TRANSCRIPT: USH2A Clinical Trial Webinar, presented by ProQR Therapeutics
February 7, 2022

[KRISTA VASI]: OK. Hello, everyone. I see lots of people coming through. We're going to give everyone a minute to sign in. OK.

I'm still seeing the numbers creep up, we've got a very large attendance today. This is very exciting.

I'm going to give another 30 seconds or so for attendees to sign in and then we'll go over the accessibility features available today before jumping into the presentation.

OK. So, hi, everyone, I'm Krista Vasi, and I'm the executive director of the Usher Syndrome Coalition, and I welcome all of you today for this presentation.

Before doing more of a welcome and introduction, I do want to go over the accessibility features to make sure everyone has full access.

We do have Spanish spoken language translation, so you can enable that by clicking the Globe icon on the bottom toolbar and selecting Spanish.

And if you select Spanish, you have the option to mute the original English audio.

I'm going to give our Spanish interpreter a minute to translate that and allow for the attendees to turn on that Spanish translation audio.

[Español]: Buenas tardes, habla Krista Vasi, el director ejecutivo de la Coalición del Síndrome de Usher.

E tenemos disponible interpretación en español.

Si ustedes van al fondo, del menú de la barra de abajo de su y hacen click en el globo pueden elegir la opción para español y eso les da la opción tambien de silenciar el ponente original en inglés.

Si e de modo que el resto de la presentación pueden escuchar la interpretada en español.

[English] OK, so hopefully our Spanish-speaking friends are jumping onto the Spanish audio right now.

I will use this opportunity to remind myself as well as our other speakers today that we're we have many different types of interpreters.

I'm going to do my best to speak at a slower pace and give the interpreters time to catch up and also identify myself whenever I am speaking or any of the other presenters.

It's always good to identify yourself first and then speak.

Let's bring our attention to the other big accessibility feature today, which is Wordly.

This is an AI-powered translation system that will translate this webinar into over 20 languages and to turn that on, you can click the link that we've provided in the chat box, or you can click the down arrow next to the live button at the top left of your of your screen and select "View Stream on custom live streaming service".

That will pull up a browser time that has the Wordly, the Wordly app that you can then select your language and see the captions in your language.

You can also, there are options for some languages to listen to your language, listen to the voice as well.

So hopefully everyone can access the Wordly translation.

For anyone looking for captioning in English, we've enabled the live transcription in Zoom so please select the CC icon at the bottom right of the screen on your Zoom menu bar and you'll turn on captioning.

You can also select subtitles settings and adjust the size to your visual needs.

Let's see. We have our ASL interpreters with us today as well. We have both Melissa and Dena, and I'd love for Melissa and Dena to wave and identify themselves. Hello.

So anyone using ASL interpretation today, you can pin Melissa and Dena so they're always visible on your personal device.

You'll do this by clicking the three dots at the top of their video and I think I think that covers the different accessibility.

I'll just do a quick accessibility check. Is the audio working for everyone? Thumbs up. Good.

Is captioning working and interpreters are visible? Good? Spanish, Spanish language interpreters are all set? Yes? I'm seeing lots of yeses.

Wonderful and great.

I'll take this moment to quickly introduce Brian. He's our tech support. If you have any questions or any trouble at all throughout the webinar, you can chat with Brian directly and he can help you out.

OK, so on to the show.

Welcome again, everyone.

Before I introduce our guests from ProQR Therapeutics, I want to say a few words to mark the significance of this moment.

The Usher Syndrome Coalition was formed over 10 years ago with this exact moment in mind.

Our reason for existence is to bridge the gap between researchers and those living with Usher syndrome.

In 2008, the Coalition was created with the sincere belief that we could find, support and connect everyone with Usher syndrome and then ensure that clinical trials for Usher syndrome would be successful.

Clinical trials can't move forward if researchers aren't in touch with enough people living with this condition.

Put simply, research cannot happen without you.

Treatments cannot be developed without you, the experts living with Usher syndrome.

That is why I am incredibly excited for this presentation today.

For the first time, there is a final stage clinical trial for a treatment for Usher syndrome.

This is a milestone worthy of being acknowledged and celebrated.

And while this particular clinical trial is for a specific population within our broader community, I know this is only the beginning of a new era in Usher syndrome research, one in which the Coalition can eventually bring everyone together for all types of Usher syndrome, with the research that will benefit them.

So I'm so pleased to introduce our speaker today, Doreen Wood from ProQR.

She recently joined the team and is the project leader for the Usher syndrome trials that you're going to be hearing about today.

So, Doreen, I'm going to pass it on to you.

Thank you.

[DOREEN WOOD]: Thank you, Krista.

Hello, everyone.

Good afternoon, good evening.

My name is Doreen Wood. As we continue these COVID days, I do hope you are all well. This is my first chance to meet you. I'm new to ProQR.

