some others have philanthropic funds. I think the reality is that each institution is handling this differently and that every institution needs funding for it and they all should get funding for it, honestly. I think one of the biggest challenges that we continue to see with the physicians is that they're doing this in their nights and weekends time, physicians who are entirely clinical who don't have any research time.

And I think for someone who's not necessarily in that space, we all cannot appreciate how busy, how many individuals, like our loved ones that they're

caring for, and then to say, okay, well, and in my own personal family time, I'm going to spend on this particular patient for n-Lorem. So I think that's what we're trying to really understand, and I'm personally spending a lot of time right now is trying to understand what are the costs, specifically? What does that actually entail and should this be integrated into what the cost structure could look like for these treatments moving forward? Because ultimately the patient should not have to carry the burden for these costs. But at a minimum, I can say there is no cost for the drug itself.

Dr. Laura Lubbers: Okay. Thank you. Yes, many unsung heroes in this process right now. So I think we should probably go ahead and close. There are some additional questions, but perhaps we can get those addressed offline. I want to thank you Dr. Glass, for what an amazing presentation. It truly has been incredibly informative and truly breakthrough approaches. So thank you for that. I'd also like to thank our audience for asking great questions. If you have additional questions on the topic or wish to learn more about any of Cure Epilepsy's research programs or webinars, please visit our website or email us at research@cureepilepsy.org. Finally, be sure to register for our March webinar that will provide information on medical marijuana and C B D in epilepsy. It will be presented by Dr. Eric Marsh from Children's Hospital of Philadelphia. So thank you again and all be well.