I'm new to ophthalmology, so I feel especially privileged to join this discussion today.

I wanted to thank the Usher Coalition for their wonderful, ongoing partnership with ProQR.

We view it as crucial to have such strong partners holding us to account, supporting our clinical development and making sure the voice of you, you, the community is heard loud and clear in ProQR.

Today, I will talk to you about what we as a small biotech based out of the Dutch city of Leiden and in Cambridge, Massachusetts.

What are we doing in our RNA science in Usher syndrome specifically and other genetic eye conditions? Just to introduce myself, my role is to lead the QR-421a project for Usher.

My expertise is in driving the development of new medicines to bring them to the patient.

Just before I share the slides, I want to say I hope my Scottish accent isn't too strong. Don't hesitate to tell me to slow down or speak more clearly.

So I'm going to talk for about 30 minutes, which should leave a lot of time for your questions.

Can I just check you can see a slide? Yes. Thank you.

These are forward looking statements.

Who are we, ProQR Therapeutics? ProQR Therapeutics is dedicated to developing RNA therapies for individuals who have a genetic eye condition, with the mission of stopping vision loss or even to reverse some of the symptoms.

In the field of RNA therapies, ProQR is at the forefront of delivering targeted therapies for people with genetic eye conditions, be they retina or back of the eye like Usher syndrome, or Fuchs endothelial corneal dystrophy, which is at the cornea, or the front of the eye.

Our RNA therapies use antisense oligonucleotides, more on what that is later.

And these are specifically designed to correct the underlying cause of the disease in a person's RNA to stop disease progression or even reverse symptoms.

So RNA, we're talking about ribonucleic acid, and it's an essential component of all living cells.

I'm sure a lot of you all have now heard of RNA or mRNA due to the Pfizer and Moderna vaccines.

I was very excited to receive the vaccine, to see the science being rolled out in a big population way.

So it is very different to how we are applying the science. It is still cool.

RNA is used for translation. This is the process in which proteins are created in the cell. RNA itself is produced from DNA.

I always find it harder to explain RNA than DNA due to everyone knowing what DNA is because of Jurassic Park. We know what happens when you mix a toad's DNA with a dinosaur DNA, and it's not pretty.

And RNA therapy is designed to correct the mutation in the RNA of someone with a genetic disease.

By correcting the mistake, the RNA can then be used to create the protein that the cell needs, taking away the underlying cause of the condition.

We just advance here, so this slide tells the story of our company.

ProQR was founded in 2012 by our current CEO, Daniel de Boer.

A few years earlier, Daniel and his family were faced with the diagnosis of cystic fibrosis in his newborn son. This is a rare, incurable genetic disease.

Daniel sought help from experts in the field of drug development and formed ProQR to help people like his son.

When viable treatments in cystic fibrosis came along, Daniel looked at other areas of clear, high unmet need.

At this reflection point for the company, we had started clinical work in Leber Congenital Amaurosis Type 10, or LCA10, and therefore the natural shift was there.

So since this time, ProQR has shifted its focus onto genetic eye diseases.

Since 2017, we have seen ProQR concentrate and bring forward clinical research, that is research involving individuals living with LCA10, with Usher syndrome type 2A, autosomal dominant retinitis pigmentosa, and most recently, Fuchs Endothelial Corneal Dystrophy.

As of January last year, we had fully enrolled our phase 2/3 pivotal study in LCA10, which takes us as a company into a new era where we could have data to take us to the likes of the regulatory agencies, to FDA, to EMA in Europe, to MHRA in the UK to register a therapy in 2022.

So, as Krista said, it's a very exciting time for the community and for us as a company.

It is estimated that five million people in the world are currently living with genetic eye conditions, but probably it's even more because of a lack of genetic testing, awareness, correct diagnosis and public knowledge.

For the vast majority of these people, there is no treatment available for the vision loss and the eventual blindness that can occur.

We believe that the best way to fulfill this mission is to develop RNA therapies for genetic eye diseases.

We have built a platform to develop these highly targeted therapies to address the underlying cause of the disease and improve vision.

And with more than 300 genes identified that cause genetic eye conditions, there is an immense opportunity to develop therapies for people in need.

For instance, LCA is a genetic disease that causes a mistake, a mutation in the patient's DNA.

Because of the mutation, an essential protein in the eye cannot function or is missing.

And this leads to the deterioration of the light detecting cells in the retina.

So in the field of RNA therapeutics, ProQR is at the forefront of delivering targeted therapies for people with genetic eye conditions.

Our RNA therapies use antisense oligonucleotides, which are specifically designed to correct the underlying cause of the disease in a person's condition and to stop disease progression or even to reverse symptoms.

So what are these -- antisense oligonucleotides? They consist of short stretches of synthetic RNA that are chemically modified to increase efficiency, and their uptake into cells.

This technique is an established approach to treat genetic diseases, and there are approved RNA therapies being used to treat patients today.

So how do we deliver the treatment? For a drug to work, first it has to get into the body.

RNA therapies work best if they are delivered directly into the affected organ.

In the case of retinal diseases, RNA therapies can be injected into the vitreous of the eye.

That's the cavity which is filled with a jelly-like fluid. This delivery method, it's known as intravitreal injection, or IVT. And it's one of the most performed procedures for eye diseases.

The procedure is performed by eye doctors for common conditions, such as age-related macular degeneration, for diabetic retinopathy, and retinal vein occlusion.

So IVT is different from subretinal injection, the method used for gene therapy, which requires delicate retinal surgery.

What is the procedure for intravitreal injection? The entire procedure takes around 10 to 15 minutes and is performed in the doctor's office while the patient is sitting in a chair. The eye is numbed, so it doesn't hurt.

Once the eye is prepared, the individual will be asked to look in a particular direction while the medicine is injected into the white part of the eye with a very fine needle.

So how can we test our RNA molecules? Our innovation team is always looking for new techniques.

We use small skin biopsies from individuals to create living optic cup models to test our medicines and see if we have target engagement even before injecting into somebody's eye.

So a little more on RNA and what is the difference to DNA.

For those on the webinar who might not be able to see the graphic, let me describe it.

On the bottom, we have a DNA double helix, as I imagine most of us are familiar with this. Above the DNA, we have a single strand RNA.

As mentioned previously, this RNA is used for translation, the process by which proteins are created in a cell. RNA itself is produced from DNA in a process called transcription.

Gene therapy generally makes permanent alterations to DNA. Gene therapies act directly on the disease-causing gene and require vectors to access the target cells. Gene editing directly changes the DNA.

In contrast, RNA therapies work at the level of RNA, have a transient effect, and do not alter the genome.

So antisense oligonucleotides do not require vectors to access the target cells. We will come on to this more later.

So thank you for being patient with me to get to the part of the talk that I think will interest most of you: our ongoing research for USH2A mediated retinitis pigmentosa and Usher syndrome.

QR-421a, that's the name of the treatment. It's an investigational RNA therapy designed to skip exon 13 in the RNA with the aim to stop vision loss. It is very specific to exon 13.

So this is really genetic science. We are in the era of personalized medicine.

I want to thank our partners at the Foundation Fighting Blindness, who have really supported financially our program.

So a little bit about Usher syndrome and the progress we are making. We've talked about the science and now I want to speak about the most recent news.

In March last year, we were pleased to announce the positive results of our Usher syndrome and retinitis program. Our clinical study, which is called "*Stellar*," which met all its stated objectives. This marks a crucial milestone in our ongoing research.

Our investigational RNA therapy, QR-421a, a catchy name, I know, it aims to stop vision loss in people with a mutation in a specific part of the USH2A gene, the part called exon 13.

QR-421a, it works by binding to the mutated section and excludes exon 13 from the RNA. This approach is known as exon skipping. The cells in the retina can then produce a slightly shorter but functional USH2A protein.

The clinical trial *Stellar* was to see if this could stop or reverse the vision degeneration in Usher syndrome. So this is an image of the design of the clinical trial.

The different phases of clinical development are all about collecting data and insights.

It's worth noting that this design consisted of three different doses tested in 20 clinical trial participants, with a follow up period of two years.

Participants were randomized to receive QR-421a or sham in one eye, and the other eye was left untreated as control.

For those sham randomized participants, the eye underwent a dummy intravitreal injection, so there was no penetration of the eye and the sham arm is used for masking purposes only.

So what do I mean by masking? It's a way of hiding what treatment you're, the patient has received to reduce bias.

Given the different rates of disease progression between participants and the small number of participants, experts believe the best control is the untreated, the contralateral eye, in the same trial participant.

So the goal of this single dose study was to identify, for registration purposes, what dose, what dosing interval based on the onset, the durability and the waning of effect and the target population for the next stage of clinical development.

And the positive news is the study met all its stated objectives.

We also found two populations: early moderate disease progression and advanced disease progression. This is important, and I'll touch on this later.

So here's a summary of what we saw in the *Stellar* trial.

It was a phase 1/2 clinical trial to test whether it is, the QR-421 molecule is safe and the effect on vision. The medicine was observed to be safe and well tolerated with no serious adverse events reported. Clinical proof of concept was established on Best Corrected Visual Acuity. That's BCVA, or you might know it as the eye chart.

Also on static perimetry, which is used to measure retinal sensitivity, and these were supported by important secondary endpoints such as OCT imaging, which looks at retinal thickness and microperimetry.

So furthermore, we've collected the key information to take the program forward, including the appropriate registration endpoint, the dose, the dosing interval to be used, and the optimal study population has been identified for the next trial.

So I'm happy to say that we then set ourselves the challenge of starting two Phase 2/3 pivotal studies by the end of last year.

One was in the early-to-moderate patient population, one in the advanced disease group.

So we had a tough challenge to start by the end of the year, and I'm very pleased to say that the first patients have now been dosed in December.

We've seen a benefit across all treated patients in the *Stellar* study, which included trial participants with both advanced as well as early-to-moderate vision loss. And this definition between the two groups will be important for the next stages of research.

We do we do have a full blog and a community briefing on our website. If people are interested to read more.

Nancy and Krista told us that a lot of people wanted to know about risks and safety. This is a critical part of clinical research. It's worth noting there is always a risk with conducting these kind of studies.

And I hope that by going through the safety aspects, we can show you how we make these clinical trials as safe as possible.

We take safety very seriously and continue to work with regulatory authorities and ethics boards to make sure participants are looked after throughout the study.

I apologize, I think we lost the connection for one moment.

Yes. Okay. One moment.

So perhaps to recap, safety was a big part of this clinical trial. The primary endpoint of the study was focused on safety. QR-421a was observed to be safe and well tolerated with over 3700 participant follow up days. That is equivalent to two years of follow up in this study.

Importantly, no serious adverse events were noted and there were no cases of inflammation. However, one patient had working- worsening of preexisting cataracts in both eyes. Both are considered not treatment related.

Cataracts are known to occur as part of background in Usher syndrome and occurs in over 30 percent of patients. No new cataracts were reported in the study.

Cystoid macular edema, or CME, is frequently associated with retinitis pigmentosa. And is part of the natural history of the disease in over 30 percent of the patients. It's usually managed adequately with topical eye drops. No new cases of CME occurred during the study.

However, one patient who already had CME was enrolled into the group receiving 200 microgram dose. The CME progressed during the study, but was classified as mild and managed with standard of care therapy.

So we're pleased to see that QR-421a shows such a safe and well-tolerated profile in this study.

But what does a successful clinical trial mean? Besides the safety profile, we also looked at the Best Corrected Visual Acuity and what we saw was stabilization in all treated eyes.

Now this is worth noting: it was only one, one injection. Stabilization of vision was observed in the treated eye versus decline in the untreated eye in all patients. So we saw a deterioration of the untreated eye in line with the natural history.

What this corresponds to is at week 48, there was a six letter benefit on the eye chart, and at week 72 it was an eight letter benefit showing a sustained effect consistent with long half life of QR-421a.

All treated participants had a wide range of vision loss or visual acuity. Therefore, seeing a stabilization like this was great to see, but we did learn something more. That the change in BCVA response is driven by the advanced disease population.

Now, why is this important? We're starting to learn what we could do in our next phase of clinical development.

Now we saw the stabilization in the treated eye after a single dose.

Focusing on the advanced population, the benefit on the eye chart was a mean change of 9.3 letters at week 48, and even better, a mean difference of 13 letters a week 72.

The week 72 endpoint is therefore the time we will look at the primary endpoint in our phase 3 trial in the advanced population, a study called "*Sirius*." So we have identified endpoints to propose to regulatory bodies, which they may consider for a new medicine, for the approval of the product.

These are BCVA for the advanced population and for the early-moderate population, we're looking instead at a static perimetry.

We saw the participants respond on endpoints or measures that are related to their baseline disease stage, and we saw also that the different endpoints move in concordance with each other.

So in this *Stellar* trial, we have collected all the information we need to move forward into pivotal stage, getting closer to registering this drug for patients.

So on this slide, we showed the study design for *Sirius*. This is in advanced patients.

We have discussed the *Stellar* data with the FDA and have submitted two protocols for phase 2/3 trials.

The FDA agreed with our proposed six monthly dosing interval and confirmed that given the safety profile, we don't have to do any more dose ranging.

So this first trial, named *Sirius* will focus on advanced population and use BCVA as the primary endpoint.

The second trial, which I'll show in a minute, is similar but will be in the early-to-moderate population and use static perimetry as the primary endpoint.

These two populations had different characteristics, so we decided to structure it as two parallel studies that will give us two shots on goals for registration.

So the *Sirius* study, it's using the gold standard of BCVA, as we know that only people with advanced disease can respond on this endpoint.

It will only include patients that are showing some loss of visual acuity at baseline.

Patients in this study will have a visual acuity of 20/40 or worse, which means that they can read everything but the smallest lines on the eye chart.

Clinical trial participants in the active arms will receive one of two different doses of QR-421a every six months.

The primary endpoint here, BCVA, and given the effect size observed in this population, we anticipate evaluating the endpoint after 18 months of follow up.

The goal will be to stabilize the BCVA in the QR-421a treated eyes, whilst the control arm could be expected to deteriorate in line with the natural history of the disease.

As BCVA is the gold standard in ophthalmology drug development, a positive benefit/risk readout on BCVA will support QR-421a registration as a drug for patients with USH2A exon 13 mutation.

So in parallel, this will look very similar, but this is "*Celeste*," the study in early-to-moderate patients and here the primary endpoint is static perimetry measured at the 12-month time point.

One of the key secondary endpoints will be a mobility course and perhaps OCT as well. This is the optical coherence tomography looking at retinal thickness.

The goal here will be able to will be to see an improvement in static perimetry in line with regulatory approval threshold data from the *Stellar* trial.

So for both studies, we are planning for the primary readout after repeat dosing, but may consider to adjust the timing or to add an interim analysis once we have aligned these plans with the regulators.

So now something exciting, QR-421a, we've finally got a name for our molecule.

It's my pleasure to let you know, it's a bit of an exclusive, this is recent news that the WHO, the World Health Organization, has approved "ultevursen," That's "ull-tuh-VURR-sen" as the name for this molecule.

What happens is we provide suggestions for this International Nonproprietary Name and WHO give their approval. So we're really excited to let you know this milestone. It's getting us one step closer to this becoming a real product.

So in closing, I would like to say a huge thank you to the Usher Coalition, to Krista and Nancy for inviting ProQR to come along, and as well to all of you for listening and coming on this journey with us in genomic science.

So I'm happy to try and answer any burning questions you might have. Thank you.

[KRISTA]: Thank you so much, Doreen.

This is Krista Vasi speaking. And yes, we have many questions coming through. And I know you have your colleague Andrew Bolan from ProQR with you as well. So we have plenty of expertise here to field these questions. Andy, give a little wave. There he is.

All right. So let's see.

I know, Andy, you were watching the questions as they come through as well, and it might be best if you kind of take your order, your preferred order.

[ANDREW BOLAN]: Yeah, absolutely.

Hi, it's Andy Bolan speaking here. It's lovely to be with you today.

I think me and Doreen can work through these questions, so we might just do a quick, quick Q&A as we go through, a lot of the questions we hope we answered in the presentation, but we can go through them step by step.

So the first one we have, Doreen, is, "I have USH2A, my doctor will not do the genetic test to confirm. What other options do I have living in western North Carolina?" Well, I'll take that one. Mike, lovely. Thank you for the question.

The Foundation Fighting Blindness has a wonderful open access genetic testing program. And really, I'm a little shocked to hear your physician won't help you take this next step as it, as Doreen presented, it is a crucial step in genomic medicine that we're developing, that you need to know your genetic gene.

So I would probably seek another doctor and really try and put forward the Foundation Fighting Blindness' free genetic testing.

Next question is, Doreen, "What is our ideal candidate for the clinical trial?" I think you kind of talked a little bit about the eligibility criteria, but do you have anything else to add to that?
[DOREEN]: Hi, this is Doreen. Yes, the critical thing is that you are both clinically diagnosed and that you have a genetic profile that confirms to this kind of USH2A exon 13 mutation. That is absolutely critical because the ultevursen is targeted only for that subpopulation.

Other things that might be of interest to know is the age.We started looking at just adult population. And thanks to the feedback from the community, we quickly realized that we had to reduce that. So now if you're aged 12 and over, you may be eligible for this trial.

[ANDREW]: That's great. Thank you. Next question from Machteld is which, "was this tested on animals?" Which is correct.

So the multiple phases of clinical development, we did go through the first stages, which are safety, and we have plenty of information on our website, if you'd like to follow up on that. But we have done all the safety elements that we needed to to get to human trials.

And Stella was that first in-human study. So answered that.

Doreen, from Brian, "What percentage of USH2A are targeted by treating exon 13?"

[DOREEN]: Doreen, again, it's a small percentage. It's true. We hope that we can start with this mutation, but we anticipate that in future drug development, we will look at different mutations.

I don't know an exact figure of the percentage, but we're taking a little bit at a time, bringing what we can to the patients.

[ANDREW]: And I'll just add to that the specific technique of exon 13, it's Andrew, Andy speaking, the specific.

Oh, Krista, do you want to come in? Do we have our interpreter back? No.

[KRISTA]: We lost our interpreter. So just one one second. I apologize. Dena is back now. Melissa, Melissa's taking over. OK. Good. OK.

[ANDREW]: It's Andy speaking here.

Doreen explained quite quite well, you know, the exon 13 skipping in its specificity is that we're trying to create a functioning usherin protein.

And so if we take out exon 13, 12 and 14 can come together and create that smaller but functioning usherin protein.

And that's what clinical development is trying to to see if that does work.

Next question, Doreen "Did you say that the upcoming clinical trial will take two years and all that, or we've already done two years as well?"

[DOREEN]: Hi, Doreen speaking. So the first clinical trial, we followed patients for two years. So you heard correctly.

The phase 2/3 trials that just started, we will be following patients again for at least two years.

In addition, we didn't mention it yet. We are providing open access through an extension study so that patients who have already been treated in the first trial can continue to receive treatment until treatment becomes generally available. Thank you.

[ANDREW]: It's Andy speaking here. Felipe asks "On Figure 3 of the PDF that ProQR published with the results of the *Stellar* study, at the end of 48 weeks, the benefit for the untreated was higher than the treated eye. How can this be? Are they reading it correctly?" Well, I can, I can have a stab at that.

So we did see that the medicine does wear off after a while, and that was a crucial piece to understanding our development because actually, it showed that the RNA medicine we've developed isn't permanent.

It isn't changing your DNA, so you will have to have it again and again.

And so that is one of the critical pieces of information we gathered for our phase 3 studies *Sirius* and *Celeste*.

Next question, we can go down. We've asked a few of these.

What is the significance of only, this is from Monica. Thank you, Monica.

"What is the significance of only measuring BCVA with respect to Usher patients who may have no visual acuity problems, but rather light sensitivity and tunnel vision? From what I understand, RP affects peripheral vision before central vision. Does the medicine only work to stabilize central vision loss?" I can have a stab, oh Doreen.

[DOREEN]: Hi, Doreen speaking. So we're looking at the patients who have early-stage disease, who are starting to see a reduction in peripheral vision.

As the disease progresses, the field will get more and more narrow so that we will start to have an impact on the visual acuity.

So the product should work for both populations because the problem is the same problem. We are replacing the usherin protein that is needed for the photoreceptors to work.

So we're measuring different parameters because the patients are at a different stage of disease.

I should just add that we mentioned the main parameters.The primary endpoint, but we will measure a whole range of secondary endpoints to to find out what's going on.

[ANDREW]: Thank you, Doreen, it's Andy speaking here. Next question, but before we do that, there are a few questions that have been coming in about how do people sign up for clinical trials? And we're extremely excited. There's a lot of enthusiasm.

Clinical development does take different times in different geographies.

We do plan to have sites all around the world from the United States, we hope Canada, Brazil and quite a lot of countries in Europe as well, but each country has a very different timeline for opening a clinical site.

We have different ethical pieces to do in each of those site locations, so we only have one site open at the moment, which was fantastic to do and get those first participants in.

But for those of those of you around the world asking when they can, when you can sign up, it will be, we hope as soon as possible our team at ProQR, we are only a small team and a small biotech so we're are working as hard and as fast as possible to get these clinical trial centers open.

But you will see more and more information, come to our website at www.proqr.com and we'll have updated information every time a new site is open.

Sorry, I just wanted to get that one because there were quite a few. Um, let's have a look at some of these. OK.

This is quite a good one at which I can answer, Doreen. This is from David, "I have the USH2A gene. I'm more affected at this time with RP as part of my disease. My doctor says I don't have exon 13. How can I tell if I have the exon 13 myself in my genetic results?" Thank you.

Well, David, that's a fantastic question. I would, and we would always ask you to talk to your physician about clinical research. I'm not a medical doctor and Doreen outlined she's not an ophthalmologist, so we can't give medical advice.

However, continue the discussion. If your doctor has said that you're missing the exon 13, that is a crucial piece of information. And you know, the clinical tests are not very easy to read, if I can be honest.

So I would always recommend if you can having genetic counseling if it's available, as well as talking to other physicians to really clarify that. But unfortunately, we can't give out medical advice directly today.

All right, let's have a look.

Doreen, one for you from Brendan, "Have we seen any reversing of sight, sight loss, or the ability to see in the dark?"

[DOREEN]: Doreen speaking. We've seen stabilization, I think, is the best way to say it. There is a degree of variability when the tests are performed with some slightly higher, slightly lower test results.

So we are always careful in the trial to ask for, for example, the BCVA is repeated several times so that we are sure that we take a representative value.

So I would say that so far we are seeing stabilization with one injection. What we don't know is what will happen with multiple injections. So this is something where we're really excited about.

[ANDREW]: It's Andy speaking here, next question. I'll just have a look. We've answered quite a lot of these. Ah, now this is a good one. “Would this treatment preclude getting another genetic treatment in the future?”

And I can try and tackle that question because it is a question we get a lot. We haven't seen in Usher syndrome, other trials that have come along yet. What is very useful with RNA is it does wear off.

So technically or hypothetically, should I say it shouldn't preclude you from any future DNA-based therapies, which I think is the the kind of underlying part of the question.

That being said, I do have the caveat.

In LCA10, and Doreen talked about our advancements, and we're excited of data pretty much by the end of this month, we hope, in LCA10 there is a competitor, gene or DNA-based, and they did preclude individuals who have had an RNA therapy in their trial.

So it really is company to company. Hypothetically, our drug does wash out or leaves your system eventually. So there shouldn't be any reason why you can't have a DNA-based treatment in the future if one does come along.

That's a bit of a tough question, but I hope I've answered it satisfactory.

Question about pricing of the medicine, so I can take this one as well.

So this is a common question that we get, as I'm sure you can imagine at the moment, the ultevursen in clinical development is just too early for us to begin to thinking about the cost of the treatment.

This will really be down to the data and how significant a medicine it can be. But we're just unfortunately too early in the process to even begin to think about that.

Right. Let's have a look. We've answered a lot of these questions.

Ah, Doreen, maybe one for you from Ricardo, "How do the results translate to visual field, a.k.a. improved peripheral vision?"

[DOREEN]: So this was, we didn't show you the data here. You can look at it on the website. In general, we saw, we saw some stabilization there up to about six months.

And then there was, it seemed to be time for another injection, which was, it was part of the reasons we wanted to give an injection every six months to keep the condition stable.

[ANDREW]: Thank you, Doreen. It's Andy speaking again here. Next question from Virginia is a very good one. “How many injections can the eye withstand or is it for life?” Now I'll have a quick stab.

Really safety data, we follow this very, very carefully and actually *Sirius* and *Celeste* will be the first time we've done multiple injections in the eye.

But we really will be studying the safety around this and just seeing how the eye can do with multiple injections. Doreen, do you have anything to add to that?

[DOREEN]: Doreen speaking just to say that in other conditions, the frequency of injection, so using the same technique for different diseases can be as frequently as every month. It's a very well-established technique.

We're using a low volume of injection with a very fine needle, only by skilled physicians who know how to use the technique. So it is, it is feasible, I think, to continue long term administration.

[ANDREW]: Thank you, Doreen. It's Andy here. We're getting a lot of questions about why exon 13 and when other exons will come next. That's a very standard question we get and I'll have a stab at that.

Really the work out of the wonderful colleagues at Nijmegen University, or Radboud Retinal Center, it really drove this, and we have a wonderful webinar that I would recommend anyone to go and watch is on our YouTube channel, where we really go into the history of exon 13.

And and, you know, from my understanding and the science, this is the one that has really taken to exon skipping. We've seen it really be effective.

The practice in the skipping itself from a scientific perspective isn't for every exon, because ultimately it really is about creating a functioning usherin protein. And we've seen that success in skipping exon 13 and connecting at 12 and 14.

So that is the difference. I would fully recommend anyone to go on our YouTube page and watch that.

It's very detailed and we have some of the, we have just one wonderful chap called Erwin van Wijk from Radboud University here in the Netherlands, who actually was part of the original team who found the exon skipping to be working and excellent in this case.

And he goes into a wonderful description of the science, so please do check that out.

We have 10 minutes left, Doreen, so let's have a look at some more questions.

Heather asks, "Is this the last phase of clinical research?"

[DOREEN]: Doreen here, typically the pivotal trials that we described should be the last stage to gain registration permission.

We're still learning a lot about what this molecule can do, and so we would expect to continue to record safety. And there may be other questions we want to address.

One question we hear often is can we dose patients younger than age 12? And this is something that we are, we are going to be looking into to see if we can do that.

So that may be a question soon, or it may be a question that we can only get permission to to test in children and younger children once we have data in adults.

[ANDREW]: Great, thank you, Doreen, it's Andy speaking here. Emmanuel asks, "I heard there's going to be a phase 3 study in Europe. And will the study have a sham group?"

So I'll start that, Emmanuel. Absolutely.

We will be hoping to open our European clinical trial sites for *Sirius* and *Celeste* as soon as possible in 2022, and there will be a sham arm.

Doreen, do you want to expand on that at all?

[DOREEN]: Yes, having having a control, it's really important for getting convincing data.

When you have a disease that can vary dramatically from one patient to another, it's an, it's a point that's not negotiable with the regulators.

They really want to be sure to protect the patient that any effect we see is a true effect and not a chance effect. And this is why they insist that we have a control and in this situation, it's a sham control.

We've been able to keep the numbers assigned to the sham group as small as possible. To keep the validity of the trial.

[ANDREW]: It's Andy speaking here, I think that's really key as all of you come along the clinical research journey with us is the fact that we do have to do certain things to make sure the data is clean and that we show as much of the effects as possible and control arms play a role in that as well.

They are also a regulatory requirement in most cases.

Let's have a look.

This is a question from Shaun, "The positive results from the ProQR data show that there is an eight letter improvement over the control of 72 weeks. This is almost entirely due to the degeneration of the untreated eye. In fact, there's approximately eight letter deterioration in the untreated eye. This seems extremely rapid. Would you consider the rate of degeneration normal for USH2A individuals? Secondly is the working theory that there will be no improvement in vision, and the best case scenario is stabilization in the treated eye, regardless of individual's deterioration rate?”

Doreen, would you like me, would you like to take that? Yes.

[DOREEN]: Doreen speaking. Thank you. Thank you, Shaun, for the question.

The rate of deterioration as part of the natural disease evolution, that is something that we, we shared that observation that it seems relatively rapid during the course of the trial.

Please bear in mind that it's a small number of patients. This is why in our pivotal studies, we're moving up. There will be a total of approximately 200 patients in the, in the phase 2/3 program to try and get a clear idea between the treated and the non treated.

So for the first part, we share what, what, what your your, we are aligned with your comment.

On the second part, "Can we expect anything better than stabilization?" Once the photoreceptors have deteriorated, they don't regenerate.

This is why we are looking to preserve the maximum number of photoreceptors and to be sure there that we can help their functioning.

So there's a degree also of the eye learning. And this may lead to slight improvements, but whether whether it's a true sustainable improvement, it's far too early to tell.

So I think stabilization is our immediate target and we will be looking very carefully to see if we can do anything better than that.

[ANDREW]: That's great, thank you. It's Andy speaking, that's great. Doreen, thank you. I'm just looking down. We have an awful lot of questions and we have five minutes left, which is wonderful to see such an engaged community.

We're trying to get through doing a bit of translating as well for our Latin American community, colleagues on the line as well.

It's worth noting we do hope to have Latin American sites. We're working with Brazil currently.

However, it is worth noting that we do, if you are eligible for the study, we have in the past allowed people to travel and pay for accommodation that is all covered by the sponsor, which is us, for the trial to get you to the right center.

It's worth noting at this point as well that I really can't go on without thanking the Usher Coalition for all of their help with this.

We have just started a new initiative with the Usher Coalition and and that's very close to my heart as the person responsible within ProQR for community outreach and that will be utilizing the USH Trust registry, really getting in front of all of you like we are doing today and really utilizing to see if we can get you into our trials.

It is worth noting, at ProQR, we found it very hard to recruit for our LCA10 trials. These are rarer conditions. This isn't heart disease or anything like that.

And so your enthusiasm and your motivation to join our trial is hugely appreciated in allowing us to fill these trials as quickly as possible and bringing these, we hope, medicines to everyone as quickly as possible.

Um, right. I will stop ranting and I will go for more questions as we go into the final straight here, Doreen.

Jim asks, "I see there's only one site in the U.S. in Texas, will there be other sites around the U.S., including the D.C. area?" I think I can take that, Jim.

We do hope to have several sites open in the USA and like I mentioned before, each site does have a different ethics procedure and we do need to go through all of the different approval processes so that we have all of the science and the safety signed off by that clinical site.

We do hope to have quite a few in America. So do watch our webpage for updates. Or you can contact me directly at patientinfo@proqr.com.

And I know a lot of you, I'm recognizing some names on here asking questions who have written to us very recently, so thank you for reaching out.

It is, we are trying our best to open the sites as quickly as possible, but some are taking, some take a little bit longer than others, which is normal for clinical research.

I think we've answered a lot of these. Yeah, I think, uh. Quite a lot of these are asking medical questions, so of course, you can't answer them directly. I wish that was the case.

Let me check that that was all the. Let me check the chat function to see what we have here.

Bear with me, everyone. There are a lot of questions, so apologies.

This is a very good one, Christina asks, "Are there any plans of injecting QR-421a into the ear as well to see if it can affect hearing loss? Would you like me to take that, Doreen, or jump again? I can, I can have a go at that.

So at the moment, we are really concentrating ultevursen in the eye. ProQR is a genetic eye condition company. That is something Daniel has really reiterated. So our focus really is on ocular or the eye specifically.

I get this question a lot because we do have an in-house committee and one of our in-house committee members really does ask about the ear as well.

We never know what will happen in the future, but at the moment ProQR is only concentrating on the eye and through that so we won't be doing the ear as well.

Right. Uh. Conscious, we have a minute left.

Krista, would you? We're not going to get to all of these, unfortunately, which is causing me a lot of stress. Do you want to take over?

[KRISTA]: This is Krista speaking. Yes, we have received an overwhelming amount of questions. This is so exciting just what we need to to see this enthusiasm.

I'll do my best to capture any questions that we may not have covered. There were a lot of repeats and everything, but I'll do my best to kind of document that and be able to do some follow up with individuals.

I know a lot of it is individual support and individual kind of medical genetic testing analysis and everything.

So this has been fantastic. This has been so wonderful. I want to thank you, Doreen and Andy again for presenting today and sharing this important information.

We'll, this is a conversation among all all 200 plus of us right now so we're going to keep it going and please keep in touch with the Usher Syndrome Coalition. Reach out to ProQR.

And the clinical trial sites, all that stuff as it rolls out, that information will become available, but the Coalition is here to help support you all to try to find out if this is something that works for you is right for you and what the next steps could be.

So we are a resource. Please don't hesitate to reach out and a recording of this webinar will be provided. We'll have transcripts, captions all of that as well.

So thank you again, everyone, for being a part of this and we'll talk soon.

Have a wonderful rest of your day and evening.

Thank you.